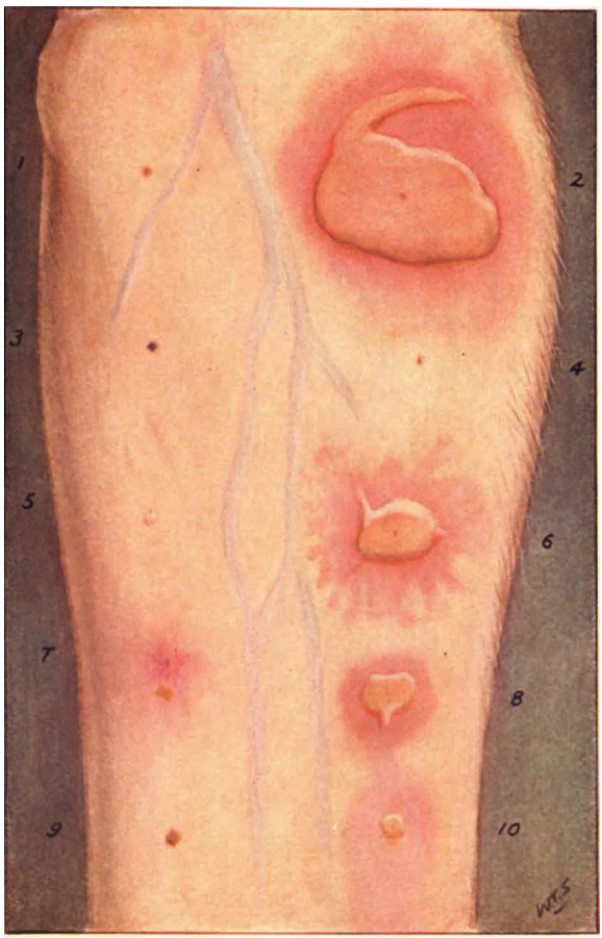

KEY.

1, 3, 4, 5, and 9, Negative reactions; 2, + + + + + reaction to Timothy grass pollen; 6, + + + reaction to horse dandruff; 8, + + reaction to oats; 10, + reaction to wheat; 7, An unusual type of reaction without the wheal appearing.

[*See page* 113.

Frontispiece

ASTHMA

BY

FRANK COKE, F.R.C.S.

WITH THE COLLABORATION OF

HARRY COKE, M.R.C.S., L.R.C.P.

Honorary Physician, Charterhouse Rheumatism Clinic

SECOND EDITION, FULLY REVISED,
AND ILLUSTRATED

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PREFACE
TO THE SECOND EDITION

DURING the sixteen years since the publication of the first edition of this book, much further experience with asthma has been gained, and a great deal of important research work has been accomplished. A more exact understanding in the last few years of the factors involved in the causation of asthma and their mode of action has made it seem necessary to publish a second edition. Revision has not been the essential cause, since practically all the original material remains of the same truth and importance as it did in the first edition. The basis of the treatment of asthma to be found in the later pages depends upon the application to the subject of new conceptions of investigation. Such, it is hoped, will not only be of interest to the practitioner and specialist dealing with 'allergic diseases', but may lead to a more general improvement in the treatment statistics of those suffering from this distressing complaint.

The main features of the changes effected in the contents of this edition are set out in the Introduction, but reference may be made here to the association of the two authors. As will be seen from the perusal of the pages of the book, the problems of the bacteriology and serology of asthma are so important as to require the fullest discussion possible. With the availability of much new work having a special relationship to asthma, the new association of Dr. Harry Coke with the special chapters dealing with these subjects has, I feel, made the review of the problem more comprehensive and complete.

The undoubted value of treatment on bacteriological lines is fully emphasized. The methods employed are modelled on the technique of Dr. Warren Crowe as used

by him so successfully in the treatment of rheumatism at the Charterhouse Clinic and elsewhere. To his knowledge and experience and for its transference to the subject of asthma I am truly grateful.

In conclusion I wish to express my sincere thanks to the publishers—John Wright & Sons—for their unstinted trouble in preparing this second edition, and for their help in all the details of its publication. For the coloured blocks of the charts on pages 169-170 I have to thank the Oxford Medical Press.

FRANK COKE

*London, W.*1

INTRODUCTION

An introduction to the study of asthma must set out in the first place a clear definition of the scope and meaning of the subject. 'Asthma' is a technical word describing solely a symptom, and, in the same manner as such other symptoms as 'backache' and 'headache', it may be due to a great diversity of causes, and can be simplified by classification into groups on the basis of causative factors.

The second edition of this book has in mind the necessity to emphasize and to bring forward three important aspects of the subject which have come to be of practical use in the therapeusis of asthma and allied complaints; while at the same time it retains the original format of the first edition, and thus develops within its covers a general review of the present state of knowledge about asthma. This entails an account not only of our own personal methods of examination and treatment, but also of the physiology and pathology of the disease, as well as a statistical survey of three thousand cases.

The first edition drew special attention to the dermal sensitivity tests, which had at that time (in 1923) not been extensively employed in Great Britain.

The main theme was the presentation of 350 cases of asthma examined and treated in the light of the new work that had then recently been carried out in America, namely, the sensitization of asthmatics to foreign proteins. It was shown that 52 per cent of these cases gave positive dermal reactions, a proportion practically the same as the 48 per cent of Chandler Walker in a series of 400 cases.

Such little criticism as this evoked came from those who frankly disbelieved the figures, and from others who argued that, having found a patient sensitive to feathers, the findings were useless if his asthma did not disappear on removal of the feather bedding, overlooking the possibility of sensitization to other undiscovered proteins.

A few years later the Great Ormond Street Children's Hospital became interested in this work and the technique was demonstrated to junior members of that hospital.

Finally, as recently as 1934 the Asthma Research Council in their report state: "These results have confirmed the value of the skin-tests, which at one time were subject to much criticism."

The amplification and extended use of these tests has duly repaid the earlier investigations, and they are now not only very widely used and accepted, but one may go so far as to state that the treatment based on the knowledge of such tests has led to the alleviation of a great deal of suffering. Great though such advances were, there still remained a large number of asthmatic patients to whom treatment on such lines afforded no material assistance. In this volume are recorded the investigations on other lines that have led to the consideration of the symptom 'asthma' on a much wider scale.

In the second place the lay-out of the subject matter has been reconstructed as a result of the serological investigations described. The application of the differential sedimentation test to the asthmatic patient has led to the very clear definition of three main groups. Since these groups correspond very closely with a similar clinical classification, we have considered that such findings form a cognate basis for the rearrangement of the problems of asthma.

The differential sedimentation test is of great assistance in the practical aspects of the disease, as well as affording a basis for the better conception of the problem of asthma as a whole.

Of the three new and important features of this edition, this fact may be considered first. It has been our purpose to put forward a simple classification of all cases of asthma as falling into one of three fundamental types. We are of the opinion that such a classification is possible and leads to a much clearer understanding of the subject, and is of a real and practical importance in the diagnosis and treatment of the complaint. It will be noted, therefore, that throughout the chapters these three main types are referred to, emphasized, and reiterated several times—but not, we consider unnecessarily, if it impresses upon the reader the fundamental importance of reviewing all clinical cases in such a light.

Type I, the allergic or protein-hypersensitive type, was fully dealt with in the first edition, and the material then discussed stands as firmly at the present time as it did sixteen years ago. To explain the specific phenomena, such as resulted from the classical experiment of Prausnitz and Kustner in 1921, together with many other reactions of the blood in cases of asthma, a term 'adzyme' was suggested and used extensively in the first edition. With the greater prominence and more universal usage of the American term 'reagin' for an identical purpose, it has been considered that it would clarify the discussion of these subjects if this term were substituted for the original term 'adzyme', and this has been done in the present edition.

In the account of the investigation and treatment of cases classed as Type II, the infective group, there is a substantial new element in this edition. Not only the bacteriological investigations, but the recognition of such cases by serological methods, and the treatment with small doses of potent polyvalent autogenous vaccines, have led to a personal experience in treatment that can only be expressed by saying that the subject is regarded as being of a practical value and importance equivalent to the dermal sensitivity tests.

The third purpose to which we have especially applied ourselves in this new edition is the more extensive discussion of the previously intractable form of asthma known as the aspirin-sensitive group, a subdivision of the fundamental 'mixed' Type III. Whereas previously these particular patients had been the despair of physicians, they have recently proved amenable to treatment with vaccines. Although apparently so typical of a simple allergic group, it was not until an additional infective element could be demonstrated by the differential sedimentation test that such infection became investigated. Here a post-nasal infection, frequently with staphylococci, has led to treatment on these lines with autogenous vaccine, and with a success that has been duly gratifying. Such a clinical observation, correlated with the extremely important work of Feldberg and Keogh, had led us to postulate the 'toxin-histamine spasm' link between distal focal infection and the typical spasm of the bronchial musculature that is recognized clinically as asthma. Along such

lines we feel sure that in the future much new work will be accomplished, and interesting evidence brought forward to explain the complicated pathology and aetiology of this complaint.

The anatomy and physiology described in the former edition remains to complete a review of the subject from all angles. It has been revised, in parts curtailed, and in certain respects enlarged where new and pertinent material has been published. As will be understood from consideration of the earlier chapters, we find no sound reason to alter the original conception of allergic or Type I asthma as being in any way fundamentally different from an anaphylactic phenomenon in man. Apart, then, from the value of a proper conception of anaphylaxis in animals in the study of 'allergic phenomena', we are of the opinion that the two conditions 'anaphylaxis in the laboratory animal' and 'asthma' in man are identical pathological phenomena, differing only in the degree of the respective organism's response to the antigenic stimulus.

In the following pages, then, asthma as a symptom is discussed from every angle. Not only are the modern conceptions of anatomy and physiology dealt with, but in the realm of actual medical practice new work is submitted that in our hands has proved of much material benefit to our patients, and as such has provided the stimulus to the publication of this second volume.

In conclusion, we have noted a modern tendency to cramp the flow of thought when reading medical literature by a superlative abundance of references. While retaining in this volume all important references, as well as those where an important or a new fact has been under discussion, it has been our endeavour to refrain from a surfeit that might be detrimental to the sequence of thought. Many additional references will be found in the first volume, while the organization of modern medical libraries has reached such a high standard that any point which a reader may wish to follow in greater detail can almost instantaneously be furnished.

ASTHMA

CHAPTER I

ANAPHYLAXIS, ALLERGY, AND SENSITIZATION

THE pathology of almost all forms of asthma, including the bacterial group, rests essentially on the mechanism of the hypersensitive state. Full understanding of the intimate biophysical mechanism of sensitization is far from complete, but sufficient is known to have made the treatment of asthma a rational procedure, and in very many cases a successful one.

ANAPHYLAXIS

Although the clinical picture of sensitization in man was very accurately described in 1868 by Hyde Salter, it was not until 1902, that the classical experiment which led to the discovery of the phenomena of anaphylaxis was published by Charles Richet.[1, 2] It prefaces every article on anaphylaxis that has been written, and from the rich trail these articles have left behind them, the original discovery loses nothing by repetition.

Richet injected a dog with a certain dose of a poison, derived from the tentacles of actiniæ, with no harmful effect. Twenty-two days later he reinjected this same dog with exactly the same dose, expecting subsequently to be able to inject larger doses, and eventually produce a condition of immunity or prophylaxis to this poison. To his surprise, hardly had he finished this second injection than the animal became extremely ill, and died in twenty-five minutes. As such a result was the exact antithesis to prophylaxis, he gave it the name of anaphylaxis.

This basic phenomenon can then be briefly described as follows: An injection of a foreign protein is made into an animal. After a period of incubation, which must exceed a certain time, a further injection is given of identically the

same protein. A clinical syndrome occurs as a result, which may vary in degree of severity up to that of death, but which is at the same time always the same, and independent of the actual specific protein. This syndrome and its essential causative pathology is anaphylaxis. On this fundamental fact is built our modern knowledge of asthma as it occurs in man.

Since the original experiment of Richet numerous experimentalists in many countries have investigated the phenomenon. The names of Arthus,[3] Besredka,[4] Theobald Smith,[5] Auer and Lewis,[6] Friedberger,[7] Nolf,[8] Bordet[9] with Dale[10, 11] in our own country, may be especially mentioned, each having studied some particular aspect of the problem. The initial investigations into anaphylaxis were made while using injections of various snake venoms and other animal poisons. It was considered, as indeed its name suggests, as being based on the same mechanism as that of immunity, though in an exactly opposite direction. Maurice Arthus, in the year following Richet's discovery, showed that the same phenomenon occurred when normal horse serum was used for the injections. Otto[12] and Theobald Smith[13] published articles shortly afterwards. We now know that anaphylaxis is not the converse of immunity, and Richet's original experiment had nothing to do with the various poisons he was using, but with the proteins contained in his solutions. It has come to be shown that protein in any form, whether horse serum, white of egg, milk albumin, or cereal, has the power of rendering an animal sensitive to another injection of the same protein, which when administered will immediately produce the anaphylactic syndrome, even to the point of death in a few seconds. Arthus has made the difference between anaphylaxis and immunity quite clear by inoculating rabbits with snake venom.

Semple[14] writes: "The toxic elements of snake venoms are always associated with proteins, but as yet it has not been possible to separate them from the proteins with which they are associated." By injecting snake venom into animals, Arthus was able to produce such a high degree of immunity that they were able to withstand an injection of several times the lethal dose. However, by these same immunizing doses the animals became sensitized to their protein content, and after an incubation period the animals died with typical

symptoms of anaphylaxis when subsequently injected with snake venom.

The first injection of the protein employed to sensitize the animal may be given intravenously, intrathecally, intraperitoneally, intramuscularly, or hypodermically. Animals have been sensitized orally (Richet[15]) and through the respiratory passages, but the experiments are successful only if the proteins gain entrance through the blood to the cells of the animal.

An incubation period of ten or fourteen days must elapse before the animal becomes sensitive. Except in the case of very massive doses this incubation period is fairly constant, and depends but little on the size of the dose. After this time has passed, a second injection will cause anaphylaxis. This exciting dose is far more potent when given intravenously than when administered hypodermically. It is a shock action, and therefore the quicker the dose is given and the more rapidly it circulates over the body, the more intense will the anaphylaxis be.

No matter what form of protein is used, the same type of anaphylaxis will follow on the second injection.

The typical picture of the symptoms of anaphylaxis as it occurs in various animals, including man, is as follows :—

After the second or exciting dose, the animal is in distress almost before the injection is finished. It becomes restless and scratches its muzzle as though it irritated ; the respiration is quickened, then laboured ; vomiting takes place ; there is diarrhœa with the passage of blood, especially in dogs ; micturition occurs ; tetanic spasms and somersaults give place to flaccid paralysis and collapse ; and the cessation of breathing brings death. Numerous blood changes take place. There is a great fall in the blood-pressure, due largely to a spasm of the hepatic veins, with obstruction to the portal circulation and intense dilatation of the whole splanchnic area.

The following are examples of analogous occurrences in human beings :—

A boy and his three sisters were given prophylactic doses of 2000 units of antidiphtheritic serum by MacCallum.[16] In two minutes the boy became extremely ill with diarrhœa and was apparently choking. He died a few minutes later. There was no ill effect of the injections upon the sisters.

In another case a man who had had injections of antitetanic serum while suffering from a fractured tibia developed erysipelas. Thirty c.c. of antistreptococcal serum were given intravenously. Within a minute he complained that he was choking and later ceased breathing in full inspiration. Artificial respiration was commenced while chloroform on an inhaler was held over the face. He was given 30 min. of adrenaline and $\frac{1}{100}$ gr. of atropine subcutaneously. In a few minutes he commenced to breathe and soon came round, one hour later being comparatively well. (Munro.[17]) But for this rapid and skilful treatment he must certainly have died.

Lamson[18] gives full details of 42 cases of sudden death, the majority of which occurred within ten minutes of an injection of antidiphtheritic serum. He calculated that this disaster may be expected to occur in one case in 70,000 of such injections.

Cooke[19] describes the death of a patient after a test injection of Le Page glue: "The boy then suddenly broke out in a general rash, his face began to bloat with an œdema, until his eyes were closed. Cough and dyspnœa were marked for a minute; he was deeply cyanotic and respiration ceased." Other cases are recorded of death from an overdose of Bermuda grass pollen and after a dermal test injection of buckwheat. (Coca, Walzer and Thommen.[20])

Attacks of asthma, urticaria, and lesser symptoms are not uncommon if the test solutions are too strong or injected in too large amounts. The following case exemplifies the minute amount of proteins necessary to cause symptoms:

Case 1.—A man who knew he was very sensitive to Brazil nuts accepted an invitation to a Christmas dinner, and was told there were no Brazil nuts in the home. In spite of this, at the end of dinner he said: "I have had some Brazil nut, and I shall soon be very uncomfortably ill"; and he was, with urticaria, diarrhœa, and sickness. Two days later it was discovered that in a mince-pie he had eaten there had been some fraction of Brazil nut.

Such patients are also examples of another typical feature of anaphylaxis, namely, the specificity of the reaction. That is to say, *anaphylaxis cannot be produced unless exactly the same foreign protein is given for the second injection as was used to sensitize the animal.*

The whole of one's work on asthma and the dermal reactions exemplifies this specificity. Taking the normal rough-and-tumble of life as a test of patients' sensitization

to scores of proteins with which they come in contact, it is only those particular proteins to which they are sensitive that give rise to symptoms.

Case 2.—A young man suffering from asthma for some months had had nocturnal attacks. I found him sensitive to hen feathers, though only giving a + reaction. He gave up his feather pillows, substituting those made of kapok. He had no asthma for eight months. He returned to me saying he had asthma for the last four nights, following a ride on a motor bicycle. I read through his case-sheet and asked if he had changed his rooms lately. He had moved to another part of London a week ago. Had he taken his kapok pillows with him? He had not. He saw me again a week later. His asthma had left him since his last visit to me; he had bought new kapok pillows on his way home. He had probably met with 200 or more different proteins during the eight months he was free from asthma, but had no attacks until he again encountered the hen feathers to which he was sensitive.

The clinical syndrome of anaphylaxis is always the same in the same animal, no matter what form of foreign protein is used to produce it; but the symptoms show variations in each different species of animal.

Roughly, we have the asphyxiating type in the guinea-pig, the cardiac type in the rabbit, the gastro-intestinal type in the dog. In the guinea-pig the type is extremely constant, a standard type. In other animals there is far more variation in sensitiveness and the subsequent anaphylaxis. As for monkeys, it has been found to be a difficult matter to sensitize them at all.

These variations in the range of symptoms caused by anaphylaxis appear to depend not so much on the animals as on the distribution in them of the smooth involuntary muscle. For instance, in the guinea-pig it is the bronchial muscle which is particularly well developed, hence the asphyxiation that occurs during the anaphylactic syndrome in that animal.

These facts must be borne in mind when considering anaphylaxis in man. It is not necessary to find another name for the symptoms of human anaphylaxis simply because they do not conform rigidly to the standard guinea-pig type.

All proteins are 'foreign' to an animal or man except those of the same species. Even homologous proteins become foreign in their action to the living cells when they die, i.e., proteins in which an intrinsic chemical change takes place on their separation from their normal environment.

After injection into the body, foreign proteins have to be dealt with and removed. The hypothesis of such mechanism, always ready to deal with foreign proteins, must be discussed. In the last edition the term 'adzyme' was suggested for the hypothetical substance which deals with foreign proteins gaining entrance to the body. A new word such as 'adzyme' expresses a suggestion that its method of action is rather a physical change of adsorption than a proteolytic change. As however in the intervening years the American term 'reagin' has come to be used extensively in the literature, it is used in this edition in replacement of the term 'adzyme' which I propounded in the earlier edition of 1923.

At this point we may review anaphylaxis as follows :—

1. A 'sensitizing' injection of a foreign protein is made into an animal.

2. During an 'incubation period' this foreign protein is gradually removed from the circulating blood.

3. In its place is formed the 'specific reagin', a neutralizing substance or mechanism, against the sensitizing protein.

4. The 'exciting dose', a second injection of exactly the same specific protein, causes anaphylactic shock, though the dose may be extremely small (Rosenau and Anderson[22]).

If anaphylaxis is a colloidal reaction as in the formation of precipitins, it must be noted that such colloidal changes take place at the moment when the opposing forces, electric or chemical, are in exactly the correct proportion to effect the change.

As the incubation period progresses, the quantity of foreign protein in circulation gradually diminishes, while the quantity of specific reagin gradually increases. There will be a time, therefore, towards the end of the incubation period when the two substances are present in equivalent reactive quantities. This then is the moment when serum rashes make their appearance. I came to this conclusion in August 1920, but found it was not a new suggestion. Dale[21] had amplified it in this manner. There are three different proteins in horse serum, and if it is possible to have a serum rash to one, why not to all three, which might possibly mature at different times ? He made inquiries from Dr. Goodall, the authority on infectious diseases, and learnt from him that three separate rashes had been noted after injections of horse serum as contained in antidiphtheritic serum.

Sensitization must mean the production of a new specific substance or biophysical state in the body. It cannot be a deficiency, otherwise we should have to imagine a separate method of dealing with every conceivable protein on this earth, and that in the sensitive people one or two of these were missing. I have patients who are sensitive to a certain fruit in India, to some strange scent or pollen in Nigeria, or to such a peculiar food as caviare. Their idiosyncrasy to these proteins does not mean that they have been sent into the world fully equipped except for a missing protection against caviare, which others possess, but that they have formed specific reagins to these articles which others have not.

Note the sensitization to crabs, lobsters, and especially pollen, proteins we may have a glut of at one time and then go months without. I would call especial attention to this incubation period.

The work of Dale[23] points to the reaction as taking place in the cells of the body, even when they are quite free from all blood. An isolated slip of the virgin uterus of a sensitized animal will contract at once when the specific protein is added to the Ringer's solution in which the muscle is suspended—a very pretty exhibition of the reaction can thus be produced. A variety of proteins so nearly allied to each other as hen's egg and duck's egg can be presented in solutions to the muscle, but it will not contract until the same protein employed in the sensitization is again used in the solution. The problem is an extraordinarily elusive one, for the slip of uterus, although free from blood, still contains its nerve-ending in the muscle. Rich[24] has produced allergic changes in sensitized cells growing *in vitro*, that is, freed from both blood and nerve influences.

This leads up to another peculiarity of anaphylaxis: no matter what physiological or biochemical cause may be suggested in explanation of the fact, *anaphylaxis does not develop if the animal is anæsthetized while the second or exciting dose is given.* Again, in dogs, anaphylaxis is said not to occur if the liver is isolated from the circulation by 'clamps'; when these are removed from the blood-vessels, anaphylaxis occurs. Complement is said to disappear in anaphylaxis.

Passive Anaphylaxis.—If the blood of a sensitized guinea-pig be injected into a fresh guinea-pig, then after an interval

of some hours the latter becomes sensitized to the original protein, another injection of which will at once cause anaphylaxis. Further, if blood from a guinea-pig sensitized, say, to horse serum, be withdrawn and mixed in a flask with fresh horse serum, anaphylotoxin, whatever that may actually be, is formed *in vitro*, and if this now be injected into a new guinea-pig the latter is once seized with anaphylaxis. Passive anaphylaxis is the basis of the Prausnitz-Küstner reaction.[25]

The blood of a patient sensitive to some protein—fish, for example—is injected into a non-sensitive patient; if the latter then eats some fish, the site of the injection will become swollen, red, and irritable. Or if fish be injected into this site a similar reaction follows. Another point of the greatest interest arises from this Prausnitz-Küstner reaction. If the site of the injection of blood from the person sensitive to fish gives a reaction when the normal recipient eats fish, it follows that the specific element of fish must pass into the patient's blood-stream. Conversely, if the blood of the fish-sensitive person be injected into a normal person who has already eaten fish, a local reaction follows. Using this method, Walzer and Walzer[26] were able to define the space of time after eating a protein when the protein is to be found free in the body.

They find that a protein enters the circulation in from five to thirty-five minutes after its ingestion. At two hours the resulting wheals were at their maximum. The protein thereafter gradually disappears during the next thirty hours. Great use is made of this method of 'passive transfer' in America. The blood is injected and the skin tests made on a neutral person, even children and infants being used for this purpose. The advantage of doing skin tests thus by proxy, instead of testing the original patient's arm, is not very apparent. I have never heard of this 'passive transfer' method being used in England except for the purpose of demonstrating the Prausnitz-Küstner reaction to students.

Considering the question of passive anaphylaxis in man, we have the extraordinarily felicitous accident of Ramirez[27]:—

A man was transfused with 600 c.c. of blood from a donor, with no immediate discomfort. A fortnight later, on going out for a drive, he was seized with violent asthma, never having had such a thing previously. It was found that the donor from whom he

was transfused was a horse asthmatic, sensitive to horse dandruff in a dilution of 1–50,000. His sensitive blood had been transferred to the other man and had sensitized him, so that he gave a skin reaction to 1–20,000 of the protein. No less interesting is the fact that another man who received even more blood from this donor did not develop asthma. How did he avoid sensitization ? Or was he sensitized without showing it by asthma ? The blood-groupings are not stated but presumably all three were the same.

Tedstrom[28] considers that the use of blood transfusions is now so frequent that further cases of the passive transmission of sensitization are bound to occur. A man developed urticaria after transfusion from a donor who actually had urticaria on him at the time. In other cases, he says, the donor having eaten largely of a food to which the recipient was sensitive, symptoms have been caused by the food so transferred.

Passive anaphylaxis from man to animals has been demonstrated, though it is not easy to do so. The serum of people sensitive to antipyrin, quinine, and iodoform has been injected into animals. These become sensitive to the drug, and are extremely ill when it is administered to them, whereas the controls give no symptoms.

Achard[29] states that when serum from asthmatics has been injected into guinea-pigs asthmatical attacks can be produced in them by injecting a solution of the Charcot-Leyden crystals.

The whole secret of anaphylaxis may be some mass colloidal action. The addition of sodium hyposulphite to the second exciting dose of serum is said to render it innocuous, no anaphylaxis resulting. (Lumière.[30])

Lastly, when a blood very full of specific reagin is mixed with specific protein *in vitro*, changes take place with precipitin formation rendering the mixture poisonous to another animal, anaphylaxis occurring. Whether this is true anaphylaxis or akin to those anaphylactoid symptoms that follow the injection of starch and serum, or agar and serum, is debatable.

The Anti-anaphylaxis of Besredka.[31]—This is a method whereby anaphylaxis can be avoided, either experimentally or for the purpose of administering a second dose of serum therapeutically. In order to cause anaphylaxis it is necessary to give a certain quantity of foreign protein which must be injected quickly; it is a shock action. In anti-anaphylaxis the specific protein is injected in doses which are individually

too small to cause anaphylaxis, thus gradually removing the specific reagin by using it up or neutralizing it.

These doses are given each hour, being gradually increased in size until the full shock dose can be given with impunity. This anti-anaphylaxis is of vast importance therapeutically, as a method of avoiding anaphylaxis and sudden death from the injection of sera. If there is any suspicion that a patient is sensitive to horse serum, a dermal test must be carried out before treatment is commenced. If it is a matter of great urgency that the patient should have an intravenous injection of an antiserum, small doses are given hypodermically and increased in size until the intravenous injection can be attempted, when rapid increases in the size of the doses can be made. An alternative method is to use an antiserum made from some other animal than a horse to which the patient is not sensitive, if such is available. The modern methods of making antidiphtheric sera by extracting the antibodies with the globulins from the whole horse serum allow it to be given with less danger from this point of view.

In these various procedures the same protein can be used to sensitize the animal, to kill it, or to desensitize it. After a fresh incubation period much of the sensitization returns; the following case exemplifies this :—

Case 3.—A young man was known to be always sensitive to horses, lacrimation, sneezing, and asthma following on in close proximity to them. He joined the Army, and was in the Field Artillery. He groomed his horse three times a day, with dire results. However, either from sheer pluck or because he had little opportunity to do otherwise, he stuck it. At the end of three weeks his asthma left him, and he could do anything he liked with horses without having any asthma. He was very badly wounded, and in hospital five months. Returning home to a farm he found he was again just as sensitive to horses as before. He gives the + + + + reaction.

It would be interesting to know whether he gave a dermal reaction during the time that he had temporarily desensitized himself in the Army.

Later I heard from the patient's doctor that desensitization by means of minute therapeutic injections had been successfully accomplished.

The various symptoms of sensitization in men are closely analogous to those of experimental anaphylaxis. The itching round the muzzle so evident in animals is copied in man by hay fever, by the sneezing from the air-borne proteins, pollen,

animal hairs and feathers, dust, and orris-root. Many patients mention an itching under the chin as a prodromal symptom to an attack of asthma. Pruritus comes into the same category.

Urticaria is the most common symptom of an overdose of pollen or mixed dust proteins, and may occur in one who has never had urticaria before. Egg-sensitive people may have urticaria from handling egg-shells. The lick of a dog may cause a patient to have urticaria, or even sitting in the same room with a dog may bring the patient out in 'hives', as the Americans call it. One of the worst cases I ever saw was in a lady after eating mussels. Other anaphylactic symptoms of animals, particularly those of the dog, are reflected again in the diarrhœa and vomiting of patients sensitive to lobsters or other shellfish. Egg-sensitive people may be sick from such little protein as occurs in the glaze on the top of a bun. Angina pectoris is at times an anaphylactic symptom, and eczemas are commonly so.

Lastly we have the asthmatic spasm in every way comparable to that in the guinea-pig, and the sudden deaths in man from anaphylaxis that have followed injections of the various antisera prepared from immunizing the horse. I have always held that there is no real difference between the various so-called allergic diseases in man and the experimental anaphylaxis in animals, except in the protective mechanism that appears to allow some people to become hypersensitive and others to remain normal.

Scott,[32] in the *System of Bacteriology*, states: "All the facts set forth above, and especially the existence and behaviour of the reagin, support the assumption that idiosyncrasy (hypersensitiveness), no matter what form its clinical manifestation may take, is simply human anaphylaxis."

Vaughan[33] also champions the view that anaphylaxis in animals and allergy in man are the same, and states that the three chief points of dissension are :—

1. *That the presence of precipitin can be demonstrated in sensitized animals but not in men.*

One can, however, well envisage that such findings are due entirely to the biochemical quantities and qualities of the serum proteins—different in animals and man (who has the highest albumin/globulin ratio of all mammals). It

is therefore rather more of a technical difficulty than an actual fact that such precipitin reactions cannot be readily demonstrated in human sera.

A patient undergoing treatment for hay fever was overdosed, with the production of a generalized urticaria; the strength of pollen in the patient's blood causing this, assuming the whole of the pollen injected hypodermically had entered the blood-stream, was one in 9,800,000, a state of dilution which would be difficult to arrive at *in vitro*.

2. *That animals can be sensitized with ease and human beings cannot.*

Using rabbit serum, Jones and Mote[34] were able to sensitize 70 human beings. Others found the same possible with guinea-pig serum. The first sign of sensitization was the second-day typical allergic reaction (cf. page 14). As sensitization increased, the typical wheal of the skin-test occurred immediately on applying the intradermal test. It was not found possible to sensitize people with milk and eggs and such other proteins as are commonly encountered from day to day.

An interesting point occurs here. In the treatment of patients with mixtures of proteins, as house dust and the animal hairs, while they tend to lose the huge wheal formation to the proteins to which they were originally sensitive, after treatment they appear to give larger dermal reactions to those protein solutions to which they were not sensitive than they did before treatment was commenced.

3. *That whereas the hereditary factor in man is so unmistakable, in animals this is absent.*

Though in man there can be no doubt of this hereditary influence, yet it would appear not to be an essential requisite before sensitization becomes possible. Colmes et al.[35] found on testing 32 bakers that 15 of them gave positive reactions, only one of whom had asthma. One may wonder if this is so in other trades.

Apart from such gross effects of sensitization as asthma and hay fever, numbers of people have lesser idiosyncrasies in themselves or their relations, particularly with regard to foods, so that it has been claimed that quite 50 per cent of the population show such tendencies.

Asthma, hay fever, and the allied complaints may, then, be definitely associated as symptoms of anaphylaxis as it occurs in man, and are more nearly a copy of the classical anaphylaxis of the guinea-pig than are the syndromes produced in cats and dogs during anaphylaxis in these animals. Two of the main arguments against asthma in man being anaphylaxis —the facts that sensitization seems difficult to produce experimentally in man and that animals do not show the same spontaneous sensitizations as occur in the human race—have been referred to. In addition to the work of Jones and Mote, Simon and Rackemann[36] claim to be able to produce sensitization in both allergic and normal persons by the injection of guinea-pig serum and also by the instillation into the nose of the serum. Guinea-pig serum is one that is novel to man, and one of which the blood cannot have had any previous experience.

Again, the skin reaction was demonstrable, at first the second-day von Pirquet reaction, but later as sensitization became more fully established, the wheal and erythema reaction appeared.

If the contention is correct that sensitization in man is contingent on his receiving a glut of some protein followed by a long incubation period, the chances of guinea-pigs becoming 'spontaneously' sensitized are almost nil. To begin with, the number of proteins met with during the simple existence of a guinea-pig is very small indeed, and such as come within its range will be taken continuously with no sudden glut and no incubation period. Placed in unusual circumstances, sensitization does occur. Thirty years ago, Rosenau and Anderson[37] showed that guinea-pigs could be sensitized by mouth.

Ratner and Gruehl[38] were able to produce anaphylactic shock in animals so fed and sensitized, by subsequent doses administered by mouth.

ALLERGY

In the former edition this term was used but once : "allergy, as hypersensitiveness in man is called in America." The usage of this word has grown and outgrown its original meaning until now there is a *Journal of Allergy* and books on allergy in which are included not only all forms of sensitization of a purely anaphylactic nature, but also all forms of

asthma, urticaria, migraine, and even epilepsy, whose aetiology not rarely has nothing whatever to do with sensitization. In reality the term 'allergy' should have a much more circumscribed meaning.

Von Pirquet[39] coined the word to provide a name for an altered reaction to a second intradermal injection in connexion with Koch's phenomenon. Koch noticed that an animal responded to a second injection of tubercle bacilli very differently to the first injection. In fact, except that live bacilli may get a footing and grow in the animal, the first injection is quite innocuous in its immediate effects.

Later, when the animal has become sensitized to the tuberculo-protein, a second injection will cause inflammation of the cells at the site of the injection, becoming so acute as to cause necrosis. The von Pirquet reaction is termed a 'second-day reaction', a sensitization of cells without there being any free reagin in the blood; because there has been no incubation period. In fact there may be and usually is free antigen or foreign protein in the blood. In discussing the nature of allergy, it will be first convenient to consider in what way anaphylaxis and allergy differ from each other and from immunity.

Allergy is akin to the Arthus phenomenon. Arthus found that if repeated injections of foreign protein were made into an animal, so frequently that no time was allowed for an incubation period to elapse, a local inflammation occurred at the site of the later injections. If the injections were continued, they caused abscesses and gangrene of the skin. Most of his work was carried out without producing very severe anaphylaxis. He regards a fall in the blood-pressure, a lengthening of the coagulation time of the blood, a quickened respiration, and the expulsion of fæces, as being the evidence of anaphylaxis. If after several sensitizing doses the animal is left for a fortnight and then given a non-fatal anaphylaxis, it will recover as usual, but later will become anæmic and cachectic.

Fried[40] found that if an animal is given an injection of horse serum every six days, increasing inflammatory disturbances at the site of the injection will occur—the Arthus phenomenon. If directly afterwards horse serum is given via the trachea, an acute exudative inflammation occurs in the lungs, a condition which is very like human pneumonia.

In man we can hardly ever expect to find sensitization caused by a single injection of protein, or by a single day's outing in the hayfield, so that we must take special notice of such work as that of Arthus, where sensitization is spread over many doses. Probably this type of gradual sensitization and continuous sub-anaphylaxis is the reason for the cachexia or thinness of so many of our patients. The cachexia of cancer may have a similar origin, as may that of rheumatism.

In these complaints there would always be an excess of the specific protein present; as in tuberculosis there would be an excess of tuberculo-protein; so that no symptoms of hypersensitiveness could take place other than the second-day allergic skin reaction.

The Arthus phenomenon is comparable with the urticaria that sometimes occurs round the site of the injection of frequent and large doses of vaccine. Again, it is not uncommon to find that when a patient is given a course of vaccine injections, a situation is chosen for the injection on the outside of the arm, just below the insertion of the deltoid. Without thought, subsequent injections are given one after the other on the same site, when hard lumps may appear that will take weeks to be absorbed, and though possibly a condition of traumatic fibrosis it may be a true allergic phenomenon. This can be avoided by choosing a different site for each injection.

The difference between anaphylaxis and allergy depends, then, on whether or not there has occurred an incubation period, and whether circulating reagins or free antigen is still present in the blood. If there are reagins in the blood, the skin reaction will be an immediate wheal and the result of injecting further protein will be anaphylaxis. If there is no reagin in the blood or if there is still antigen present, the result of further injections of the specific protein will be a second-day von Pirquet reaction, but no anaphylaxis.

Where the protein is ever present as in tuberculosis, the effect is like a continuous injection and much local damage occurs. The effect of tubercle bacilli on sensitized cells in their immediate neighbourhood is to cause the formation of tubercles with inflammation and necrosis of cells.

The very harmful, even lethal, effect of tuberculosis is due to the allergic state induced in the cells. Exactly the same thing occurs in syphilis and many other complaints.

Ramel[41] claims that tubercle formation with the presence of giant cells and caseous centres is also to be found in leprosy, syphilis, leishmaniasis, and actinomycosis. He considers that these are formed by allergic irritation, as are lupus and the tertiary syphilides.

The immunizing effect after a cold is so slight that cold after cold can be caught, each followed by a sufficient incubation period in which to allow sensitization to develop, and it may well be that the gross nasal symptoms so like hay fever are anaphylactic in nature.

Allergy and Immunity.—Much proof exists that allergy and immunity are entirely different processes. Rich[24] and his co-workers in America define these differences: "The state of hypersusceptibility to the bacterial protein is ordinarily spoken of as allergy; the ability of the body to inhibit growth and invasion of the bacteria and to neutralize the toxins which they produce, constitutes acquired immunity."

The first experiment to be considered makes use of cells growing *in vitro*, from an animal sensitized to tuberculin. If tuberculo-protein is added to these washed cells, growing either in the plasma of the sensitized animal or in plasma from a normal animal, the growing cells are killed at once.

The addition of tuberculo-protein to washed normal cells growing in allergic or non-allergic plasma has no ill-effect. The deduction from this is plainly that sensitization occurs in the cells without regard to the plasma in which they are growing.

Sensitization and immunity are different; the sensitized cells have no immunity against the tuberculo-protein, On the contrary, they are killed by the exhibition of such quantity of tuberculo-protein as has no effect upon normal cells. Rich produces further arguments:—

1. The luetic reaction in syphilis is only obtainable in the secondary and tertiary stages. Animals infected with a second dose of spirochætes did not respond with a local reaction nor did they become reinfected. Therefore, although there was no allergy, immunity was perfect.
2. Animals were rendered highly allergic and immune to pneumococci. On passive transfer, the immunity was present but not the allergy, presumably the blood being free from reagins.

3. When allergy is abolished by desensitization, full immunity remains.
4. Animals made allergic with large doses of purified tuberculo-protein have no protection against an injection of virulent bacilli.

Therefore the allergic reaction gives no clue to the degree of immunity present. Again, a microbe which may be harmless as a producer of toxin may cause gross symptoms by the state of allergy it produces.

This may explain the fact that a patient may give a positive pathogen-selective test to a microbe, showing that his blood has no immunity against that organism, and yet it may be the cause of the rheumatic or asthmatical symptoms in virtue of this allergy to it.[42, 43]

As a further point, observers who have held to the belief that the beneficial effects of tuberculin therapy are referable to the "mild reactions" that "promote fibrosis" have nevertheless agreed to Neumann's law of "the well attested clinical operation that the average tuberculous patient shows, simultaneously with his improvement under tuberculin, a tolerance for the tuberculin by whatever route it is administered".

It has also been noticed that allergy diminishes during pregnancy, intercurrent infections, and especially conditions of massive tuberculous infection. We may note here the great improvement in many cases of asthma under exactly the same conditions—pregnancy, and intercurrent infections—probably a non-specific desensitizing process in each case.

Willis[44] also demonstrated that animals with practically no allergy may still show a high resistance to tubercle bacilli.

The term 'allergy' is used in this chapter to refer to this condition of cell sensitization, as distinct from anaphylactic sensitization with contraction of the smooth muscles and response to further intrusion of the foreign protein. In tuberculosis the bacilli are inside the body, in asthma they are outside even in 'ethmoiditis'; but the probability is that the inflammation, the formation of polypi, and the necrosis of the bone are all allergic responses.

Those using peculiar proteins to sensitize human beings artificially, notice that cell sensitization with its second-day skin reaction appears before full sensitization and wheal formation. It may be that a similar alteration takes place

in the changing of the eczematous infant into the asthmatic child.

To recapitulate the above :—

1. Specific reagin in the cells only = allergy, the von Pirquet second-day reaction, and a negative 'passive transfer' or Prausnitz-Küstner reaction.

2. Specific reagin in cells and blood with excess of foreign proteins in the blood = allergy, the Arthus phenomenon to urther injection, and a positive Prausnitz-Küstner test.

3. Specific reagin in cells with excess in blood but no free antigen = hypersensitiveness with a positive Prausnitz-Küstner reaction and wheal formation to the dermal test.

4. This sensitized state (3) + the rapid addition of specific protein = anaphylaxis.

5. The sensitized state + small doses of the specific protein given slowly produces anti-anaphylaxis or desensitization, with disappearance of the wheal to dermal reaction.

Throughout this chapter the term 'allergy' has been used in its strict sense, and not as synonymous with 'anaphylaxis'.

Hereafter, bowing to popular usage, asthma, urticaria, and hay fever will be called 'allergic' when due to sensitization to foreign proteins, with the protest that the word 'allergic' shall then be in inverted commas. I do, however, strongly object to calling those forms of asthma which are not due to sensitization to foreign proteins 'allergic' complaints, and shall not do so.

HISTAMINE

The reaction of the body to histamine is so exactly similar to anaphylaxis that it is best considered in this chapter. Histamine, or β-iminazolylethylamine, is formed from the amino-acid histidine by the splitting off of CO_2—decarboxylation.

Histidine is produced by the digestive disruption of most of the common food proteins, and it can be liberated during bacterial and other enzymic forms of digestion. It can be derived from the blood in globin and in the serum proteins and in muscular tissues. Histamine is an active principle of the hypophysis of the pituitary gland and can be extracted from ergot. (Barger and Dale.[45])

Therapeutically histamine is used as pituitrin and ergamine (or ergotamine) biphosphate to cause contraction of the uterus during labour.

It plays an important role as a stimulant to the gastric and intestinal musculature and as a dilator of capillaries during digestion. We daily make use of a considerable quantity of histamine. (Abel and Kubota.[46])

The outpouring of histamine consequent upon food may explain the increase of symptoms so commonly felt after meals by most asthmatics. Bacteria are the chief agents in converting histidine to histamine, as was first discovered by Ackermann.[47]

Berthelot and Bertrand[48] found bacilli akin to the *B. lactis aerogenes* that could accomplish this change in the bowel. Friedlander's bacillus has the same power. The action is helped by acidity in the medium and in the tissues. The work of Dale shows the presence of histaminc to be very widespread throughout the tissues, naturally in very small amounts. The symptoms produced by histamine are so exactly like those of anaphylaxis that it may well be wondered whether anaphylaxis may not be due to the formation or liberation of histamine on the receipt of the second or exciting dose of the sensitizing protein (*see* Dale's Croonian Lecture[49]).

The following features of similarity may be noted:

1. The application of histamine to a skin scratch produces the typical + 5 wheal reaction, a fact I have made use of many times on my own arm for demonstration purposes. This reaction is now known as the triple response of Lewis,[50] an immediate local redness, followed by an erythematous area, with a wheal in the centre. Similar wheals can be formed by injury, such as freezing or even a simple scratch, and in such cases Lewis has shown that they are due to the local formations of histamine or H-substance.

2. Taken by mouth, histamine causes a rapid fall of blood-pressure with tachycardia in a few minutes, a general redness of the skin is observed, with marked headache, vertigo. and tremor; and there is nausea and hypersection from the lacrimal, salivary, and gastric glands. With larger doses dyspnœa and loss of consciousness may be produced.

3. On injection into animals, all the symptoms of anaphylaxis are seen.

4. A further remarkable similarity is that the symptoms vary in the different animals in exactly the same way as do those of anaphylactic shock. In the rabbit there is a tremendous dilatation in the splanchnic area, leaving insufficient

blood for the heart to carry on the circulation and life. In the guinea-pig, death occurs from contraction of the bronchial muscle. Kupper[51] finds that rats are very resistant to both histamine and anaphylaxis.

5. Adrenaline has the same beneficial effects upon the symptoms of both; in fact, as noted by Schenk, there appears to be a direct antagonism between adrenaline and histamine; enormous doses of the latter can be given if balanced by adrenaline.

6. Adrenaline contracts the blood-vessels, raises the blood-pressure, while it dilates the bronchi, an action exactly opposite to histamine.

7. More histamine is to be found in the lungs of a sensitized animal than in the normal.

One may well wonder whether it is not the freeing of this excess of histamine that is the cause of anaphylaxis? The part played by histamine in the anaphylactic syndrome is thus described by Dale[52]:—

> "We may picture the anaphylactic shock, therefore, as the result of cellular injury, due to the intracellular reaction of the antigen with an aggregating antibody. Whether this is general or localized in a particular organ, histamine will be released, and its effects will be prominent in the resulting reaction, imposing a general resemblance to the syndrome produce by histamine itself on the symptoms seen in each species.
>
> "The cell injury, however, is not limited to the degree required to produce a release of histamine, and involves other and more direct results. Such a conception is in accordance with all the facts as yet available, and it has the advantage of rendering intelligible, not only the striking resemblance between symptoms of the anaphylactic reaction and those produced by injected histamine, but also the various and equally significant points of difference between the two syndromes."

Bartosch, Feldberg and Nagel[53] have shown that when fresh egg-white is added to the perfusing fluid in an animal already sensitized to egg-white, histamine is to be found after the bronchial contraction takes place. Schild and others corroborate this.

The intravenous injection of barium sulphate, kaolin, and many other substances of a coarse colloidal nature produces

symptoms again indistinguishable from anaphylaxis, hence known as anaphylactoid reactions. But in spite of the fact that the bronchial muscle is contracted to the maximum by these injections, no histamine was produced or discoverable in the perfusate by Schild.[54]

8. Histamine produces an eosinophilia locally and in the differential blood-count.

Dragstedt and Mead[55] find a substance in the blood of animals dying from anaphylaxis that will cause contraction of smooth muscle. They identify this substance with histamine, " because both are inactivated by incubation with kidney powder, containing the enzyme histaminase of Best and Henry ".[56]

9. The reintroduction of blood from an urticarial patient (from food) into the same patient is followed by a hæmoclasic crisis and more urticaria. This fact was the origin of the treatment by autohæmotherapy. (Joltrain.[57])

10. There is much evidence that desensitization by very small doses of histamine is an effective remedy for these anaphylactic complaints.

11. The action of histamine on smooth muscle appears to be through stimulation of the parasympathetic; caffeine, atropine, and adrenaline countering this action.

12. Knott and Oriel[58] found an increase of nitrogen and amines in the blood and urine during an attack of asthma. Jacquelin and Ungar[59] have estimated (by the amount of histamine necessary to produce the same degree of contraction of a strip of isolated intestine) that the histamine content of the blood of an asthmatic is doubled during an attack; that large quantities appear in the urine which may have been free from histamine before the attack; and that in the sputum the amount varies with the degree of eosinophilia.

Histamine is very rapidly destroyed after injection.

Dragstedt and Mead[60] injected 0·5 mg. per kilo weight into dogs. They were able to recover histamine from the blood two minutes later, but it had disappeared at the end of five minutes. Apparently much is destroyed in the liver.

From these items of evidence it would appear that histamine plays a large part in the production of anaphylactic shock, but histamine can by itself produce the complete anaphylactic syndrome without previous sensitization being necessary.

Certain minor differences exist. "In the guinea-pig especially when death from shock is delayed, the blood also shows a loss of clotting power, which histamine does not produce." (Dale.[46]) "There may be capillary hæmorrhages in the shock, which histamine again does not produce", probably from localized sensitization of the endothelial cells.

Histamine, then, can provoke practically every symptom of anaphylaxis, and in every symptom of anaphylaxis histamine can be shown to be present.

It is difficult to see what other conclusion we can come to than that the major portion of anaphylaxis is histamine formation and histamine action.

In the treatment of asthma there will be the necessity of preventing the formation of histamine by the interaction of reagins and the proteins to which they are specific, and also the formation of histamine by other means, metabolic and microbic. The latter endeavour may explain the benefit so many patients receive from limiting their protein intake, the original source of histamine, in perfecting their digestion by hydrochloric acid and pepsin, in colonic lavage, purges, exercise, and other methods of spring-cleaning the intestinal tract, and in all such measures as increase the efficient working of the liver and of the adrenals to neutralize the histamine effect.

As has already been mentioned, a syndrome exactly similar to anaphylactic shock can be produced by the intravenous injection of a coarse colloid such as barium sulphate. Lumière,[30] using a fine colloidal suspension for intravenous injection into guinea-pigs on successive days, found that as the colloidal particles gradually became aggregated, so the injection was followed by symptoms of increasing violence, until at the end of a fortnight the guinea-pig injected on that day died with all the symptoms of anaphylactic shock. On this he based a theory that anaphylaxis was due to irritation of the nerves of the blood-vessels by these colloidal particles reflexly stimulating contraction of the adjacent smooth muscle of the bronchi, uterus, and intestinal wall.

However, Schild[54] has shown by perfusion experiment that no histamine is found during this process, and therefore that the shock obtained by barium injections is not true anaphylaxis, but more suitably named anaphylactoid. Lumière's theory cannot provide an explanation of all forms of anaphylaxis, but there is no reason why anaphylactoid reactions

should not be obtained in man and be of clinical importance, so that Lumière's work and the deductions drawn from it must not be passed over too lightly or dismissed without full consideration.

THE HÆMOCLASIC CRISIS

A hæmoclasic crisis consists of a number of changes that are found to take place in the blood in anaphylaxis, in protein shock, after histamine injections, and also in asthma, urticaria, migraine, epilepsy, and a variety of other conditions.

French literature was at one time full of the subject. Widal, Abrami, Brissaud, Joltrain, Pagniez, Vallery-Radot,[61] and their collaborators carried out a large amount of interesting work on what they called a "crise hémoclasique initiale".

The changes consist of a fall in the blood-pressure, a leucopenia, and an alteration of the differential white count. The normal preponderance of the polymorphonuclears over the lymphocytes alters until they become equal in number, later actually showing an inversion of the normal, the lymphocytes predominating. There is a slight eosinophilia. There are changes in the viscosity of the blood, and the refractive index is lowered. The clot may lose its power of contraction and the colour may be a brighter red. The coagulation time is shortened.

Joltrain[62] mentions in addition that there are modifications in the sedimentation rate, the amount of Ca ions, the alkali reserve, and the *p*H, and glycæmia.

These changes take no part in the anaphylaxis, asthma, or other occurrence, but seem to take place between the receipt of fresh protein and the production of the clinical symptoms; for instance, with certain cases of paroxysmal hæmoglobinuria all that is necessary to initiate the paroxysm is to place the patient's hands in cold water for a few minutes. The hæmoclasic crisis follows at once and hæmoglobin appears in the urine later.

All the cases mentioned in the French literature are very fully and beautifully worked out. The following two cases roughly describe the sequence of events.

The first patient, a *marchand de mouton*, had dealt in sheep for nearly forty years, during the last three of which he had become so sensitive to the smell of sheep that he had to give up his trade. In hospital, of course, he had no asthma. For the experiment he entered a pen of sheep. His leucocyte count and blood-pressure were taken every few minutes. After two hours both

fell—the leucocytes from 12,000 to 6000. They then returned rapidly to the normal. During this time he felt no difference to himself. At the end of three and a half hours, when the crisis was completely over, he developed a very bad attack of asthma.

The second patient had migraine, especially after taking chocolate, but only at times. He had chocolate every morning in large quantities, followed each time by a normal digestive leucocytosis, until there came a morning when the blood-pressure and leucocyte count both dropped. Shortly after this, gastric disturbances and a bad attack of migraine commenced.

Clinically the method can be made use of to test the reactions of a patient to specific foods. The food is given, and the blood taken at frequent intervals afterwards to see whether there follows normal leucocytosis or a leucopenia with the other blood-changes.

Rinkel[63] describes his use of this method on testing the patient against foods.

The hæmoclasic crisis, however, has been found to occur so frequently and from so many different causes that little clinical use has been made of the method in England.

Another point complicating the application of this method, and in fact all methods of testing patients against foods, is this, that except in the case of asthma there are days on which the patient is sensitive to a food and many other days on which he is not sensitive, neither the hæmoclasic crisis nor clinical symptoms being produced. Therefore too much reliance must not be placed on negative reactions to foods, except I think in the case of asthma, where they seem quite reliable.

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CHAPTER II

THE DEFINITION OF ASTHMA: THE ANATOMICAL AND PHYSIOLOGICAL ASPECTS

FROM the earliest days of medicine, no affection can have been more obvious in its symptoms than asthma.

The dictionary meaning of this Greek word is panting or gasping, and though this may have included many forms of dyspnœa, the description of the asthmatic and his symptoms as given by one Aretaeus[1] is very clear and accurate. Gradually the term has become narrowed down to refer to a condition of dyspnœa that most typically develops suddenly in paroxysms, in which both expiration and inspiration, but more particularly the former, become extraordinarily difficult. What little air can be forced in and out of the lungs escapes with wheezings and sonorous sounds. In spite of the fact that the patient is sitting up in bed, with all the accessory muscles of respiration brought into play, the obstruction remains, and the chest, which is distended with air, can neither be emptied nor refilled to any satisfaction.

As the asthmatic syndrome became more and more clearly defined, so the affection came to be looked upon as a separate disease of the lungs, and theories sprang up as to its causation. In 1868 Hyde Salter[2] described his symptoms as a cat asthmatic with minute detail, including the formation of wheals from the scratch of a cat. In 1877 Brackley discovered that grass pollen was the cause of hay fever and demonstrated the sensitivity of his nasal mucosa to the pollen.

In each case this brilliant work was lost sight of because, although it showed the specific cause of the condition in these two cases, it failed to provide an aetiology for asthma in general as a 'disease' of the lungs.

In the main, argument ranged between those who believed the cause of asthma to be a spasm of the muscle surrounding the bronchioles, and others who attributed the chief pathological factor to a congested or inflamed state of the mucous

membrane. To-day it is recognized that asthma is a symptom and not a disease. It is caused by a number of main factors, aggravated by other lesser influences. For instance, exercise will often bring on an attack of asthma, but the asthma has to be there beforehand, lying dormant and waiting to be awakened by the forced breathing of exercise.

THE DEFINITION OF ASTHMA

"Asthma is a form of dyspnœa in which the calibre of the bronchi and bronchioles is diminished, either by a contraction of the bronchial muscle acting alone, or together with turgescence of the mucous membrane and the formation of secretions into the lumen."

It may be said that this definition is too large a generalization, but asthma is a symptom and not a disease. Anatomically this obstruction occurs in several different places; physiologically it is due to a great variety of totally different factors: the only feature common to all is the obstruction to respiration.

This definition excludes all other forms of compression that may occur from causes outside the bronchi. Obstructions in the nose and throat, at the larynx from inflammation, at the trachea or bronchi from the pressure of an aneurysm, a growth, or enlarged bronchial glands—any of these conditions may provoke dyspnœa, but not asthma.

The air hungers, the shortness of breath in various heart conditions, must be distinguished from true asthma. Dyspnœa from uræmia, diabetes, or epilepsy is more easily differentiated. On the other hand, it must not be forgotten that true asthma may exist in combination with a weakened heart, a high blood-pressure, or with various urinary disorders.

In the previous chapter anaphylaxis and other experimental conditions are described because of their close resemblance to and practical identity with asthma in man. Having defined asthma as above, we are now ready to approach the aetiology of asthma by considering:—

1. The anatomy and physiology of the normal bronchi, bronchioles, and lungs;

2. The changes that take place in these tissues during a paroxysm of asthma; and, in due sequence,

3. The various influences which primarily cause these obstructive changes.

The last two, dealing with the aetiology of asthma, will form the subject-matter of Chapters III to V.

THE ANATOMY AND PHYSIOLOGY OF THE NORMAL BRONCHI, BRONCHIOLES, AND LUNG TISSUE

Anatomy.—The trachea divides at its bifurcation opposite the 4th or 5th thoracic vertebra into a right and a left bronchus. Further divisions take place at fairly sharp angles to one another into the main bronchi, whose lumen is kept patent by means of the cartilaginous rings in their walls.

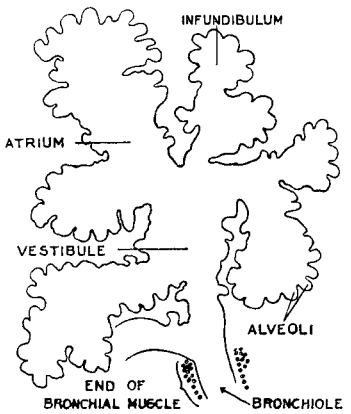

Fig. 1.—Diagram to show the terminal divisions of a bronchiole.

Further subdivisions lead to all parts of the lungs, the calibre becoming smaller until in the bronchioles it is less than a millimetre. Finally the lobular or terminal bronchiole leads by way of a vestibule, atria, and infundibula to the small saccules called air-cells or alveoli. These various names only denote spacing arrangements by which each bronchiole can supply the largest possible number of air-cells or alveoli. Not to lose any opportunity of dealing with the maximum quantity of air, little air-cells bud out directly from the bronchioles wherever there is room for them. *Fig.* 1 represents the divisions of a terminal bronchiole.

The histological structure of the bronchi is of extreme importance in considering the pathology of asthma.

The cartilaginous plates which encase the front and sides of the trachea, making it roughly a three-quarter hoop, continue in all the larger bronchi. They are found to be complete circles in bronchi of medium size, forming them into cylindrical tubes. As the calibre of the bronchi lessens, cartilage disappears, and its place is taken by connective tissue. The smaller bronchi and bronchioles are therefore more easily compressed or flattened than are those tubes which have cartilage in their walls.

Elastic tissue in longitudinal bundles is found throughout the whole of the bronchi and bronchioles, disappearing from the smallest tubules to become a general reticular tissue supporting the alveoli. It assists in the normal expiratory collapse of the lung.

Two layers of *muscular tissue* are described, a longitudinal and a circular. The latter is by far the more important. This muscle surrounds the bronchial tubes as a continuous layer of annular fibres lying internal to the cartilaginous plates. It is found beyond where the cartilage ceases to exist, and appears as irregular annular fasciculi, even in the smallest tubes. (Schafer.[3]) Besides this annular arrangement, other muscular bands extend up and down in a manner called geodic in technical language, a word recently brought into prominence as a method of binding used to strengthen aeroplane struts. Piersol[4] says: "The muscle is arranged as a sphincter-like band around the openings by which the terminal bronchiole communicates with the atria." The position of the muscle is shown in *Fig.* 1. It will be seen that the atria, infundibula, and final air-sac have no muscle present either to support or compress them.

Blood-vessels of twofold origin accompany each bronchus. The *pulmonary artery*, carrying the venous blood to be aerated, passes along the bronchioles to the alveoli. Here the vessels break up into an immense network. The terminal vessels are so small that they will only allow corpuscles to pass through them in single file. They are so close together that even less space than their own width separates them. The venules do not return by exactly the same route, but collect together first, before joining the bronchi in their return to the hilum of either lung on their way to the left

auricle. The *bronchial arteries* are branches of the aorta. They supply nutrition to the various coats of the bronchi and the bronchial glands. This blood returns by the azygos veins to the right auricle. There is said to be some anastomosis between the bronchial and the pulmonary veins. This may afford some slight relief to either circulation which may be unduly full.

The *nerve-supply* is by medullated fibres of the vagus and by non-medullated fibres of the sympathetic. These will be considered subsequently in relation to the physiology of the bronchial muscles.

The air-sacs have no *lymphatics*, only the intercellular lymph-spaces in their walls. Rich plexuses of lymphatics surround the bronchial tubes.

Mucous membrane lines the whole of the respiratory tract, becoming naturally thinner as the smaller bronchioles are reached. Ciliated epithelium extends throughout the surface of the trachea, bronchi, and bronchioles, in which are the mucous and mucoserous glands. Many of the deeper mucous glands reach the lumen of the tubules by passing through the muscular coat of the bronchi. In the smaller tubules the mucous membrane becomes folded into longitudinal ridges.

Briefly reviewed, a great change in the structure of the tubules takes place where the terminal bronchiole opens into the vestibules of the final air-spaces. The muscular coat ends in a sphincter-like termination; the ciliated epithelium and the lymphatics cease at this level; mucous cells give place to ordinary columnar cells, and then to the plain flattened cells which line the air alveoli.

Physiology.—The physiology of many portions of the bronchi is that of similar structures in other parts of the body. The ciliated epithelium constantly tends to move material on the surface of the mucous membrane towards the large bronchi, the trachea, and the larynx, from which such secretions may be expelled by clearing the throat or by coughing, and it is significant to note that the ciliated cuboidal epithelium at the termination of the bronchioles always extends further than the seromucous glands. The chief characteristics of the lung are its expansion and contraction with the acts of inspiration and expiration.

The actual movements of the chest walls will be considered under the symptoms of asthma; suffice it to say here that,

with the pleura intact, the lungs will expand or diminish in size correspondingly with the chest wall.

We may first inquire: where does this expansion take place? The trachea and large bronchi, with their smooth mucous membranes not thrown into folds, are incapable of any effective expansion. In the small bronchi and bronchioles, where the mucous membrane lining the lumen is found in longitudinal folds, some small expansion is possible.

Ingenious experiments by Ellis[5] throw much light on this question. A thin brass tube is passed down into a bronchus, having at one place outside it a rubber bag, *D G H*, connected at *C* to another small tube, *E*, running inside the larger one (*Fig.* 2). Contractions of the bronchus during

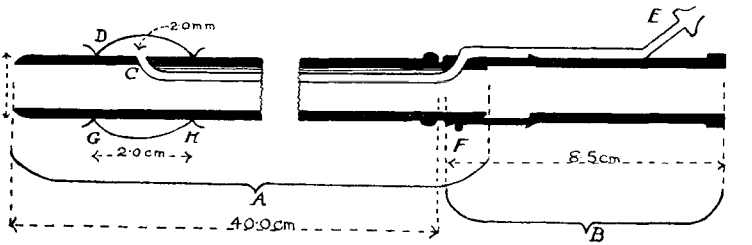

Fig. 2.—Horizontal section of Ellis's tube. (*Re-drawn from the 'Journal of Laryngology and Otology.'*)

normal respiration or under drugs can be read through the smaller tube.

The main lumen of the larger tube allows air to pass through into the alveoli. Although there is regular contraction and expansion of the bag at each respiration, in Ellis's opinion this is entirely due to movement of the chest wall and not to the instrumentality of the bronchial muscle, for it occurs after the vagi have been severed. Ellis admits, however, that the bronchial muscle is in a state of tone, to be demonstrated by its relaxation with adrenaline, and in a tube whose calibre alters with each respiration it must be difficult to distinguish tone from muscular contraction when the calibre lessens.

Again, measuring fluctuations in the size of the lumen of a bronchus by Ellis's tube is only possible in a large bronchus, owing to the size of the instrument. It was used in dogs, in whom there is no bronchial spasm from anaphylaxis.

The main part of the expansion undoubtedly takes place in the vestibule, atria, and infundibula, and in the passages or hall through which air passes from the end of the bronchiole into the alveoli. Having no muscular tissue in their walls they must play an even greater passive part than the bronchi, filling with air as the chest wall expands and emptying with the elastic recoil of normal respiration.

This would appear to be the case, since in asthma and in anaphylactic shock the lungs are filled with air to their greatest capacity, while at the same time the bronchi are tightly contracted by spasm of the bronchial muscle.

The Action of the Bronchial Muscle during Normal Respiration.—The very marked and well developed bronchial muscle that can be determined histologically in man would seem to point to the deduction that it has a function or functions of some considerable importance. Although from the nature of its situation and anatomy it is extremely difficult to determine what exact part it plays in normal life, it would seem that it must take an active part in each respiration.

We can learn much, however, from histological and biological preparations of isolated bronchial muscles as they are affected by pathological or experimental procedures. When an isolated lung preparation from a sensitized animal is examined, it is noted that a contraction takes place almost immediately after the protein to which the animal was sensitized has been brought into contact with the bronchial muscle. The contraction is so violent and the grip on the bronchioles so tight that air cannot pass it, thus causing death in the anaphylactic animal. This proves that it is a strong and effective muscle in otherwise normal animals, and ready for immediate action.

When a person is stifled by smoke, or by a noxious gas such as sulphuretted hydrogen, contraction of this muscle no doubt takes place together with closure of the mouth, the nose, and vocal chords, a tightening of the abdominal muscles, and fixation of the diaphragm. It is on record that those soldiers who responded to mustard gas by an asthmatical seizure escaped death more commonly than those whose bronchial muscles gave no hindrance to the poison gas reaching the alveoli.

But the necessity for this use of the bronchial muscle is extremely rare in everyday life, and must have been still

more uncommon in man's earlier existence, when he had not to encounter chemical warfare, London fogs, and similar acquisitions of modern civilization. Still less can such experiences afford an explanation of the power of the bronchial muscle and its readiness for action in the guinea-pig.

I am inclined to think the muscle must take part in every normal respiration, contracting during each expiration. Such an action would help to distend the alveoli at each breath and keep them patent—witness the overdistension of the lungs that takes place in asthma consequent upon the contraction of the bronchial muscle. It follows as a corollary that if this muscle contracts at each normal expiration, it will have an exaggerated action in all forms of forced expiration consequent upon exertion, laughing, or coughing. This is exactly what one observes in the asthmatic. Coughing may lead to wheezing or even, in the aspirin-sensitive asthmatic, to a full paroxysm, while a laughing fit may precipitate an attack.

I think we have an indication of this contraction in the wheeze that many cigarette-smokers can produce on deep expiration.

Asthma, then, becomes the exaggeration of a normal action of the bronchial muscle, continued as a spasm through the whole of expiration, and often remaining during inspiration as well. Some pseudo-voluntary power over this muscle may exist, just as there is similar control over a great many other muscles in the body whose natural movements are reflex and automatic. I have noticed how extremely difficult it is to cure persons of asthma who grunt at each expiration. Von Strubing[6] had two healthy students who imitated the breathing of asthmatics. In one of them asthma developed which it afterwards took him some time to eliminate.

The Effect of Stimulation of the Vagus Nerve.—The bronchial muscle, like all other involuntary muscles of the body, is under the dual influence of the sympathetic and parasympathetic systems, described together as the vegetative or autonomic portion of the nervous system.

The sympathetic nerves pass through the sympathetic cord and the great plexuses of the thorax and abdomen. Many ganglia exist along their course. The parasympathetic nerves proceed from the midbrain, the medulla, and spinal cord.

The vagus is the principal example of a parasympathetic nerve.

Stimulation of the vagus nerve produces spasm of the bronchial muscle. In many situations these two sets of nerves are so intimately mixed, either by following the same course or by entering the same plexuses, that any anatomical identification becomes impossible. The chief method of differentiating between them is in their several reactions to various drugs. We learn that for the most part the sympathetic and the parasympathetic nerves convey impulses which are diametrically opposite to each other in their reactions. In many cases both are in action at the same time, maintaining between them a balance or state of tone in the muscle. We can thus understand that stimulating the sympathetic by adrenaline will produce the same result as depressing the action of the vagus by atropine. Either may relieve a spasm of the bronchial muscle.

The action of the vagus nerve on the bronchial muscle was thoroughly investigated by Dixon and Brodie[7] in 1903. Their conclusions were arrived at by measuring the size of a lobe of the lung during movements of air pumped into or out of the lung. When obstruction to the air flow existed, as by constriction of the bronchial muscle, the amplitude of expansion and contraction of the lobe was necessarily lessened. As the animals were mostly pithed, this investigation could not take account of any contraction of the bronchial muscle that might occur during normal respirations, but many important results were obtained.

They were unable to make the bronchial muscle contract in response to any of the nerves which they stimulated except those of the respiratory tract. However, on touching certain portions of the nasal mucous membrane, more especially the posterior and upper part of the septum, contraction of the bronchial muscle took place. Together with this, they found " a closure of the glottis, and arrest or slowing down of the respiration, some cardiac inhibition, and a dilatation of the peripheral arterioles ". All these changes are of a protective nature, preventing the vapour or particles of dust which are irritating the mucous membrane from reaching the deeper portions of the lung.

Possibly stimulation of that part of the vagus supplying the stomach might provoke the same spasm of the bronchioles.

The relationship between irregularities of diet, biliousness, constipation, and asthma would suggest direct reflex contractions of the bronchial muscles as being likely, especially in patients in whom the spasm of asthma is easily provoked. In contradiction to these findings, Ellis is of the opinion that although contraction of the bronchial muscle can be brought about by stimulation of the nasal mucosa, the strength of the current or other stimulation required is so great as to be outside the range of normal experience, but clinical data very strongly support the contentions suggested by the experiments of Dixon and Brodie.

Apart from stimulation of the vagus from normal or abnormal reasons, the nerve and parts of it may be unduly sensitive to stimuli, giving rise to the condition known as vagotonia.

Vagotonia is a term applied by Eppinger and Hess[8] to a condition of increased tone and irritability of the vagus. The word connotes an increased tonic current in the vagus, thus upsetting the balance in its favour over that of the sympathetic system. A dose of a stimulant of the vagus, such as pilocarpine, that would be without effect on a normal individual, may then cause, in a vagotonic, "gastric symptoms to appear resembling those of hyperacidity, or those of pylorospasm or cardiospasm; or it may happen that heart symptoms resembling mild angina are found. In other cases there are respiratory disturbances, salivation, or even asthmatical attacks. In connection with the injection, diarrhœa, urgency in micturition, ptyalism, or sweating may also appear." (Eppinger and Hess.[8])

A relationship between these various disorders may thus be shown to exist, and indeed I have noted it as a very definite fact that in many cases of asthma a series of symptoms indistinguishable from those of pylorospasm occurs as a prodromal sign to the onset of an asthmatic paroxysm.

An essential part of vagotonia, as explained by Eppinger and Hess, is that it is not an affection of the vagus in which all parts of that nerve are equally excitable. If this were so the clinical picture would be of more standardized syndrome. Certain portions of the vagal area may be more affected than others, thus making the symptoms much more variable.

With regard to asthma, then, in the light of these authors' views on vagotonia, we should consider that that portion of the vagus supplying the respiratory tract is abnormally sensitive to small stimuli which would be without effect upon ordinary people.

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CHAPTER III

AETIOLOGICAL FACTORS

I. HEREDITY AND OTHER ANTECEDENTS

THE INFLUENCE OF HEREDITY

IN asthma and hay fever a family history of similar complaints is commonly obtainable.

In examining the present series of 3000 cases, the relationship taken was that of the parents, grandparents, brothers and sisters, and aunts and uncles, unless otherwise stated. These patients were practically all of what might be termed the 'private' class, of various ranges of society, from all parts of the Empire, with a few Indians, Chinese, and Negroes.

One half of them, 49·8 per cent, gave a family history of asthma or hay fever. The inquiries made into each case on the score of heredity were not exhaustive, being only such information as was forthcoming at the original interview, so that 50 per cent may be taken as a conservative estimate.

The points to be considered are: (1) The proof of this hereditary influence; (2) Does this hereditary factor follow any distinct law or is it comparable to any of the other familial complaints known to medicine, as hæmophilia? (3) How is the influence transmitted?

1. Proof of Hereditary Influence.—The Asthma Research Council has calculated that there are 250,000 cases of asthma in England, an average of 1 case in 170 persons, or 0·6 per cent. Disregarding the fact that the chance of an asthmatic's marrying must be rather less than that of the normal individual, on these figures one person in 85, or 1·1 per cent, might be expected to have an asthmatical parent; but we find that these 3000 cases had 705 parents (23·5 per cent) afflicted with asthma or hay fever, a proportion of 1 in 4·2, or twenty times the normal expected frequency. The chances of any person having both parents asthmatical are 1 in 28,900. In the 3000 cases this dual parentage of both mother and father occurred 28 times, or nearly once in every 100 cases. A history of asthma or hay fever in the parents, mother or

father or both, is therefore vastly more common than it should be on the ordinary law of average.

The effect of the hereditary influence is shown also by the fact that asthma appears much earlier in those having a family history of like complaints than in those without,

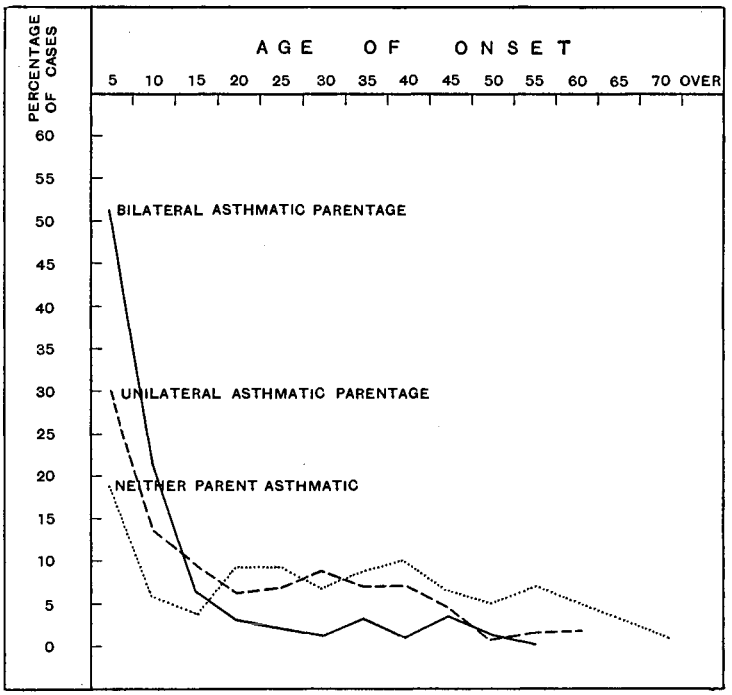

Fig. 3.—Graph showing effect of heredity upon age of onset in asthma or hay fever. ————Bilateral asthmatic parentage; - - - - - Unilateral asthmatic parentage; . . . . . Neither parent asthmatic.

reaching its maximum in patients who have a bilateral history. The accompanying graph (*Fig.* 3) from my cases is made on the same basis as one constructed by Spain and Cooke;[1] the two graphs are almost exactly similar, and they show the great effect of heredity on the age of onset of the complaint in both American and British cases.

Balyeat[2] finds that the stronger the hereditary influence, the more likely is the patient to show multiple sensitizations. This is amply confirmed in my cases from the fact that the

younger the age of starting asthma the greater the likelihood of the patient's being sensitized to some protein.

Another manifestation of the hereditary influence is the fact that the relations of asthmatic patients tend to have asthma rather than hay fever, whilst hay fever patients more commonly show hay fever in their relations than asthma.

The relations of asthmatic patients had: asthma, 74 per cent; hay fever, 15 per cent; both, 10 per cent. The relations of hay fever patients had: asthma, 35 per cent; hay fever, 53 per cent; both, 12 per cent.

In the above figures, such asthma as only occurs during the height of the hay fever season is not considered; the asthma referred to means asthma due to causes other than pollen and occurring outside the hay fever season. Similarly, hay fever refers only to that caused entirely by grass pollen, and not the popular 'hay fever' that arises from dust and so forth at any time of the year.

2. Does the Hereditary Influence follow any Particular Law of Heredity?—Our records fail to give any help in this direction at all. Neither male nor female seems to have an increased family incidence, or to inherit the complaint from one branch of the family rather than another.

The following figures in 3000 cases, 1560 males and 1440 females, demonstrate this most clearly. The relations of the patient are named at the side, while the two columns of figures represent the percentages in which asthma or hay fever affected these relations.

INCIDENCE OF ASTHMA IN RELATIONS OF ASTHMATICS.

	MALE PATIENTS *Percentage*	FEMALE PATIENTS *Percentage*
Brothers	5·5	8·0
Sisters	6·0	7·2
FATHER	**12·1**	**11·8**
Father's brothers	3·8	4·4
Father's sisters	3·8	5·8
Father's father	3·8	3·1
Father's mother	3·7	2·9
MOTHER	**11·0**	**11·3**
Mother's brothers	3·9	4·4
Mother's sisters	3·9	3·8
Mother's father	3·9	4·8
Mother's mother	3·9	4·4
FATHER AND MOTHER	1·0	0·8

The figures in the two columns are so exactly alike over this large number of cases that any suggestion that asthma

is transmitted more commonly through the female line is entirely contradicted.

The only variance, and that a very slight one, is in the greater number of sisters affected than brothers of the male patients, and the greater number of brothers than sisters of the female patients, but this is only natural, because each male is more likely to have sisters than brothers and vice versa; at least, with small families that is the general tendency.

Some writers, as Cooke and Van der Veer,[3] consider asthma to be inherited as a dominant trait; others, as June Adkinson,[4] as a recessive trait.

Without doubt we are all subject to the laws of Mendel, but it must be remembered that from four black grandparent mice it is possible to breed parent black mice whose offspring will be three black and one white or all four black, according to whether the original black grandparents were hybrid bred or pure black—the dominant strain.

To settle this question in the human race it is necessary to know how each of the four grandparents was bred—pure dominant or hybrid, and to observe their children and grandchildren throughout the span of their lives. This would seem to be as impossible of accomplishment in asthma as it is in cancer, no one person living long enough to see the experiment through.

3. How is the Influence Transmitted?—Transmission of sensitization through the mother's blood to that of the fœtus is extremely rarely observed. In animals, if the mother is sensitized shortly before the birth of the offspring, the young are found to be passively sensitized for a short time, the sensitization soon disappearing. The following case seemed to show a similar circumstance:—

Case 4.—A lady aged 32, had asthma in a very severe form, of twenty-five years' duration. She was aspirin-sensitive and also extremely sensitive to milk. She had two children: the first, a boy, died from asthma in five weeks; the other, a girl, also extremely sensitive to milk, outgrew it and became healthy and well.

According to the statistical evidence given in this chapter, inheritance is equally common through the male as through the female. From the father's side transmission can only occur through the chromosomes, and this is almost certainly the same route in such inheritance as comes from the mother and her relations.

In hay fever we very commonly find the parent and the child both sensitive to the grass pollens. Occasionally we find this direct transmission from parent to child occurs in relation to proteins to which people are very rarely sensitive.

Sensitization to mutton is extremely rare, but a relative of mine was sick at once after partaking of mutton; as was her father before her. In the multitudinous duties and feats of memory undertaken by the chromosomes it is difficult to imagine how room could be found for the transmission of such a peculiar abnormality.

Laroche, Richet, St. Girons,[5] mention a family in which sensitization to egg occurred in four successive generations, the descent from the third to the fourth generation being through the male.

In a case of ours the patient was an aspirin-sensitive asthmatic. Her mother fainted whenever she took this drug, and her son became unconscious for many hours after taking five grains. Nevertheless, the main method of transmission, and the one that must occur from all paternal relatives, is by means of the chromosomes.

Lastly, we are left to wonder what the essential fault is that is transmitted: an inability to digest foreign proteins completely and effectively in the blood-stream and cells, an increased faculty for producing histamine or setting it free in the cells, an endocrine dysfunction, or some lapse in vagotonic control.

SENSITIZATION BY A SURFEIT OF PROTEIN

In making inquiry into the antecedent cause of asthma, one would not expect to be told that the patient's troubles started after a surfeit of a protein. Nevertheless this fact frequently emerges after some close questioning. The ingestion of a protein in large amounts for a short time seems liable to sensitize a patient. By a short time is meant that there follows a considerable period during which the patient does not again meet with the protein. After the large primary sensitizing feed comes the incubation period, and at the next meal or meeting with this protein the patient shows allergic symptoms, sickness, and diarrhœa with collapse, a paroxysm of asthma, or a profuse urticaria.

This explains the fact that such articles of food as strawberries, mushrooms, nuts, crabs, lobsters, and honey are so

frequently proteins to which the patient is sensitive. They are unusual proteins, taken in large quantities, and followed by a prolonged incubation period. On this score an excellent example is provided by hay fever.

Foods such as beef and mutton are unlikely to sensitize us, being taken in small quantities and very regularly. Sensitization to egg can often be explained by the child having been given albumen water for a few days while it is otherwise wholly on milk. The fact that there is commonly some gastro-intestinal upset for which the albumen water is given, helps to allow the foreign protein to enter the body and so makes sensitization easier.

SENSITIZATION IN SUCKLINGS

The Prausnitz-Küstner reaction has shown that even in normal people proteins taken by the mouth pass rapidly all over the body. In nursing mothers they may pass into the milk, so that the baby's eczema may be due to proteins which it has never taken except as they have passed through with the milk. The eczema ceases when the mother gives up eating the articles to which the child is sensitive.

This affords an explanation of many idiopathic sensitizations to articles apparently never before taken. Touching on the same subject is the possibility of pollen sensitization from milk taken either to supplant the human mother's milk or at later periods of life. If human milk contains proteins that the mother has taken, may not the same thing happen to cow's milk when every blade of pasture is covered with pollen, as is the whole countryside in June ?

A further circumstance may be taken into consideration. The Thames and the New River, ambling along through miles of meadows, must collect a tremendous amount of pollen during their transit to London. Is this not enough to sensitize patients and give them hay fever when sensitized ?

I am inclined to think that we shall eventually come to the conclusion that any one may become sensitized to some protein, given the right combination of circumstances to produce the condition.

OCCUPATIONAL ASTHMA

This is a little different from other forms, but in many cases a man's work is definitely the predisposing cause of

his asthma, because he becomes sensitized to something which he handles daily—usually the protein with which he has dealt for a great number of years.

Bakers and millers become sensitized to wheat; ostlers, farmers, and hunting people become sensitized to horses; cowmen and milkers to cows; woodworkers to the fine dust of the various woods with which they work; while the celebrated case of the *marchand de mouton* that figures so constantly in the French literature is well known.

Case 5.—A baker, aged 50. Has been baking all his life. Had no asthma until coming to London from South Africa. Possibly an incubation period on the boat. Asthma began when he commenced baking in London, but ceased when he used a mechanical mixing machine, thus avoiding the flour, to which he gave a + + + + + reaction.

Case 6.—A horse breeder, aged 30. With horses all his life. At 24 sneezed while grooming horses. Eye irritated and commenced asthma. Horse hair, + + + + scratch method. Desensitized and has continued his work with horses ever since.

Case 7.—A flour importer, aged 35. Watery catarrh and sneezing for many years when at work, supervising the unloading of 6000 to 8000 bags of wheat per day. Now much asthma at night. Cereals, + + + reaction.

Exactly on a par with these cases is the following:—

Case 8.—A lady of 40 years had taken porridge as far as she could remember every day of her life until 19 years old. At that time she caught a chill and had a gastric attack. Since then she was unable to take anything that contained oatmeal without it producing a severe urticarial rash. She had also suffered from asthma from that time. She gave a + + + + + reaction to oats. During the gastric attack she ate no porridge, allowing an interval—the incubation period—to occur, after which sensitization followed.

PREDISPOSING ILLNESSES

Heredity seems to predispose the individual to become sensitized to a protein. Occupation and other circumstances tend to determine which protein this shall be. Certain inflammatory conditions—gastro-intestinal, and those of the respiratory tract—allow easy access of the foreign protein, either a food or an air-borne dust, into the system in such

a flood that it sensitizes the patient. Apart from these factors, microbic infections may lead to sensitization of the patient to the invading organism, so that a condition of chronic sepsis or the resulting mechanical irritation may cause asthma as a sequel.

1. Infectious Diseases.—A great many cases of asthma are said by the patients themselves or their parents to date their first symptoms from a time shortly following an infectious complaint or some other inflammation of the respiratory tract. Chief amongst these direct antecedents is whooping-cough. When it is remembered that asthma is a spasm of the bronchial muscle, and that perhaps as suggested elsewhere a contraction of this muscle is part and parcel of every expiration—remembering also the close association with the vagus nerve of both laryngeal spasm and that of the bronchial muscle—we can well imagine the state of agitation into which the bronchial muscle must be thrown during the long-continuous paroxysms of whooping-cough.

Measles is given as an antecedent in other cases, but it is a very bad second. Other infectious complaints are but rarely mentioned. They probably occur with no greater frequency than would appear in the history of any child, whether asthmatic or not. If the asthmatic child catches whooping-cough, one might expect a truly horrible combination of events; but as a matter of fact, as occurs in all acute infections, especially those accompanied by fever, the one counteracts the other, and the asthma will be in abeyance during the whooping-cough, and for a short time afterwards.

With the more acute infections, such as typhoid or pneumonia, the immunity may last some months, even to the extent of some permanent amelioration of the general type of asthma. Recently, Dr. Gibson of Brentwood wrote me that this had happened to a case of his after diphtheria, not forgetting to give some credit as a factor for good to the non-specific action of the horse-serum content in the anti-diphtheritic serum that was injected.

In the atopic or 'strange' diseases, as the American call asthma and its allied complaints, no matter how clearly we seem to obtain a view from one angle, experience teaches us to expect to see a different or an exactly opposite picture from another view-point.

2. The Injection of Sera and Vaccines.—

Case 9.—A lady, aged 29, had typhoid at 7, and diphtheria at 14, when she had three doses of antidiphtheritic serum. Since then has always had heartburn and attacks of sickness; is sick on waking in the mornings; wheezes frequently, and at odd times has sharp attacks of asthma; used to have nettle-rash; catches cold very easily; has frequent sneezing turns when she may sneeze thirty times, this occurring especially in the early morning and in bright sunlight. She gave small reactions to beef, beef serum, horse serum, and feathers.

The whole of these troubles dated from the injection of the doses of horse serum.

A similar occurrence took place in another patient, urticaria developing :—

Case 10.—A lady, aged 28. Urticaria started one week after two injections of antidiphtheritic serum, and lasted for a year, day and night. If she placed her hands in cold water the rash appeared in twenty minutes. She did not have diphtheria. Years ago in South Africa she had a pin-head rash all over her after the second injection of antityphoid vaccine.

An exactly parallel case is one reported by Pasteur, Vallery-Radot, Haguenau, and Watelet[6] :—

Case 11.—A lady, aged 32. In 1911 had two injections of antidiphtheritic serum; after the second dose she became very ill and was comatose most of the night; fifteen days later fits of sneezing commenced and recurred regularly each morning; three months later these were accompanied by much hydrorrhœa; this continued in America, on the Continent, and in the tropics. In 1915 the attacks came on regularly after each meal; in 1918 she commenced to have attacks of asthma at night and urticaria after her bath; she was found to have a hæmoclasic crisis after each meal, the white-cell count falling from 7000 to 5000 in half an hour. She was given peptone by the mouth three times a day before each meal, and these accumulated troubles gradually left her.

Other patients state that their troubles commenced after injections of vaccines, stock anticatarrhal vaccines in particular and coliform organisms, the dose of which is oftentimes enormous. Some condition of equilibrium in the body is upset by these injections, though the exact mechanism is very obscure.

In his *Maladies Chroniques* Dansyz blamed the presence of "*l'anticorps en excès*"—too much antibody or specific

reagin—as the cause of a great variety of chronic illnesses. He noted that, if after rabbits had been injected with several doses of horse serum they were left without further injections, they all died within the year from alopecia or other skin diseases, arthritis, and bronchial affections—the same syndrome of ill-health, anæmia, and cachexia that follows in the Arthus phenomenon. Clinically we may note the wasting and eczema that is so often apparent in the grossly allergic individual.

The following case seems to substantiate this argument :—

Case 12.—A lady, aged 30. Ten years ago she had swelling of the eyelids and mouth after catching a severe cold. Two years ago she had another very severe cold. Urticaria commenced and persisted day and night ever since. She was quite incapacitated from work. She sneezed a great deal and had attacks of migraine. During these two years she did not have a single cold, although she had nursed others with colds. She thought the nettle-rash was worse while doing so. This may, of course, have been due to the fact that she was very overtaxed at these times.

The excess of protection against colds, *l'anticorps en excès*, caused the urticaria. I injected her with mixed coliform vaccine and removed this excess of reagins; her migraine and urticaria disappeared, but she *at once caught a fresh cold*, the first she had had for two years.

Whatever the exact mechanism of these occurrences, there seems little doubt that the injection of sera and vaccines into the body may lead to the starting of many of the 'allergic' complaints. A long-continued sepsis, as from a partially blocked sinus or antrum, causes asthma in the same way. Many cases of hay fever—that classical 'allergic' phenomenon—develop into chronic asthmatics unless successfully treated.

3. Infections of the Respiratory Tract.—A common statement in the history is that the asthma started after a bad cold or an influenzal chill, less often after pneumonia. A thorough physical examination will usually allow the site of the resulting infection to be discovered—a sinus, perhaps, or a patch of chronic bronchitis at one of the bases.

4. Other Sepsis.—If a microbic infection in one part of the body can cause asthma, it can do the same wherever it is situated, as from dental sepsis, septic tonsils, appendicitis, pyelitis, or from a septic gall-bladder or tube. In the latter

conditions, although they are rightly termed predisposing causes of asthma, their culpability often escapes notice until the appendix or gall-bladder is removed by operation, when the asthma disappears forthwith as though miraculously.

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CHAPTER IV

AETIOLOGICAL FACTORS

II. THE AETIOLOGY OF ASTHMA TABULATED

BEARING in mind the anatomy and physiology of the bronchi, narrowing of the calibre of the bronchioles and consequent obstruction to the passage of air through them may be caused by :—

A. A contraction of the bronchial muscle.

B. A swelling of the mucous membrane.

C. A secretion from the surface of the mucous membrane.

D. Any variable combination of these causes.

A. CONTRACTIONS OF THE BRONCHIAL MUSCLE

Contractions of the bronchial muscle may be brought about in the following ways :—

1. Stimulation of the Vagus Nerve.—

a. By the forced expiration consequent upon exercise, coughing, or violent laughter. Once this factor has been brought into play and a state of asthma exists, the forced expiration necessary in trying to overcome the asthma and the obstruction to the free passage of air through the bronchioles starts a vicious circle which is kept up by the increasing demands for more air to compensate for the severe muscular exercise that the paroxysm entails.

b. By reflex irritation from the nose.

c. By reflex irritation in the trachea and bronchial mucous membrane from a breath of cold air, of foggy air, of air heavily laden with tobacco smoke or that from wood fires, of sulphurous smells, and other poisonous atmospheres reacting on a mucous membrane which is inflamed by infection.

d. By the irritation of a foreign body in the lungs.

e. By vagotonia, in which the reflex is so sensitive that stimuli too weak to affect normal people may provoke a spasm of asthma.

f. By emotional stimuli.

g. By a lessening of the action of the sympathetic nerve, whereby the vagus is allowed uncontrolled and unbalanced action, causing its normal effect to be multiplied and excessive.

2. Stimulation of the Bronchial Muscle Indirectly.—Through the nerves of the endothelial blood-vessels, as in the experimental anaphylactoid reactions.

3. Stimulation of the Bronchial Muscle Directly.—By substances acting through the blood :—

i. *In anaphylaxis*, the mixture of the reagins in the blood and cells, with free antigen to which they are sensitized, causing the contraction of smooth muscle wherever that is situated and predominantly in the bronchial muscle.

ii. *By histamine*, appearing during anaphylaxis. Manufactured by bacterial action in the bowel, or from toxins of another infected part.

iii. *By Vaughan's split protein.* Vaughan[1] found that every protein contains a poison group which can be split off from the specific protein, whether microbic, animal, or vegetable. The poison group is quite different from the bacterial toxins ; it is just as poisonous whether it is split off from the protein of the typhoid bacillus or that of an egg. After the poison group has been split off, an animal can be sensitized with the non-poisonous residue ; but to cause anaphylaxis with a second dose the poison group must be left in the protein. The presence of the poison group is therefore essential to the phenomena of anaphylaxis. Messrs. Allen and Hanbury kindly removed the poison group from a specimen of horse dandruff for me by means of an alcoholic solution of sodium hydrate. The residue still contains a strong solution of protein. On using this for a dermal test on horse asthmatics who are sensitive to 1–1,000,000 solutions of horse dandruff, I found that no reaction whatever was obtained.

Now if the poison group is administered alone to the animal, we are told that exactly the same symptoms occur as with histamine or with anaphylaxis. Again, the symptoms vary in the different animals exactly as those of anaphylaxis. Heart and blood-pressure symptoms predominate in the rabbit, asphyxial symptoms in the guinea-pig, and gastro-intestinal disturbances in the dog.

We have, then, three methods by which bronchial spasm can be produced in animals: anaphylaxis, histamine, and the poison group. I therefore advance the proposition that we may go a step further than saying that asthma may be due to sensitization to a foreign protein, and can say that it may be due to poisoning by protein derivatives, whether they are formed parenterally by anaphylaxis, or liberated in the gut or elsewhere by the action of bacteria or some other abnormal proteolytic digestion.

Although I wrote the above three paragraphs fifteen years ago, there seems little to add or alter, except as to the paramount importance histamine is gaining in modern conceptions of asthma. One point of special interest is the disappearance of asthma in many women during pregnancy. All the three causes mentioned above, anaphylaxis, histamine, and Vaughan's split protein, have the power of causing contraction of the uterine muscle. Gross physiological contractions of this organ are obviously in abeyance during pregnancy, and the asthma disappears at the same time. In other cases, perhaps due to other causes, the asthma continues during these nine months.

4. As a Result of Bacterial Infection.—Explanations as to how microbic infection can cause asthma are largely of a theoretical nature, but we may note here shortly a matter which has recently come to light, and which is elaborated more fully in Chapter XI—that is, the very important observation of Feldberg and Keogh.[2] They have shown that it is not the staphylococcus in the posterior nares irritating the vagal area of Brodie and Dixon, nor the production of histamine by itself as a protein catabolite, that produces the asthma syndrome, but the toxin of this organism that travels to the lung and bronchial muscle and there liberates the store of histamine, which we have previously noted to be especially present in this organ. This I would regard as a very fundamental observation in the causation of the so-called microbic type of asthma.

The presence of microbic infection may be associated with asthma in the following ways:—

a. Secondary Infection.—Superimposed upon an asthma of 'allergic' origin. Sooner or later all asthmatics become infected. Clinically the symptoms change at this time from pure spasmodic dry asthma towards the type that

may seem little different from a chronic bronchitis with plentiful daily sputum whether there is an asthmatical attack or not.

b. Primary Infection.—Asthma may result from a primary infection of the lungs in non-allergic persons. The history and the finding of physical signs in the chest will denote these cases.

c. Infections of the Nasopharynx.—Asthma is very commonly secondary to infections of the nose, post-nasal space, and pharynx. The aspirin-sensitive type would appear to be wholly of this nature.

d. Infection Elsewhere.—In reviewing a series of follow-up cases, one is not infrequently told that the patient's asthma continued unabated until an appendix or a septic gall-bladder was removed, when the whole thing cleared up, leaving the patient entirely free from any further asthma. Such sepsis is difficult to diagnose as the cause of the patient's asthma. The operation has been performed for purely surgical reasons with no thought of benefiting the asthma, yet the result has shown beyond doubt the nature of the cause of the asthma. I have known asthma to disappear after the removal of septic teeth, and on one occasion of a chronically infected uterus, or perhaps of the infected tubes that were removed with it.

e. Toxic Poisoning.—Besides other effects of microbic action there may well be irritation and later degeneration of certain nerves, more especially of the sympathetic ganglia. Such may be the cause of vagotonia, a lessening of the counterbalancing action of the sympathetic.

5. Endocrine Dysfunction.—Any lessening of the supply of adrenaline, especially as an antidote to histamine, will cause asthma, or allow such normal stimulation of the vagus as may occur to cause spasm of the bronchial muscle, and any extra stimulation of the vagus to act with increased and compelling violence.

B. SWELLING OF THE MUCOUS MEMBRANE

1. Inflammatory.—In the course of bronchitis.

2. Urticarial.—From air-borne proteins meeting the specific reagins circulating in the blood, forming histamine locally with wheal formation of the bronchial mucous membrane. The protein inhaled is thereupon locked up in the bronchi;

the attack of asthma thus brought about will be of great violence and prolonged until it can be coughed up again.

C. SECRETION INTO THE LUMEN OF THE BRONCHIAL TUBES

1. Inflammatory.—As in bronchitis.

2. The Typical Asthmatical Sputum.—When lipiodol is instilled into the trachea during an attack of asthma, it may be seen by a radiograph to have entered the whole extent of some bronchi and bronchioles; in others it ends abruptly as though meeting a plug in the bronchus stopping its further extension by thick tenacious secretion.

D. CAUSES IN COMBINATION

Any combination of the causes already enumerated may occur to effect narrowing of the calibre of the bronchioles and consequent obstruction to the passage of air.

A great number of subsidiary causes will add their quota to make the asthmatical paroxysm more severe, more prolonged, and recurrent.

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CHAPTER V

AETIOLOGICAL FACTORS

III. SUBSIDIARY INFLUENCES

AN attack of asthma is usually caused by an accumulation of stimuli, and I am led to believe that it is a matter of adding up 'points' until a threshold is passed, when an attack of asthma will develop. Suppose our threshold value for the onset of an attack of asthma to be 100 points. We can then formulate an instance of a patient who is rather constipated (30 points), goes out to have a heavy meal (20 points), and has a chronic post-nasal catarrh (40 points). This amount adds up to 90 points, and is therefore in itself not quite sufficient to cause a paroxysm. After the heavy meal, however, there is much smoking, so that the air becomes laden with smoke and the CO_2 content is somewhat raised, thus adding another 15 points, and reaching the level of 105 points. The threshold having then been passed, an attack of asthma supervenes.

Many patients say that in some places a heavy meal is 'fatal', in others they can eat what they like and when they like with impunity. It is therefore necessary to recognize all such subsidiary influences, so that their avoidance may help to keep the patients as far below the asthma threshold as is possible.

In addition to the identification and avoidance of proteins that cause asthma, there are influences that tend to lessen asthma, and if actively pursued will take off points. All such must receive due consideration.

1. Physical Fitness.—The influence for good of hard training and the maintenance of a high degree of physical fitness is so strong that many men during the war seemed to lose their asthma entirely for the duration of their service. This was so even in cases of hay fever where there was no question of being removed from the offending pollen. Such a degree of fighting fitness is impossible for most people in civilian life, but by the sacrifice of five or ten minutes to exercises

each morning much can be accomplished. With exercise comes a quickening of the heart-beat, a flushing with blood of every part of the body. Carried a step further, 'all the pores of the skin' function by sweating. With deep-breathing exercises the blood circulated can be so superoxygenated as to give each cell a certain efficient oxygenation at least once a day. The liver and intestines are 'shaken up', and metabolism is improved in every way. The methods of putting these precepts into practice are given in Chapter XV.

2. Diet.—The majority of us eat far more calories a day than are necessary for us, and with no great harm to our constitutions, nor perhaps in any way comparable to the gluttony of our forefathers. But it must be remembered that in those days, 'the good old days', kings and noblemen, and all who could, hunted or shot, walking up to their birds. Trouble came when they continued to overeat but ceased to take exercise, just as it does when famine, war, and disease cease to decimate rapidly-breeding populations, and the whole of the progeny survives to overcrowd the land.

Overloading the stomach with more than it can digest produces imperfect digestion. The excess of food, digested and absorbed, chokes the whole machinery of metabolism, while such as remains undigested provides a suitable pabulum in the gut for irregular microbic fermentation.

In asthma, food should be taken in the smallest quantity possible, and late meals should be avoided. As Hyde Salter said: "The patient should go to bed with his lacteals empty."

Perfection of the whole digestion entails perfect digestion of each of the main food groups—the fats, the carbohydrates, and the proteins. Such dishes as contain these three foods cooked together, and so intimately mixed in the cooking as pancakes, pastry, and Welsh rabbit, must be avoided, as must supermilks, excessive creams, and all such attempts to 'keep the patient's strength up'.

3. Purgation.—Faulty intake, faulty digestion, and faulty metabolism may be rendered still further harmful by faulty elimination of waste products. With a minimum intake, perfection of digestion, and as high a metabolic rate as possible, purgatives and colonic lavage should not be necessary; but in subduing a prolonged and acute attack, full and abundant

purgation, as by castor oil, is often necessary and at times imperative.

4. Menstruation.—Numbers of asthmatical women are worst just before the period. When I was working on the colloidal particles of the blood some time ago, I found these tending to become aggregated at this time. In one case in particular the colloidal particles in the plasma, examined a few moments after being taken, were so aggregated as to appear abnormal, and even pathological. This blood was taken from a control, a perfectly normal nurse, and its condition was probably closely associated with the fact that menstruation commenced a few hours later.

The asthma seems to be particularly of this menstrual type in those patients in whom the period is painful and scanty.

5. Pregnancy.—Conversely, the state of pregnancy often gives the asthmatic patient nine months' freedom from symptoms, an inhibition made more striking by the fact that asthma may return within a few hours of delivery. It is said that during pregnancy there is great increase in the activity of the suprarenal glands, both cortex and medulla, the former hypertrophying more than the latter. (Appleton.[1])

But to find an explanation, if there is one, for the increased asthma just before the periods and its absence during pregnancy, the action of the female gonads and their internal secretions must be examined. The whole subject is enormously complicated by the very diverse terminology used to denote the hormones, many writers using the trade names under which the hormones are sold. Some slight clarification of the subject is therefore necessary before any discussion can take place.

In Martindale's *Extra Pharmacopœia*, twentieth edition, there are thirty-two trade names for the various ovarian hormones extracted. Œstrin will be used here for the main ovarian hormone, and progesterone for that from the corpus luteum, names by which they are known in the *British Pharmacopœia*.

The ovarian tissue forms a hormone which has the effect of producing œstrus or heat in spayed animals. The amount necessary to cause this in a mouse is the international unit of one mouse-unit—0·1γ, or one-thousandth of a milligramme of crystalline œstrin. Five slightly different chemical substances have been isolated in this hormone.

Ascheim and Zondek[2] discovered that this œstrus-producing substance could be extracted from the urine of pregnant animals. It was crystallized by Doisy.[3] Preparations on the market are benzoylated œstradiol, and are sold under some fifteen different names.

The formation of œstrin in the ovary is regulated by a hormone, prolan A, of the anterior pituitary gland. Excess of formation of œstrin leads to inhibition of the production of prolan A.

Both œstrin and prolan A can be recovered from the urine, and the amounts assayed to give a correct indication of the amount of these hormones active in the body. It is therefore possible to tell whether the patient has the correct normal amount of these hormones, is short of them, or if they are present in excess.

The only clinical use to which this has been put, according to the literature, is in the examination by Riley et al.[4] of some thirty patients suffering from migraine, a complaint of 'allergic' nature and akin to asthma. Normally throughout the menstrual life of a woman, 10 to 20 rat-units of œstrin appear per litre of urine, no prolan being present. A rat-unit is four or five times the size of a mouse-unit.

When prolan does appear it means that there is some under-action of the ovaries. Daily examination of the urine was carried out over a fortnight or more, which included a period and one or more attacks of migraine. As in the asthmatics who are worse before the periods, the attacks of migraine tended to increase at the menstrual period, and in many cases disappeared during a pregnancy.

Riley found that œstrin was almost always absent or only present in very small amounts in these cases of migraine. Prolan A was often to be found on isolated days, and in 20 out of 29 cases on days directly before the migraine attack. In two menopausal cases of continuous migraine, large amounts of prolan A were present almost every day. Prolan also appeared at all the menstrual periods. Lastly, if injections of prolan were administered to these people, attacks of migraine were produced. It would appear that the attacks of migraine were connected with either a shortage of œstrin or excess of prolan.

Soltz[5] treated a series of cases of migraine with (1) histamine, (2) œstrin, (3) phenobarbitol. Seventeen out of 31

cases were markedly improved by histamine, and 18 out of 32 were markedly improved with œstrin, but the latter group could not be identified with those cases whose previous histories had shown a freedom from symptoms during a previous pregnancy. The counts of the hormones present in the blood and urine do not appear to have been carried out daily.

Glass[6] found that œstrin was very useful in migraine where there was hypo-ovarian function present. Similar work has not been reported on asthma, and there would appear to be a large field ripe for investigation on this subject.

Goldberg[7] reports the case of a woman who had urticaria after exercise. A great many treatments were tried without benefit. As this came on at the climacteric, œstrin (theelin) was given, with immediate and almost complete relief.

The corpus luteum forms after the ovum has been shed from the Graafian follicle. Its hormonal influence prepares the uterine wall for the reception of the ovum and for the production of the placenta. If gestation takes place the corpus luteum remains in full function. If it does not, menstruation occurs as a result of the renewed preponderance of the follicular activity of the ovary over the failing activity of the degenerating corpus luteum.

The corpus luteum is therefore at the height of its action during pregnancy when asthma usually lessens, and is absent just before the period, when asthma is often at its worst. Very little is known about the chemical nature of this hormone, nor is any test of its presence available as yet. It would seem that the hormone of the corpus luteum might be tried on cases of asthma that are of the menstrual type or that have had experience of freedom from asthma during a previous pregnancy. The unit of dosage is as follows: "A rabbit-unit (Corner and Allen[8]) is that amount of the hormone which divided into five daily doses produces on the sixth day a state of the uterus equal to that of the eighth day of a normal pregnancy." (Martindale.[9])

As both œstrin and the corpus luteum hormone are capable of crystallization, it is to be hoped that dosage in decimals of milligrams may soon displace these complicated animal units.

For the past ten years or more I have been using collosol manganese intravenously in the treatment of this type of

case. Enough is injected to produce a considerable flush of the whole skin, that is, from 1·0 to 1·5 c.c. In those patients suffering from scanty and painful periods the subsequent period is usually normal and painless. In others in whom the breasts become swollen and tender just before the period, easement may be produced in one hour after the injection of collosol manganese. It is difficult to suggest how this effect is produced, but it may be remembered that collosol manganese was originally produced to procure an effect on the blood " by splitting up the colloidal particles into smaller ones ". (McDonagh.[10]) Its rapid action could thus be explained as dispersing the colloidal particles which are tending to become aggregated at this premenstrual phase.

6. Coughing and Laughing.—These produce effects common to all forms of forced expiration, the overaction of the bronchial muscle being sufficient to initiate an attack. With the aspirin-sensitive type, a fit of coughing is the usual premonitory symptom. A good sneeze, however, is often welcomed as likely to break an attack.

7. Cigarettes.—Over-indulgence in cigarettes produces smoker's cough or a nasal catarrh in most people, and I feel sure that it is the paper and the burning of it, together with inhalation of noxious gases from the matches, which provides the constant irritation to the mucous membrane of the nose and throat. Cigarettes should therefore be avoided entirely, and particularly when working indoors at sedentary occupations—reading, sewing, writing, and card-playing, also when gardening. With the head bent over the work and the cigarette held constantly in the mouth, most of the smoke is inhaled. On the other hand, cigars in moderation seem less harmful, while pipe-smoking is quite permissible with any ordinary mild tobacco.

8. Locality.—To those hypersensitive to air-borne proteins, a change of locality of such short distance as to the next room may prove effective in removing the asthma. Dr. Schlemmer of Mont Dore told me of a case under his care in which the 'locality' was finally tracked down to a cupboard containing a patch of mould. Such may happen in individual cases, but there are larger influences that affect all asthmatics more or less. Most notable perhaps is the beneficial effect of high altitudes, not only for asthmatics but for hay fever patients.

Firstly, it would seem that, in the more rarefied atmosphere of high altitudes, pollen and other air-borne dusts tend to fall more quickly to the ground; and secondly, that in the cold winters of the Alps mould spores will be less likely to survive and flourish than in lower, warmer, and more humid atmospheres, as that of Holland. Of additional benefit, as Hudson of Davos writes,[11] is the fact that the diminished pressure of oxygen leads to deeper breathing, and an increase in red cells and their hæmoglobin content. The invigorating air, and the increase of exercise now found possible, soon lead to healthier conditions all round and an increased metabolism—benefits which may remain long after the stay in the Alps is over.

Many patients have a great aversion to places situated near ponds, lakes, and amid trees. The seaside is commonly 'bad' for most asthmatics, Devon and Cornwall being much more so than Norfolk and the east coast.

9. Atmospheric Conditions.—The east wind is notoriously unkind to the asthmatic. It is a cold wind, often of considerable force, and in England is usually the prevailing wind from the beginning of March till well into May. But it seems to be more than its coldness that affects the asthmatic, who appears to be aware of a change to this quarter almost before the curtains are drawn in the morning. Even in the summer its effects are noticeable and accompanied by an east wind haze, such as did its best to spoil the Coronation Review at Spithead by causing such poor visibility. This haze vanished the following day with a change of wind.

Some asthmatics object to any high wind, especially those in whom there is an irritability of the bronchial mucous membranes by oversmoking or infection. Similarly, patients are affected by fogs, and more so by the London or other smoky fogs, in which every particle of moisture contains a carbon granule with sulphides and oxides of sulphur.

Strangely opposed to these are a few asthmatics who like a fog, and in fact used to find benefit from the green sulphurous atmosphere of the old Underground Railway before electrification—conditions more foul than the modern strap-hanger could conceive possible.

To others an atmosphere of tobacco smoke is fraught with danger, making their lot an unhappy one under modern conditions. The care taken to cleanse the water in an up-to-date

swimming bath contrasted with the dreadful conditions prevalent in most cinemas is a striking anomaly of our times. Smoking is *verboten* in cinemas in Germany, and the difference it makes in the atmosphere therein is truly remarkable.

In short, atmospheric conditions affect the asthmatic in virtue of their cold temperature or the impurities such as dust and tobacco smoke that they contain.

10. Bedclothes.—Apart from the avoidance of those articles to which the patient is sensitive, it would seem an absurdity to bare the legs to the north-east wind by day, as is the custom with most women and children, and then to pile blankets and eiderdowns, overheated by hot bottles, on them at night. Unless the patient is awakened by a nightmare due to the heat, attempts are made to cool the body by evaporation from the nose and lungs, with an ultimate congestion of both.

It does not require a vast stretch of imagination to see a sufficient cause of enlarged tonsils and adenoids in this overcooking of children at night. A sharp walk for ten minutes last thing will ensure going to bed warmed; the removal of the hot bottle before going to sleep, and a minimum of bedclothes, will prevent nightly attacks of asthma due to overheating. The eiderdown should be placed crossways over the patient's body, leaving the legs with less clothes on than elsewhere.

11. Exercise.—Walking up steep hills, and even going up a few flights of stairs, may produce an attack of asthma. This is due to the increase of forced respiration that takes place, and it merely calls forth an asthma that is already there. It is usually easy to distinguish this shortness of breath from that caused by myocardial weakness, and indeed if patients persevere they often lose the asthma again by continuing the walk or other exercise, just as runners develop a second wind.

12. Psychological Causes.—My experience is that in a very large majority of cases of asthma there is no psychological cause for it, nor can the patients as a class be considered in any way neurotic, or the subjects of nervous manifestations.

Children who have been sheltered with an excess of care on the one hand and cautioned with endless lists of prohibitions on the other, naturally feel that they are different from other children, and under some curse, the meaning of which

they cannot understand. In so far as this is so, they become unnatural in their outlook on life and in their behaviour. Of older cases, there was a patient of mine who on demobilization spent the whole of his capital in starting a small tailoring business in the city; when incapacitated by asthma he was said to be "so nervous", but who would not be under such dreadful conditions, with ruin staring at him with more clear-cut features every day? Such neurotic manifestations are the results of asthma and not among the causes. Many of our finest citizens are asthmatics, men of great ability, capable of immense work and energy.

An American investigation by Balyeat[12] found that asthmatic children showed a higher degree of intelligence than their fellows. The fact that their time would be more likely to be spent in sedentary occupations—reading, Meccano, and so forth—rather than in wilder outdoor amusements, might account for much of this increased intelligence. This evidence has been challenged by Sullivan and Macqueen.[13]

On the other hand, sudden bereavements, shocks, financial embarrassments, and marital troubles do at times form the starting-point of a patient's asthma—of this there can be no doubt. Probably such patients are always near the asthma level, and any small additional stimulus will suffice to produce attacks.

Not being a psychologist myself I no doubt miss many psychological causes that others would read into my cases. Gillespie[14] gives much sound advice on this point, but the cures he mentions are all taken from foreign articles. Now, however ingeniously a psychological cause may be made to fit the case that is being treated, more important still is to find a cure that will relieve the patient of his symptoms.

I have no patience with those who state that sensitization to feathers is due to patients as children having seen things they should not have seen occurring on a feather bed! And how do those who make this astonishing statement propose to make use of this assumption in treating a girl in her teens whose asthma is due to sensitization to feathers?

The mere fact that the child gives a skin reaction to feathers —one of the most specific reactions known to science—should rule out any suggestion of a psychological basis, quite apart from the fact of the patient's being totally unaware of what proteins are being applied to the skin.

Finally, the Prausnitz-Küstner reaction, in which the arm of a total stranger is used to demonstrate the reaction, must settle any argument. If the patient can influence the reaction on his own arm in some subtle way, he surely cannot do so by means of the blood which is transfused to another person. I make no doubt that I have used the denomination 'psychologist' far too loosely, and that these views, which seem to me so peculiar, are not generally held by any great number of physicians. In short, I am more in favour of materialistic explanations than of psychological theorems.

If one turns pale with fright and trembles with anger from an outpouring of adrenaline, then I think one may quite well look for a material cause of the asthma which follows upon sudden shocks, fears, and bereavements.

13. Habit.—Lastly we come to habit, one of the strongest psychological urges to which man is subject.

Having gone through the same routine in dressing, we read the same paper at breakfast, place the same foot first into our boots, catch the same train and sit in the same corner of it, go to the same restaurant for lunch, are offended if the same girl does not serve us, smoke the same cigarettes —the mere smoking of which is ninety per cent habit; and so on through the day, any departure from the routine requiring a considerable mental effort to accomplish.

We have considerable control over the nature of our respirations, and if a breath is made faultily, stressing the expiratory phase, this effort automatically tends to contract the bronchial muscle, and having done this, and being such creatures of habit, our tendency is to make the next expiration exactly the same.

Patients are often somewhat apologetic for not having asthma when one sees them, and may unconsciously by forced expiratory effort produce the necessary wheeze. I am always pleased when this occurs, because it gives one the opportunity of showing them how to breathe properly, using the diaphragm for inspiration and allowing the air to flow out of the chest with the minimum expiratory effort.

Patients whose every expiration is accompanied by a grunt are particularly difficult to deal with. The grunt is made in the larynx and is of no help to them, being merely a habit, and a very irritating one at that. Similarly, if they

wake one night with asthma, habit will make them do so the following night. For this reason a small dose of a mild sleeping drug, such as ½ gr. of luminal, is often of great assistance in breaking the habit and so restoring confidence.

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CHAPTER VI

SIGNS AND SYMPTOMS OF A PAROXYSM OF ASTHMA

THE Prodromal Symptoms.—Sometimes patients and their friends notice warning symptoms before an attack develops. In one patient it may be an unusual vivacity, in another a tendency to lethargy and yawning. Mothers may notice that the child becomes very irritable and touchy the day before. In some cases there will be slight symptoms for a night or two before the big paroxysm begins; others. observing a dirtiness of the tongue and feeling of liverishness, will ward off the onset by the help of a sharp purge.

A prodromal symptom which I have noticed, and which is first mentioned in Hyde Salter's book written seventy years ago, is an itching under the chin and round the throat. Some patients notice that their lips swell, in which case this and the asthma will be due to a food that has been eaten. Asthma follows each time a particular patient catches cold, while some discomfort about the tonsils warns others of an attack. More often, however, there are no premonitory symptoms.

The Commencement of the Attack.—The patient may go to bed perfectly well and wake in the night with an attack of asthma. The mother or nurse will often hear the wheezing long before the child awakens. He turns over and becomes more restless until he drowsily sits up, and then wakes in an attack. The troubled sleep may give him a nightmare, which his unhappy awakening will turn into reality, and on the first few occasions when this happens the patient may be really frightened. Not less so will be his relatives. The suddenness of the onset in the middle of the night, their ignorance of what is really happening, the apparent possibility that the patient will choke and die straight away, are all very alarming.

Fortunately such a sudden commencement of asthma is rare. Slight attacks give patient, friends, and the doctor a warning of the severer attacks that eventually develop. In

childhood the lighter attacks of asthma may pass as bronchitis for a year or more before the real nature of the malady is discovered, and in this way the patient becomes accustomed to his complaint without being frightened. An account appeared in the papers some while ago of an inquest held on a young asthmatic man who cut his throat with a razor trying to get some more air. Such a state of panic is extremely rare; in fact, the patient is often the least frightened person in the room, and will crack a joke with the first few words he is able to utter.

The Mechanical Effects of the Bronchial Obstruction.—As argued elsewhere in this book, the essential element in the paroxysm is a narrowing of the calibre of the finest bronchioles by a spasm of their muscular coats. The normal interchange of gases between the air in the alveoli and the air in the larger bronchi is interfered with, necessitating some extra exertion on the part of the patient to obtain more oxygen. Very rarely, and I think hardly ever in quite typical asthma, is there much increase in the rate of respiration. A greatly increased muscular effort is made and a violent excursion of the chest movements of respiration takes place, in the hope that by this means the patient may be able to pass the same amount of air through the narrowed bronchioles as goes through them when normally dilated.

Without touching on the various laws governing the pressure of gases in passing through pipes, it is obvious that if 100 men have to pass through only one turnstile in the same time they usually take to pass through two, they must be rushed through at double the pace. The air being forced through the narrowed bronchioles at an increased pace gives rise to the wheeze, at first just such a musical collection of little squeaky notes as most of us can produce by using a slightly extra effort right at the end of expiration. I think we produce these small 'rhonchi' in exactly the same way that the asthmatic produces his, namely, by a contraction of the bronchial muscle during forced expiration; perhaps this occurs at the end of every normal respiration. These sounds are not made in the larynx, for if they were we could produce them at any time during expiration.

With the asthmatic this wheeze—this contraction of the small bronchioles—becomes a spasm which continues during inspiration as well, though probably to a lesser extent.

Expiration becomes more difficult to accomplish than inspiration; it occupies a longer time; and if we agree that normally there is some contraction of the bronchial muscle during every expiration, and that this becomes exaggerated in asthma, we have a simple explanation of much that takes place during the spasm.

To start with, if the bronchial muscle is more contracted during expiration than inspiration, the lumen of the bronchial tubes will be smaller at that time, and it will be more difficult to breathe out than to breathe in. Hence we shall expect to find that expiration takes a larger and longer share in the respiratory cycle than normally; in fact, it will not have finished before inspiration commences again. This will give a slight balance in favour of inspiration and rather less air will be able to leave the lung than enters it. But even if this balance should be only a few cubic centimetres at each breath, the total quantity of air in the lung will immediately begin to be increased, and will finally give us lungs distended to their utmost, as in a condition of acute emphysema. This is exactly what does happen in asthma.

If, again, we allow that contraction of the bronchial muscle follows on forced expiration, we can see why it is that asthmatics, whose bronchial muscles are ever ready to contract on the slightest stimulus, should so easily begin attacks after such expiratory efforts as coughing, laughing, sneezing, or the hard breathing that follows upon exercise. Occasionally, when listening to the chest of an asthmatic which is at the time perfectly clear, the patient will cough. We continue to listen. The cough ceases, but for the next few breaths the chest is full of rhonchi. As we continue listening these gradually disappear, until the breathing becomes perfectly quiet and normal once more. The forced expiratory effort has for the time being caused a spasm of the bronchial muscle.

1. *The Air Capacity of the Lungs.*—The total capacity of normal lungs from the emptiness of collapse to the complete fullness of the deepest inspiration can be divided into ten parts of some 500 c.c. each. *Fig.* 4 shows in three parts the condition of the lungs in (I) normal respiration, (II) an acute attack of asthma, (III) chronic bronchitis and emphysema. In (I) normal respiration, the lowest 1000 c.c. is the residual air that cannot be forced out of the lungs by

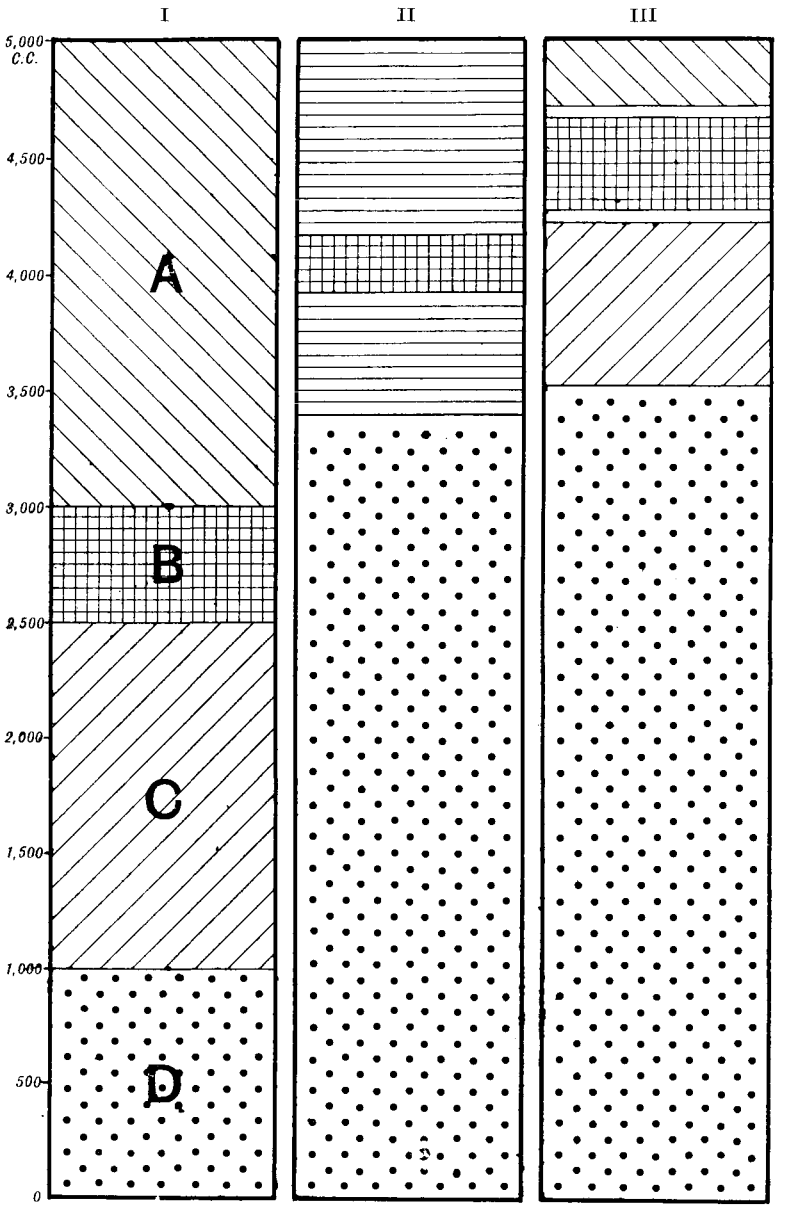

Fig. 4.—Diagram showing air capacity of lungs. (I) Normal respiration; (II) Asthma; (III) Chronic bronchitis and emphysema. A, Complemental air; B, Tidal air; C, Supplemental air; D, Residual air.

voluntary effort and will not leave the lungs unless they are collapsed by pneumothorax or hydrothorax. Above this is 1500 c.c. of supplemental air, which can be emptied by deep expiration. Next we have 500 c.c. of air which we exchange in and out during normal quiet breathing, the tidal air. Above this again comes a further 2000 c.c. of complemental air, which can be taken in by deep inspiration. These various portions are indicated by similar markings in each of the three sections.

The patch where horizontal and vertical lines cross each other is the tidal air that we normally breathe in and out during each quiet respiration. Of the component parts on the diagram, the horizontal lines represent the excursions of the chest wall and diaphragm, and the vertical lines the actual amount of air that passes in and out at each breath. In (I) they fill identical spaces. We can extend this quiet breathing upwards and downwards on the diagram by forced inspiration and expiration until, at any rate theoretically, we could respire the whole of this 4000 c.c. of air in and out at each breath.

In (II) we have the condition of affairs in a maximal attack of asthma. Such respiratory exchange as is possible takes place with the chest in a position of very full expansion. At the height of inspiration the chest walls reach a position in which they are as fully expanded as is possible with the aid of every accessory muscle of respiration. After the expiratory muscles have made their maximum effort to empty the lungs, the level which is reached is still far above that at which normal respiration takes place. These movements of the chest walls are shown on the diagram by horizontal lines. Owing to the obstruction of air through the bronchioles, the amount actually exchanged—the tidal air—is far less than it would be if the lungs were able to expand and follow the movements of the chest walls. The expansion of the lungs is shown by the vertical lines. Directly below these vertical lines is the residual air, the whole of which—some 4000 c.c.—cannot by any manœuvre on the part of the patient by expressed from the lungs. This is a picture of the condition found in very severe paroxysms of asthma. There is hardly any complemental air above or supplemental air below this small amount of tidal air. Such air as does pass in and out at each breath

is the maximum amount possible even with the maximum effort that the patient can put forth.

(III) is discussed in the next chapter.

2. *The Muscular Mechanism of Respiration.*—We now pass on to consider the muscular mechanism by which the movements of respiration are carried out in normal breathing and the manner in which it is altered in asthma. Perfect respiration consists of muscular movements which will ensure an equal distribution of the inspired air throughout the various portions of the lungs and the millions of air alveoli they contain. When all parts of the lungs are thus properly ventilated, the blood has the fullest opportunity of taking up as much oxygen as it requires, and of dispensing with any excess of carbon dioxide it may contain. Though these exchanges balance one another, they do not do so in any fixed or exact proportion. If a part of the lung is thrown out of action the blood passing through it fails to be oxygenated, and returns to the left heart in a 'blue' condition. It circulates round the body and causes a greater or lesser degree of cyanosis. The carbon dioxide part of the exchange may be very little affected, being carried on efficiently in the remaining portion of the lungs.

Three separate actions take a part in normal inspiration. First, the scalene muscles fix the first rib. Secondly, the various intercostal muscles approximate the ribs; taking their fixed point from the first rib, each swings upwards and forwards after the manner of a bucket handle. The actual excursion of each rib is its own degree of movement towards its neighbour plus the movement of all those ribs which lie above it. This at any rate is the motion of the upper part of the thorax and the upper six ribs. The ribs below these are affected by the third action, that of the diaphragm. Normally the arch of the diaphragm is considerable, and its attachments to the ribs and the spine take place at a very acute angle with those structures. The motion of the ribs in expanding the lower portion of the margin of the thorax will tend to flatten the diaphragm, but owing to the high arch of the latter it can contract very considerably and lower the floor of the thorax without there being any action that would tend to pull the rib margins together or counteract the ribs' own movement of expansion.

Widening or narrowing of the costal angle can be taken as the criterion of whether the lower rib margin is expanding or contracting.

Although the angle widens during ordinary respiration, the action of the lower ribs is not a very powerful one, and under certain circumstances the angle may become narrower and more acute. If the diaphragm should lose its arch, become pressed down and so horizontal, any pull it can then exert will be a direct one that may easily overcome the feeble action of the lower intercostals. The lower ribs will consequently be pulled in, instead of expanding with inspiration.

In an attack of asthma the following changes will attract our attention. Compelled by a lack of aeration in the blood, a great inspiratory effort will be called forth. Not only the scalenes but all the accessory muscles of inspiration, not content with merely fixing the first rib, will be endeavouring to raise that somewhat immovable structure, and through it the whole cage of the ribs below.

The muscles which take part in the second action, the first six intercostals, will function freely, not being impeded in their movements, but rather assisted by all these accessory muscles and the elevation of the first rib. There will be considerable expansion of this part of the chest, whether the lung is able to expand with it or not.

The third action—that of the diaphragm and the lower six ribs—undergoes remarkable changes in an attack of asthma. The enormously distended lungs will have flattened the diaphragm until it is nearly horizontal. In this position its contraction will have no effect in lowering the base of the thorax, and it will do nothing to assist the intake of air. If it has any power of contraction left in this position, when it is shortened almost to the chord of its original arc, it must approximate the lower edges of the ribs, making the costal angle a narrower one.

This inward pull on the lower ribs is increased by another factor, whatever part the diaphragm may play. Let us suppose that the diaphragm is unable to do more in its new position than maintain itself taut horizontally. We then have the powerful accessory muscles of respiration and the first six intercostals expanding the upper part of the thorax; but the lungs inside the chest walls are unable to expand with inspiration because of the obstruction about the bronchi

and bronchioles. It therefore follows that, to prevent a vacuum being formed, those portions of the chest wall not under the control of muscles strong enough to expand them must in a compensatory manner be sucked in. This will occur at the upper opening of the thorax in the neck, and at the lower opening of the thorax about the diaphragm and the lower ribs. Moreover, if the diaphragm should be raised by this negative pressure, without in any way relaxing its tone, the lower rib margin will be still further drawn in.

The Symptoms at the Height of the Attack.—The mechanical disturbances above described provide the main symptoms of asthma as we see it at the bedside.

The patient's trouble may be audible before one enters his room. He will probably be found sitting up in bed, occasionally in a chair, and more rarely at the window. A nurse or relative may be fanning him. He will be using every artifice to get the air in and out through the narrowed bronchioles. Supporting himself on his hands or elbows, the shoulders will be thrust upwards and forwards until the clavicles make an acute V with one another, instead of lying practically horizontal as in normal people. The accessory muscles of respiration—the scalenes, the pectorals, the trapezius, the serratus magnus—will be acting strongly at each inspiration. The sternomastoids will stand out as tight cords. The head will be raised at each inspiration, the mouth opened, the tongue even thrust out in an attempt to help to raise the chest and clear the airways, the occipito-frontalis may elevate the eyebrows in a vain endeavour to help. The larynx will be pulled down to the chest, or rather the cage of the ribs pulled up towards it. Expiration will be assisted by firm contraction of the abdominal muscles. With the raising of the shoulders, the back becomes very rounded; and though the patient may occasionally be standing up, perhaps by the mantelpiece, he is much more likely to be found sitting with his head forward in a very doubled-up position in bed. In spite of all the muscular efforts, a vast obstruction to breathing remains. As the lung is therefore not able to follow the expansions of the chest wall, there is a sucking in at all those places which are not under control of the muscles of inspiration. The supra-clavicular spaces and that at the suprasternal notch are drawn in at each breath, leaving the taut sternomastoid

muscles standing out alone. We need not argue as to whether these spaces are drawn in by a negative pressure inside the chest, or, more correctly, driven in by the atmospheric pressure from the outside. The lower portions of the chest wall and the præcordia are sucked in at each breath, just as they are in a child with laryngeal obstruction. The sternum seems to possess a visible joint between the manubrium and the gladiolus; the upper part, the manubrium, facing forwards and upwards, the lower part, the gladiolus, forwards and downwards—that is, in inspiration with the patient upright. Ludovic's angle becomes especially prominent, and many other typical deformities result which will be considered in the next chapter. If a hand is placed on either side of the chest at its lower part, no expansion can be felt there.

As the attack continues, beads of perspiration may be seen on the face, and in anything like hot weather the sweating is general, from the great muscular effort necessary to carry on. The lips, the cheeks, and the nose will become blue from the anoxæmia, due to the fact that much of the blood that passes through the lower portions of the lungs does so without receiving any fresh oxygen *en route.*

By palpation, the heart may be felt to be beating rapidly, often in a bounding way. Later, in severe paroxysms, both the heart-beat and the pulse may be barely perceptible. On percussion, the note is hyper-resonant over the whole chest. A peculiar boxy note is sometimes elicited in the axillæ. The heart dullness is lessened, the emphysematous lung encroaching on it from either side. On auscultation, the squeaks, the wheezes, and the rhonchi are so noisy that little else can be heard; such sounds are conducted to all parts of the chest. It will be noted that while there is very little entry of air even at the apices, at the bases there is practically none at all; the respiratory murmur is absent. Another peculiar fact is that different parts of the lung will at times be more patent than others, suggesting that the spasms may be more pronounced in one lung, or in one part of it, than in the other. Expiration will be longer than inspiration. Any interval there may be between the two seems to come more at the end of inspiration than expiration—the reverse of the normal. But this pause may not be real. Probably what happens is that the whole of the muscular effort of

inspiration takes place at one mighty heave; the full inspiratory position is held for a moment to give the air time to pass into the lung. A movement by the muscles of expiration then takes place which is slower, and which follows the emptying of the chest as the air leaves it.

Many of these movements can be seen easily by the following experiments. Stand stripped to the waist before a mirror, close the mouth and take one or two deep breaths through the nose; the abdomen protrudes, the lower ribs expand. Now pinch the nose tightly and execute exactly the same muscular inspiratory action; this time the abdomen is drawn in, and with it the lower ribs. This is especially well seen, of course, in children. If these movements are commenced with the chest already full of air, an exact representation of the chest movements in asthma results.

The heart beats more rapidly and with greater force than normally, without any great accentuation of the pulmonary second sound. But it is surprising how very little temporary or permanent effect on the heart results from even a most ghastly life of asthma. Inhalations and potent drugs are much more liable to harm it than the asthma alone.

So much for the asthma as a spasm of the bronchioles; but further trouble soon takes place. The bronchi, even the bronchioles, commence to exude a thick, sticky mucous secretion. When this comes up as sputum and is teased out it contains casts of even the smallest bronchioles, so that it is surprising asthma is not a more fatal complaint. The occurrence of death during the spasm of asthma is a matter of the greatest rarity, even when the patient becomes cold, blue, and insensible. With the secretion of this mucus the patient's troubles reach their height.

The Cough and the Passing of the Attack.—The first sign of improvement is a series of short, sharp coughs, perhaps five during one expiration. Now a cough is the result of suddenly opening a closed glottis and letting out air which is at pressure behind it. When the asthmatic coughs during a spasm there are two obstructions to be overcome, one at the larynx, and the other at the bronchi. The patient closes the glottis, and pumps up pressure in the trachea and large bronchi by squeezing air through the bronchioles from the alveoli. He then opens the glottis, but there is only sufficient pressure behind it for a short cough; he therefore closes

the glottis, works up more pressure behind it, and coughs again.

After several of these efforts a little pledget of hard mucus is expelled and one road becomes cleared. Gradually more and more mucus follows, until the patient ends by bringing up great quantities of thick, glairy mucus, and the attack subsides. Whilst he is coughing, the head sinks down on the chest, and the chin touches the sternum, as in a child with whooping-cough.

Unusual Symptoms.—Naturally, in such a many-sided complaint as asthma, we have many variations in the copies of this picture, and a few forgeries.

One is always suspicious when a patient says that he breathes very rapidly in an attack. The attacks are then usually not the ordinary uncomplicated asthma. If the reader agrees with the mechanism of asthma as portrayed above, he must also agree that it is practically impossible to breathe fast in asthma. I think these cases are usually those that have very little asthma, but a quantity of bronchitis, or a flabby heart.

The following case is of interest, though I did not discover its true significance until the end of the examination. The history of rapid respirations should have made one suspicious from the start.

Case 13.—A married lady, aged 43, had had asthma ever since running in a race in childhood. She was better whilst looking after her children and going out to employment during the war. The attacks occurred chiefly at night, when she made a crowing noise audible to the neighbours; various smells brought attacks on. She gave no dermal reactions to any of the ordinary test substances. An attack of asthma gradually began to develop during my examination of her, chiefly noticeable for the very rapid breathing. During an examination of the nose and throat, while I was using the tongue depressor, she held her breath. Noticing this, I prolonged the examination and she continued to hold her breath. I then told her that if she took a deep breath when I removed the tongue depressor she would find that her asthma would be gone. It was, and she continued to make ordinary slow respirations. Here was certainly a neurotic element, but the asthma was atypical. She had probably had true asthma as a child which had developed into this abnormal variety.

In children, rapidity of breathing is sometimes combined with a high temperature, another very unusual symptom.

In this case we may especially examine the tonsils, which will often be found inflamed and covered with septic follicles. At other times the temperature is part of a definite cold which is the accompanying cause of the asthma. The temperature should always be taken, as when it is above normal we must employ more caution and 'coddling' than is necessary when fever is absent. In fact, a case which gives a long history of frequent attacks of 'bronchitis' without any temperature can best be treated by all the open-air methods available, in contradistinction to the closed window, poultice, and steam-kettle regime that is often in vogue.

General Symptoms.—There is usually constipation, often a dirty tongue, and a complete voluntary starvation. The passage of a large quantity of limpid urine is common with the attacks.

Convalescence.—If we can call it such, convalescence sets in rapidly. Directly the spasm ceases, the return to the normal takes place with surprising rapidity. One may be called to see a patient at midnight and have to exercise all possible skill to afford her any relief; next morning one may learn that she has gone motoring, perhaps even driving herself.

There are compensations in everything. Most of these patients are blessed with wonderfully pleasant dispositions which stand them in good stead.

The neurotic lady of the variety portrayed in *The Mollusc* has no patience with the girl who suffers from asthma because the latter turns up at a dance looking the picture of health a few days after she had been said to have had a really bad attack of her complaint.

THE SPUTUM

The sputum that is coughed up in an acute paroxysm of asthma differs from the sputum in any other complaint. Similar contents are found in some cases of bronchitis, but there is probably an underlying basis of asthma.

The presence of Curschmann's spirals, Charcot-Leyden crystals, and eosinophil cells, pleasant mouth-filling terms, summed up all the knowledge of asthma with which many of us entered the examination room. Even to-day little is known as to how and why they are formed, or their biological significance in asthma.

When the patient brings up the first tiny pledget of sputum, he knows the paroxysm is passing its height. A number of short hoarse coughs, a long inspiration, and another series of coughs will produce a few small pearly globules of mucus that resemble grains of cooked tapioca. Later the sputum becomes more abundant, and a cupful may be quickly coughed up. This has the appearance of clear white of egg in colour and consistency. It is thick and tenacious, with froth on the surface.

Curschmann's spirals are to be found in the first sputum that is brought up. These are tightly coiled casts of the bronchioles. Teased out on a glass plate they may be a few centimetres long, but rarely more than five. There is a central line round which the spiral is formed. They consist of mucus with a few leucocytes and eosinophils. In places there may be a tiny bubble of air enclosed during the formation of the spiral. Considerable doubt exists as to how these casts acquire their spiral form. It is suggested that this effect is due to the rotary movement of the cilia lining the bronchioles, or to alternate lengthening and shortening of the tube into a corkscrew shape. It is more likely, I think, that they are given the twist after formation and during their expulsion from the bronchioles. One knows the spiral movement of water running out of the morning bath, clockwise in this country, and I believe anti-clockwise in the antipodes!

The Charcot-Leyden crystals, previously thought to be colourless octohedra, are now known to be hexagonal in cross-section. They are more easily found in specimens that have been coughed up some hours previously than in fresh specimens. They are thought to be made of tyrosine, and like the eosinophils they are present in patients afflicted with animal parasites, and may be found in the fæces.

Eosinophil Cells are found in the asthmatic sputum and have some considerable diagnostic value when found in this situation. The presumption is that the case is one of asthma, but in my opinion not necessarily allergic, that is to say, from a patient sensitive to some foreign protein. They are found in similar numbers in an infected appendix. In one case in which there was an eosinophilia of 53 per cent, the patient's asthma appeared to be of very typical microbic nature, with a patch of chronic bronchitis in the

lung, and it was cured by a vaccine. In such a case four or five of these beautiful leucocytes may be seen in each field of a Leishman stained film, large to a 'ripe' size, the protoplasm plentifully dotted with brilliant red granules and the nucleus a deep purple red.

Cowie and Jimenez[1] think that an eosinophil count of 25 per cent in a nasal smear signifies a sensitized individual. They have noted further that the eosinophils disappear during infection with a cold. They are very easily found and counted, but no great relationship between their number and the asthmatic symptoms has been noted.

Present in practically all normal bloods, their presence in a differential white count in greater number than 4 per cent constitutes an eosinophilia. At one time I used to count every blood, but they did not appear to be constant in any one type of asthma. Counts of 10 to 15 per cent are common—really high counts are very rare. Excess of eosinophils in the blood is in no way pathognomonic; they are found in a number of other complaints. High counts have been noted in all the allergic complaints: in asthma and hay fever, in urticarial wheals and bullæ of a great many skin diseases, in mucous colitis and pellagra, in epilepsy and hemicrania.

Spangler[2] conducted a differential white count on 100 patients with a positive Wassermann and 100 normal people. Of the syphilitic cases 40 per cent had an eosinophilia of 5 to 10 per cent, and only 4 per cent of the normal cases counted from 5 to 6 per cent of eosinophils. Excess may be found after an injection of tuberculin and in tetany. An eosinophilia appears to be in some way a response to the injection of a foreign protein, but is perhaps more probably a chemiotactic phenomenon associated with the local production of histamine.

In experimental anaphylaxis, eosinophilia can only be demonstrated during the stage of anti-anaphylaxis, according to Peskin and Messer.[3]

When a new food is added to a child's diet Berger[4] found that a temporary eosinophilia occurred which disappeared as the child became accustomed to the new food.

Van Leeuwen and Nickerk[5] found no difference in the eosinophil counts while patients were asthma-free in dust-free chambers, nor does the size of the counts agree in any

way with the severity of the attacks. Eosinophilia is decreased by fasting for 48 hours, by an acute infection, or by the injection of sulphur.

Peskin and Messer agree that relief of allergic symptoms in man does not appear to be followed by changes in the eosinophil count. Crotalin, a venom poison, raises the eosinophil count, but during acute fevers it has no such effect.

Another group of diseases in which eosinophilia is notably present is that comprising the infections with animal parasites—hydatids, intestinal worms, and trichinosis.

Kilduffe[6] states that the presence of an eosinophilia may be of diagnostic assistance in outbreaks of trichinosis. No deductions of any certainty can be made from these various circumstances, except that an eosinophilia appears to have some relationship to the entrance into the body of foreign proteins.

A very interesting article by Peyre and Manuel[7] seeks to show how the eosinophil is formed, and to give a reason for its presence. In shed blood they will form from other leucocytes, given any condition that leads to an increased acidity of the blood. Unfortunately these writers give no figures, no exact *p*H's, and no protocols of any of their work, but the main argument is as follows :—

Liebreicht[8] in 1913 set out to demonstrate the change of neutrophil white cells to eosinophils. Freshly shed blood is citrated sufficiently to hinder coagulation and render it incomplete. This engenders the production from the leucocytes of a substance that is the forerunner of Charcot-Leyden crystals and the eosinophil granules. From the blood of a chronic eczema and from that of a patient with a primary chancre, beautiful examples of eosinophil cells can be produced. The simplest way is to let the blood age. Another method is to allow the blood to continue for some time in a venous stasis before withdrawal, when waste products will accumulate, notably CO_2. If the citrated blood is centrifugalized after an interval of several hours, a gelatinous layer of white cells forms below the plasma, consisting largely of eosinophil cells and Charcot-Leyden crystals. They appear after coagulation, not in virtue of the fibrogen, but from ageing. They will also occur in serum, the clot being removed by spinning and again after ageing.

In 1911 Achard produced eosinophil cells from the leucocytes in ascitic fluid by diluting it with water. In cover-slide experiments remarkable granular transformation takes place, but not the production of eosinophil cells, especially if weak acid is added to one corner. In all these cases—ageing, dilution, venous stasis, and anaphylactic shock—there is a diminution of the alkalinity of the blood.

Peyre and Manuel suggest that there is in serum and cells a lipoprotein which undergoes a rupture of its equilibrium, when it crystallizes in round or oblong masses, being adsorbed to the granules. By this lipoid nature the granules are then able to fix toxic heterogenous proteins introduced by injection or from faulty digestion. They constitute a kind of buffer system tending to prevent alteration in the *p*H of the blood by their crystallization. Evidence of these two assertions seems to exist.

Weinberg[9] has shown that the hydatid antigen is completely adsorbed by eosinophil particles. The liquid remaining is unable to give the reaction of the deviation of complement, but if the granules are washed it is possible to recover the antigen, which will then play the role of antigen correctly. Hajos[10] has shown that the multiplication of eosinophil cells and the formation of antibodies goes hand in hand. The formation of eosinophils, then, seems to depend upon physical changes in these complex colloidal states. Further work on this subject should be of the greatest interest, and the action of histamine on the formation of eosinophils should be tried out.

Aubertin and Giroux[11] published two extraordinary cases, in which leucocytosis or a total white count of 100,000 to 200,000 occurred, no less than 70 to 90 per cent of these being eosinophils. The *p*H of such bloods would be interesting in confirming much of this work, as would information regarding the sensitization of such individuals. Of the close connexion between the eosinophil cells and the Charcot-Leyden crystals there would seem to be no doubt.

CLINICAL TYPES OF ASTHMA AND THEIR SYMPTOMS

I have at times and in former articles described no less than seventeen different types of asthma. Many of these were merely subdivisions of the three main types as we now

recognize them, or depended upon the prominence of some particular symptoms, as 'the menstrual type', 'the thin type', or 'the type with a high blood-pressure'.

The subdivisions have now been gathered up again into their respective main types, while the symptoms, though mentioned throughout the book, cease any longer to claim a specific type nomenclature. The only 'type' that it is difficult to absorb into one of the three main types emphasized in the present edition, and which cannot be simply regarded as a symptom type, is 'the colloidoclasic type'.

Probably dependent upon endocrine imbalance, the symptoms are so constant and peculiar to the type as to merit some special mention. The term 'colloidoclasic' is of French origin, and refers to a pathology in which the colloidal particles of the blood are supposed to play the important role. I neither support this supposition, nor do I know of any evidence which would do so; the fact simply remains that here is this particular type.

These patients are always ladies of the menstrual age, of a plumpness that some might term fat, or more politely, as my brother Men of Kent would say, " not as you might call fat but middlin' comfortable like ". They are blessed with beautiful skins without hair or blemish. They are cursed with a proclivity for sneezing fits, urticaria, and asthma, and not unusually all three. They complain of a blown-up feeling after meals. Their menstrual history is one of pain and scanty flow. They thrive on intravenous injections of collosol manganese.

Of the three main types—the allergic, the microbic, and the mixed—there is little to distinguish the first and second in the symptoms seen in any one attack. The term 'dry spasmodic asthma' perhaps fits most closely the allergic type, at any rate in its early stages, bronchial asthma denoting rather the infective type, especially those cases in which there is an infection present in the lungs. For the rest, diagnosis between the allergic and microbic types depends more upon the history of the case, and alternatively upon the signs of infection, than upon the features seen in any one paroxysm. The third or mixed type is commonest in later years. Included in this type are the aspirin-sensitive cases, distinguished by the signs, symptoms, and history particular to them, as described in Chapter XVIII.

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CHAPTER VII

CONDITIONS BETWEEN THE ATTACKS

GENERAL BUILD AND FACIES OF THE ASTHMATIC

IN a collection of normal people there is no distinctive peculiarity about any one of them suggesting that he rather than another might become an asthmatic. Neither on the other hand is there any known feature indicating immunity to asthma; no guarantee can be given that any one of us may not develop the disease. Therefore every characteristic by which we recognize the asthmatic results from the asthma itself, or is intimately connected with the complaint.

We may divide the asthmatics who are met with in the street—that is, those who are not confined to their rooms with the acute spasm already described—into three classes. First there are those who fail to show anything abnormal, their bouts of asthma leaving no trace behind when once the paroxysm has passed. Next we have those in whom the asthma has been of such long standing, especially during childhood, that they have the typical asthmatic deformities stamped indelibly upon them. Lastly there are patients in all conditions of distress from the actual asthmatic spasms. It may be well to discuss the last class first. The symptoms described in the previous chapter are those of an acute paroxysm of asthma of such severity that the patient would be quite unable to get about.

Numbers of asthmatics, however, not only do get about, but conduct a considerable amount of business while suffering from asthma which is only a degree less severe.

Spasm of the bronchial muscle in these chronic cases is nearly always present to a greater or less degree. The patient is always short of breath, even wheezing as he passes us. The slightest exertion or a fit of coughing or laughing will produce a temporary paroxysm. We notice that he walks slowly and deliberately, carefully avoiding undue exertion. He is round-backed, and his raised shoulders and chest make

the neck appear shortened. The head is sunk between the raised shoulders. The whole chest is large because the emphysematous condition of the lungs keeps it in a considerable state of expansion.

Though asthma may lead to the patient's becoming round-backed and developing a stoop, it does little to stop a child from growing in height, though he may grow misshapen.

Many patients are thin, and some are anæmic. The cheeks and nose may be red, purple, or blue, depending on the severity of the anoxæmia and consequent cyanosis of the blood in the numerous congeries of small venules that crowd their features. Many other patients show a peculiar duskiness of the face, and have rather bulging watery eyes. The blueness of the cheeks may also be paralleled in the hands; and to quote Salter, " they are cold, blue, thin, and bony ". From the stooping attitude and discoloured face, patients often appear older than their actual age; boys may look like little old men.

As in coughing, so in speaking, the asthmatic has two obstructions to the outlet of air—at the larynx and in the bronchioles. The latter impediment prevents any powerful use of the voice. We may frequently note from the voice that the patient suffers from nasal obstruction. At other times the larynx itself may become affected, apart from spasmodic muscular contraction, with the same catarrhal or congestive condition that exists in the other air-passages. Sometimes it is even affected by the protein to which the patient is sensitive. Occasionally a patient will lose his voice each summer for the duration of the pollen season, and will give reactions to timothy grass when tested. All these circumstance weaken the voice and tend to make it husky.

The typical asthmatic patient, then, will walk slowly and with a stoop. He will also be large-chested and round-shouldered. His face will bear a rather anxious expression, and the cheeks and lips may be in any state of cyanosis. His breathing may be somewhat laboured, and even audible. All these symptoms will be aggravated by a chronic bronchitis and a weakened heart, sequelæ that so commonly accompany the bronchial spasm.

Though these deformities, the characteristic stoop and facies of asthma, may have remained constant for years,

they will disappear with remarkable rapidity when the patient is receiving effective treatment.

Case 14.—A girl came to me looking well over 30, round-backed, and her shoulders hunched up; her face was dusky, with bluish venules on her cheeks and nose; her lips also were somewhat cyanotic; she spoke in a short, jerky way, coughed occasionally, and was very short-winded. She had had asthma continuously since she was a year old. She was sensitive to milk.

She came to see me six months after treatment, looking only her proper age, 25. Her complexion was quite clear; her cheeks and nose merely showed some brick-red discoloration such as might be expected in one living in the country. Her shoulders were level, her clavicles horizontal, her stoop was gone. She had been entirely free from asthma for six months. As this was the first experience of the kind she had ever known, she was looking at life "through very rose-coloured spectacles".

In spite of their continuous troubles, these patients have wonderfully bright and pleasant dispositions. Their joviality is very marked, and I wish especially to make a point of this. It seems that there must be some definite biochemical reason connected with the asthma to account for it. What a discovery it would be if we could find the factor that causes this pleasant symptom and dispense it wholesale to the world. An angry temperament is probably caused by some hormone—why should not jocularity be so too?

Leaving the individuals who have some degree of asthma actually present, we may pass to those who, though free from the complaint, still bear its imprint in its typical deformities.

TYPICAL ASTHMATIC DEFORMITIES

There are three different kinds of asthmatic deformity, depending upon the age of the patient at which the asthmatic attacks commenced (*Figs.* 5–7): (1) That of infancy; (2) That of childhood; (3) That of the grown adult. In each case the deformity is but a permanent picture of the position the chest wall assumes during an acute paroxysm at that age. As air cannot enter the lungs, because of the contraction of the bronchial muscle, a negative pressure arises and the chest wall gives at its weakest spot.

1. In Infancy.—In infants the bones and cartilages are relatively soft and pliable. During an attack of asthma, the 'give' takes place at the cartilages on each side of the

sternum. This bone is sucked inwards and may remain a deep concavity throughout life.

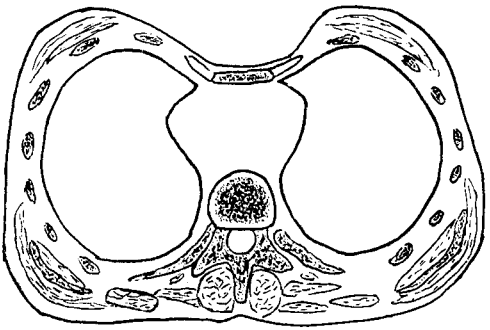

Fig. 5.—Asthmatic deformity of the chest in infancy, showing the sternal concavity.

2. In Childhood.—In the childhood deformity a condition of pigeon-chest results. The bony and cartilaginous cage is hardening, but not sufficiently to withstand the pull of

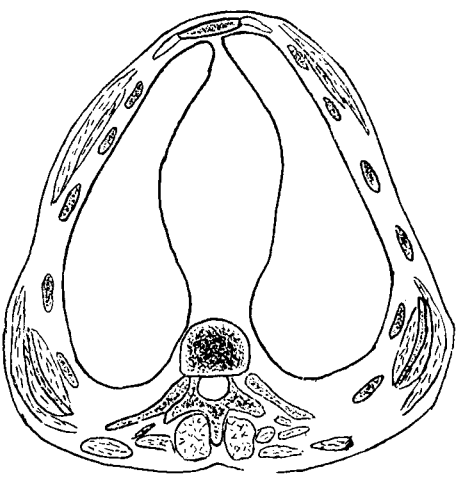

Fig. 6.—Pigeon-breast deformity of the chest in childhood.

the diaphragm. The lower edge of the fixed ribs is drawn in and the chest wall buckles, being pulled in at the sides and pointing forwards in front. The sternum protrudes, and the buckling often has the effect of tilting the sternum

laterally, thus making the costal cartilages of one side very prominent, to be felt like a row of sharp points beside it. The xiphoid appendage falls back at a sharp angle from the sternum. The side-to-side diameter of the chest becomes less than the anteroposterior diameter. The shoulders, which are raised during the spasm, do not necessarily maintain that position after the paroxysm has passed; so that the clavicles may be quite horizontal.

A considerable amount of kyphosis will, however, remain permanently. The scapulæ do not protrude like immature wings from the back of the chest, but move round to the sides of the chest wall.

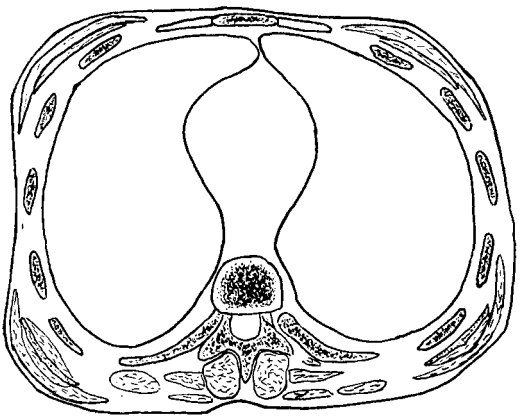

Fig. 7.—Barrel-shaped emphysematous deformity of the chest in the adult.

3. In the Adult.—The third group of deformities occurs in adult life. The bony cage is fully hardened and worked by strong muscles, the result being the formation of the barrel-shaped chest and the production of emphysema.

Emphysema of the lung is the distension of the air-passages and alveoli distal to the bronchioles. This is caused in exactly the same way as the other forms. We have here the same pull of the respiratory muscles tending to expand the chest and admit more air against the contraction of the bronchial muscles. In the adult the thoracic cage consists of fully ossified bone and strong cartilage pulled upon by powerful muscles. As in every similar pathological condition where a deadlock of this nature occurs, the structures give

way at the weakest point. This point is now shifted from the pliable cartilages of the infant to the very air-cells themselves. Applying the words of MacCallum[1] to the particular instance in hand we may paraphrase his description as follows :—

Extensive distension of the alveoli may be produced rapidly in the lung, when the tissue of the alveolar walls is quite normal, so that if the air is then allowed to escape, the alveoli at once return to the normal size, and their stretched walls to the normal thickness. In the first place, then, if there is a minor degree of obstruction to the outflow of the air, there will be a progressive distension by the air entering on inspiration, being unable to be completely exhausted before the next inspiration. The capillaries of the wall will then be widened so that the nutrition of the wall may be kept up. When, however, there is a much greater distension as a result of a severe obstruction consequent on the marked spasm of the bronchial muscle in an asthmatic attack, then the greater distension in the air-cells narrows and compresses the capillary walls, so that the blood passes with difficulty or not at all. Nutritive changes possibly dependent on this great stretching and the impaired blood-supply weaken the elastic alveolar wall after a time, so that it may remain permanently stretched, or, after the breaking of its elastic fibres, may give way at one or more points. Then the margins about the hole retract and two alveoli are thrown into one.

The return of the air-sacs to their normal size from this state of distension in these cases will depend on the relaxation of the bronchial spasm allowing the lungs to collapse by the recoil of their elastic trabeculæ. Should these elastic fibres become torn or permanently injured a complete return of the lungs to the normal becomes impossible, and a permanently inflated condition of the air-sacs results, which is emphysema.

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CHAPTER VIII

PATHOLOGY, DIAGNOSIS, PROGNOSIS, AND PROPHYLAXIS

PATHOLOGY

THE changes found in the lungs of persons who have died from asthma depend rather upon the coexisting complications than upon the violence of the asthma itself in the last and fatal paroxysm.

When the asthma has been of short duration and the patient has died a sudden death from some other cause, as by accident, nothing abnormal will be found in the chest. Even when death occurs during a condition of status asthmaticus, or from anaphylaxis, as from an injection of horse serum in one hypersensitive to it, there will be hardly any pathological change beyond signs of inflammation and the presence of secretion in the bronchial tubes, eosinophil cells, and mucus.

When the patient has been asthmatic over a period of years, the bronchial muscle may show some hypertrophy and the mucous membranes evidence of bronchitis, in accordance with the clinical symptoms and the course of the complaint before death. The spasm of the bronchial muscle and other changes that take place during the asthmatic paroxysm disappear when death takes place, while the results of the asthma and the complications it has caused remain. A deformed chest, the presence of emphysema and bronchitis in the lung, and a ruined heart will show the trail of havoc that the bronchial spasm and asthma have left behind them. Evidence of anomalies of the nasal mucous membrane and sinusitis may be found. Various stages of chronic pulmonary fibrosis may be discovered, as in miner's asthma.

Death from uncomplicated asthma is naturally rare. Huber and Koessler[1] quoted fifteen cases in 1922. Two are of special interest, because the cause of death of one asthmatic was "suicide by drowning", and the other had

died from the intravenous injection of one minim of horse serum. The condition of the lungs could therefore be examined uncomplicated by the effects of the chronic bronchitis, emphysema, and heart failure that usually terminate the asthmatic's life. By an ingenious method of comparative measurements of a large number of bronchi in each case, the writers arrived at the conclusion that hypertrophy of the walls of the bronchi and the bronchial muscle and of the glandular elements may each or all of them be found, corresponding to the clinical type of the asthma.

Lamson and Butt[2] give a very full description of two cases of asthma examined by them and the collected records up to date. Their findings lend confirmation to what has already been said.

In short, pure asthma, no matter how severe the spasm, leaves little to be found post mortem, and no evidence upon which the condition can be diagnosed, or by which, in the absence of a clinical history, the patient can be said to have died from asthma.

DIAGNOSIS

Although asthma is not a disease, but only a symptom, the actual paroxysm is sufficiently understood to enable us to recognize the asthmatic syndrome without much difficulty in the majority of cases.

The chief points which indicate that a dyspnœa is true asthma are the spasmodic nature of the complaint, the complete return of the patient to normal during the intervals, the periodic return of the spasms—often at very regular times and intervals, especially in the night and early morning—the slow, laboured breathing, the obvious difficulty in forcing the air in and out of the chest, and the orthopnœa. The general physiognomy of the patient and the presence of the typical asthmatic deformity may assist us. The presence of an eosinophilia in the sputum or blood during an attack, and the characteristic elements which are found in the asthmatic sputum, will help to confirm a diagnosis of asthma in those cases where a doubt exists.

"Asthma is a form of dyspnœa in which the calibre of the bronchi and bronchioles is diminished, either by a contraction of the bronchial muscle, acting alone, or together with turgescence of the mucous membrane and the formation of

secretions into the lumen." The main difficulties, therefore, will be to distinguish true asthma :—

1. From dyspnœa due to other conditions which cause an obstruction to the free passage of air from the outside atmosphere to the alveoli.

2. From dyspnœa caused by non-obstructive conditions.

3. Where it exists together with a dyspnœa due to some other cause.

1. Dyspnœa due to other Obstructive Conditions.—A variety of influences outside the lung may cause obstruction to the respiration. Nasal deformities, enlarged tonsils, and adenoids may cause a deficient aeration, a mild bronchitis, a disturbed sleep, snoring, and a catch in the breath, which may lead a mother to think that her child has asthma. Laryngismus stridulus in the infant is probably a very near relative of asthma, and should be treated in exactly the same way as that complaint, together with any tetanic or rachitic elements.

Clarke[3] stresses the importance of suspecting some allergic cause in children who suffer from bronchitis and recurrent colds. Such advice can be extended to all forms of paroxysmal rhinitis at all ages.

Other forms of laryngeal obstruction of various kinds may tend to simulate asthma, such as new growths or syphilitic strictures. The papillomatous condition sometimes found in children is that which may most easily be mistaken for asthma. Pressure on the trachea or bronchi of an enlarged thyroid or thymus gland, of mediastinal growths and glands or aneurysms, must all be considered in cases where the diagnosis seems to be in any doubt.

In many of these conditions there will be some alteration in the voice, a loss of weight, and a progression in the symptoms, rather than a simple recurrence of the paroxysms, that will arouse suspicion. An X-ray examination must always be carried out in doubtful cases.

The stridor to be heard in most of these forms of obstruction is inspiratory in nature, rather than expiratory as in asthma. It gains its crescendo on auscultation over the trachea and is of the same timbre all over the chest, whereas the asthmatic wheeze is often localized and heard more distinctly in different parts of the lung.

A correct diagnosis of the cause of the stridor may present

many difficulties, but asthma can often be ruled out the moment the stethoscope is applied to the chest. Occasionally, having relieved a patient of his asthma, it has been one's experience to have a friend sent along in the hope of similar assistance, but one who is found upon examination to be suffering from tuberculosis of the lung with no suggestion of asthma. No question of diagnosis arises in these cases; the home-made diagnosis is wrong, often very tragically wrong, and the case is transferred elsewhere.

Foreign bodies present unusual difficulties in diagnosis, especially in the absence of a history and without radiographic assistance. Help may be obtained by bronchoscopy as advised by Clerf.[4] The dyspnœa from an aneurysm may be of long standing, as noted by Ravina[5] in a case of six years' duration.

2. Dyspnœa due to Non-obstructive Conditions.—This class includes all those conditions which cause symptoms like those of asthma. Chief amongst them are various cardiac affections causing the patients to be short of breath. Almost any failure of the heart to function fully and properly will give rise to conditions that may be mistaken for asthma. The dyspnœa, the cyanosis, and the bronchitis that very often accompany any backward pressure in the lungs make a picture which is very similar to that of asthma. A further similarity is to be found in the disturbed nights from which so many heart cases suffer. As is the case with asthmatic patients, they lie propped up in bed with many pillows behind them, and having dozed off they wake again in a short time with palpitations and dyspnœa.

In patients suffering from cardiac dyspnœa, which is sometimes called cardiac asthma, there is no difficulty in getting the air into the lungs; it is an air-hunger with rapid breathing rather than an obstruction to respiration that troubles them. The drum-like expanded chest and laboured breathing will point to true asthma, the rapid gasping breath to cardiac trouble. Often there is some anginal pain in cardiac dyspnœa, and between the attacks the heart does not settle down as it does in asthma. The presence of an eosinophilia may be sought for as an important diagnostic point. Many of these cardiac conditions are distinguished easily enough from asthma, but we must remember that an exactly similar state may eventually

be reached, beginning with pure asthma, as the following case shows :—

Case 15.—A stout married lady of 55 had attacks of asthma which used to awaken her each morning between two and five. She was quite exhausted after walking up a flight of stairs. In the street she walked very slowly, panted a great deal, and held on to the railings occasionally. She was very cyanosed, complained of being troubled with much wind in the stomach, and was often sick. Her systolic blood-pressure was 200 mm. of mercury. Her heart beat irregularly, it was somewhat enlarged, and she had a very sharp pain in the left breast and down the arm whenever she took any exercise. There was no albumin present. One might consider this lady a typical case of cardiac asthma. However, she had had hay fever at the age of 17, and asthma ever since for thirty-eight years, during the last fifteen of which she had suffered severely. She gave no skin reactions.

She commenced a very strict diet, the barest amount of food on which she could exist. She was given a mixture of valerian and bromide and iodide of potassium, and had a course of mixed coliform vaccine made from her own intestinal flora. This was continued for six months.

I first saw her in an August ; by November her asthma had practically left her, and one year later she had been entirely free for ten months. She was able to go about anywhere, and had just returned from a tour in Germany. Her blood-pressure was still remarkably high, but she did not seem to suffer any inconvenience from it.

Uræmia and its convulsive interference with breathing is more easily distinguished than are the foregoing cardiac conditions. The patient is ill, his intelligence is dulled, he presents a totally different picture from that of even the severest form of asthma. Examination of the urine, the blood-pressure, and the condition of the heart and retinæ will leave little doubt as to the diagnosis.

3. The Recognition of Asthma when it Exists together with Dyspnoea of Other Origin.—This is largely a matter of the care with which we examine every case and the perfection of our routine. A most important point is to recognize the true asthmatic basis of many of the chest troubles and much of the bronchitis of children.

Although the combination is rare, tuberculosis may coexist with asthma, a fact one should always bear in mind. Though the presence of both complaints necessarily makes the general prognosis and risk of life much worse, there should be no hesitation in treating the two complaints simultaneously. If one can give the patient relief from the asthma by

removing his feather pillows, much help will be afforded to the treatment of his tuberculosis.

PROGNOSIS

It has been said, "once an asthmatic, always an asthmatic", and when we consider that asthma is merely the unruly contraction of a muscle abundantly present in every one's chest there is little doubt that there is much truth in the saying, and no guarantee that the best of us may not one day develop the complaint.

Modern methods have helped remarkably by virtue of making it possible to discover the cause of a patient's asthma. Having found the cause in any case, even of long standing, patients are often quite easily cured by removing the cause, by its avoidance, or by methods of desensitization. Nevertheless, the patient may remain free from asthma only as long as he observes a few rules and undergoes a few privations. The basic condition may still be present, and the symptoms will recur if the patient fails to observe the specific restrictions necessary to his case.

The list of possible causes of asthma is constantly increasing. Of these house-dust, which was hardly mentioned in the first edition, has sprung to enormous importance. But even when provided with potent stock solutions, it pays to make prolonged search for peculiar dusts in the patient's surroundings, amongst the hidden contents in the stuffing of furniture, and for the presence of dry-rot, patches of mould, and fungi in and under the house.

The prognosis in the case of asthma has improved enormously, and may be expected to improve still further when the differential sedimentation test becomes more widely used, and the treatment of bacterial types of asthma is as well understood as the treatment of the allergic group. Progress is naturally slow, when even to-day one sees cases of ten or more years' standing on which none of the modern methods of treatment, such as the dermal tests, have been carried out.

In an article on the prognosis in asthma, Witts[6] found that 20 per cent were completely relieved for some years, 15 to 20 per cent were absolutely resistant, and the remainder were more or less improved. Since then I should expect these figures to be slightly better, and recently, with the knowledge that even the aspirin-sensitive type is amenable

to bacterial vaccines, one may reasonably hope for a further percentage of improvement.

Prognosis is of course adversely affected by the complication of bronchitis and emphysema. The structural changes may be so pronounced and the lungs so severely injured that little hope of a return to the normal can be entertained. I would emphasize the fact that it is quite impossible to give a correct prognosis until the patient has been through the whole routine examination and the effect of several lines of treatment has been ascertained. One case of asthma, to all appearances perfectly straightforward, may utterly defeat one; another with continuous asthma of many years' standing may respond to treatment in an astonishing way, and return a year later entirely cured. No patient is either too old or has had asthma too long to prevent his receiving benefit from treatment carried out on present-day lines. I should say 90 per cent are improved, while a great proportion lose their asthma entirely.

The prognosis with regard to longevity is notoriously good. " Oh well, you never die from asthma " is a pleasantry patients get a little tired of hearing from their acquaintances, who have no idea of the distress caused by the nightly paroxysms. Death in the acute spasm is very unusual, but it does occur, while as a precursor of bronchitis, emphysema, and a failing heart, asthma claims a considerable number of victims.

PROPHYLAXIS

With regard to children of asthmatic parentage, much valuable advice can be given in preventing them from developing a sensitization to hair, feathers, foods, or pollens. To begin with, the nursing mother should be careful as to her diet. Undue indulgence in any one article, such as fish, fruits, vegetables, or eggs, should be avoided. Proteins taken by the mother can pass into the milk and thus sensitize the infant, quite apart from any sensitization to the specific proteins of the mother's milk. Similarly, honey spread on a dummy teat, or albumen-water, or patent foods containing much wheat or oats, should be avoided. After the infant is weaned, no food should be given that is not included as a part of its regular everyday diet. Sensitization most easily occurs with foods that are taken in large amounts at one time and then not touched for a considerable period.

Little children should not be encouraged to run about amongst high grass when it is pollinating. Their noses are at about the same level as the tall timothy grass and the meadow foxtail. It is better that cats and dogs should not be kept at all, but if they are, it should be out-of-doors only. Feather pillows, eiderdowns, etc., should give place to those made of some vegetable down. The tick coverings and the pillow-slips should be substantial.

So many cases of asthma date their commencement from an attack of whooping-cough, bronchitis, influenza, or pneumonia that we should be particularly careful to make sure that not only have the gross elements of these complaints subsided, but that the causal bacteria and secondary infections also have completely disappeared. Fortunately this bronchial type of asthma is more easily cured by autogenous vaccines than many other varieties. But the earlier it is dealt with the better, and therefore, best of all, before the asthma even starts.

The fact that cases of complete colloidoclasic upset (*see* p. 80) have followed injections of horse serum should make us chary of using these antisera unless there is a real necessity for doing so. The heroic doses in which vaccines are sometimes given should be avoided whenever possible, because we know so little of what really happens in these parenteral injections of foreign proteins. Even one case in which urticaria, sickness, a morning rhinorrhœa, and finally asthma follow an injection of antidiphtheritic serum is sufficient to demonstrate our ignorance on the subject.

Glaser and Landau[7] confirm much of this advice, and make the further suggestion that marriage between members of allergic families should not take place—may we add, where it is possible to prevent it.

Secondary prophylaxis, the prevention of the paroxysms, forms the fundamental treatment of asthma, and its exposition is the main object of this book.

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CHAPTER IX

EXAMINATION OF A CASE OF ASTHMA

APART from a very occasional case of acute pulmonary tuberculosis, or perhaps an aneurysm or papilloma in the trachea, the cases which are sent to one are all true asthma and already correctly diagnosed. The detailed examination of a case of asthma is therefore directly aimed at determining the line of treatment.

The examination consists of a series of questions to be put to the patient or his relatives, of the application of the dermal tests, of a physical examination, of blood tests and bacteriological investigations, all aiming at discovering the cause of the asthma.

On a case-sheet for each patient all pertinent matters are duly recorded. Before considering the manner of examining a case in detail, the accumulated evidence derived from 3000 cases allows certain facts to be recognized in the age and sex incidence of asthma that are of value in setting out to treat the condition. Such a question as " Do women tend to develop asthma at the menopause ? " is answered most emphatically by these figures, and in this particular instance in the negative.

SEX AND AGE INCIDENCE, AND SENSITIVITY DATA

Of the sexes in this series, I have seen 1561 males and 1439 female patients, that is, about 8 per cent more of the former. This slight preponderance of males is in agreement with the findings of others. (Rackemann and Walker.)

Patients attend for treatment at all ages, but in order to see whether there has been any change in the average age of patients and whether they are coming for advice earlier, I have worked out the average age of the patients in three separate thousands.

For the first thousand, the average age of the patients as they came to me was 34·5 ; for the second thousand 34·4 ; and for the third thousand 34·2. We may regard,

therefore, as tentatively proved, the hypothesis that patients are coming to see one at an earlier age!

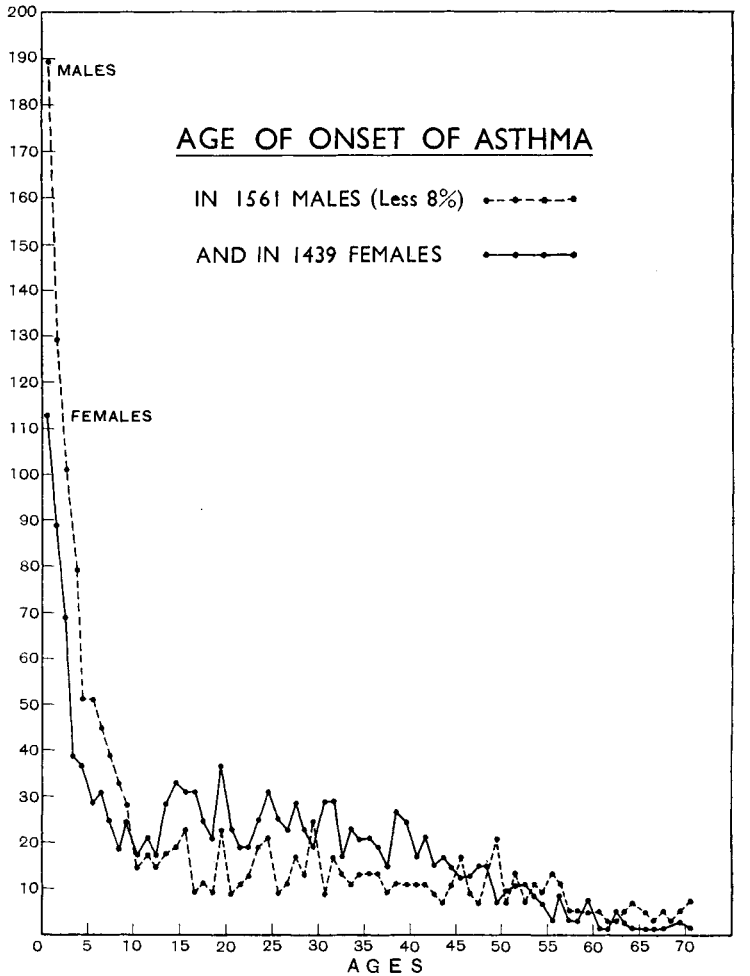

Fig. 8.—Graph showing age of onset in males and females.

These figures are, however, of little importance—the point of greater value is: At what age did the patients commence to have asthma? The graph of *Fig.* 8 answers this question. In it 1439 females are plotted out (the continuous line), and 1561 males (the dotted line), but the latter figures have all

been reduced in order that the numbers of the sexes shall be equal and exactly comparable. There will be noted in both sexes the enormous preponderance of patients who

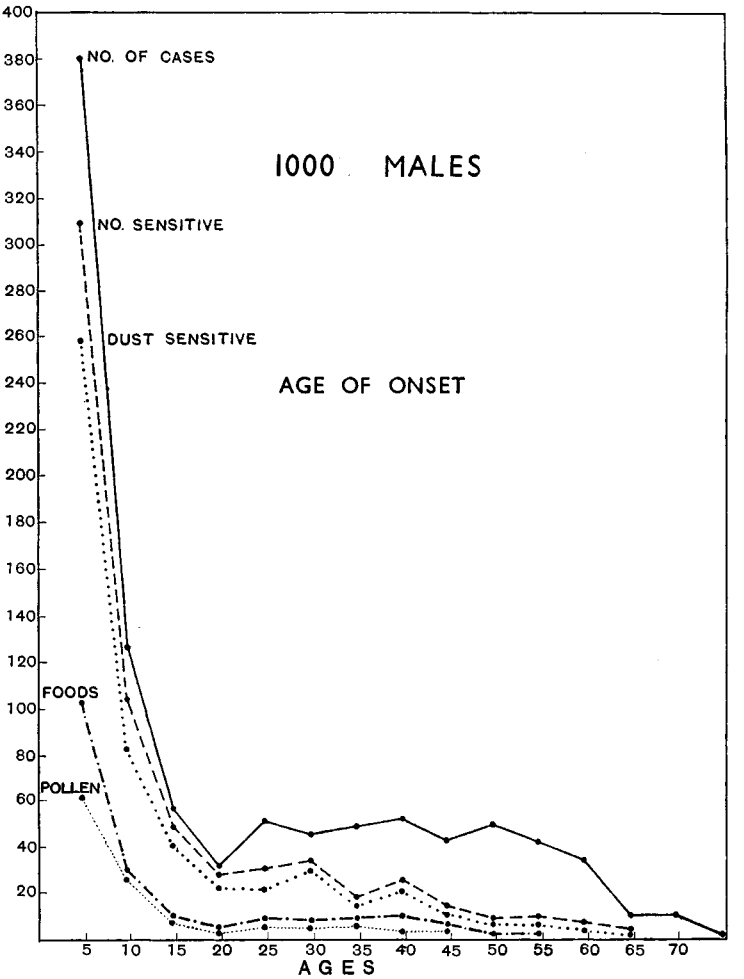

Fig. 9.—Graph comparing age of onset and causal factors in males only.

commence their asthma in the first ten years of life, and that up to this age the boys far outnumber the girls. From the ages of 12 to 45—that is, throughout the whole duration of menstrual life—the female incidence far exceeds that of the males.

On examining the graphs in *Figs.* 9 and 10 it will be seen that very little of the excess is due to sensitization. It would therefore seem as though some aetiological factor intimately

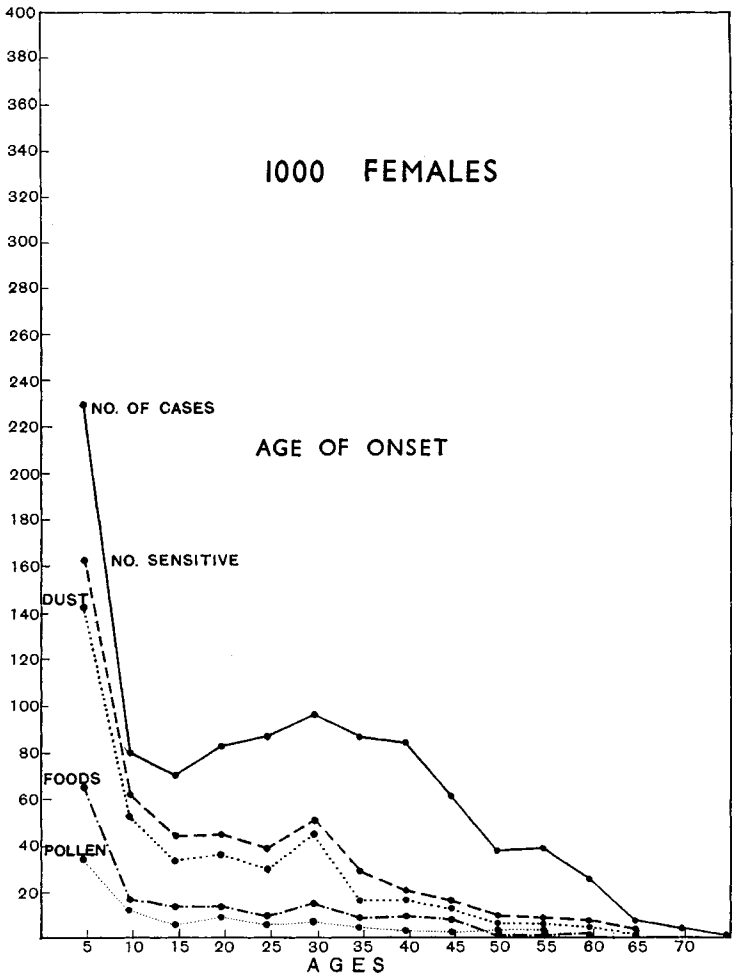

Fig. 10.—Graph comparing age of onset and causal factors in females only.

connected with the biochemistry of menstruation is responsible for much of the asthma that occurs in women during this child-bearing age. From 45 onwards the frequency with which asthma commences slowly decreases in the two sexes.

The average age at the onset of the asthma was 23·7 in the females and 19 in the males. On this reckoning, therefore, patients have asthma for some twelve years before seeking treatment, thereby very materially hazarding such benefit as modern treatment can offer them.

The whole trend of one's questions to the patient and the other examinations is aimed at discovering the cause of the asthma in the individual patient presented: primarily, to find out if he belongs to the allergic or microbic group, or to a third group which includes the 'aspirin-sensitive' type; and secondly, to discover the actual protein at fault, or the nature of the microbe and its habitat in the patient's body.

The statistical evidence is seen in *Figs.* 9 and 10. In these graphs 1000 cases of each sex are plotted as they occur in each five years of life. Each chart contains five lines across it. The uppermost is the total number of cases commencing during the ages stated beneath the chart. The second line denotes the number of cases in which dermal reactions are obtainable belonging wholly or partly to the allergic group. The space between these first and second lines denotes the number of the non-allergic cases. The third line records the numbers of those sensitive to the air-borne dusts, hairs, feathers, and orris-root; the fourth and fifth lines those sensitive to foods and pollens respectively. Both sexes show a rise in the incidence of sensitization to the air-borne dusts around the age of 30, much of which is due to sensitization to feathers. All five lines touch their highest point in persons still under 10 years of age. The total figures are as follows:—

Of 1000 males—633 were sensitive, 526 to the air-borne dusts, 182 to foods, and 135 to pollens.

Of 1000 females—492 were sensitive, 407 to the air-borne dusts, 162 to foods, and 117 to pollens.

With these data we can now proceed to examine the suppositious case before one.

ROUTINE OF EXAMINATION

My case-sheet consists of a double foolscap sheet, giving four folios of foolscap size. The top of the front sheet is suitably lined to hold the patient's name, age, sex, address, etc. Below this is a row of numbers from 1 to 70. A line

is drawn through this from the age at which the patient commenced to have asthma to the age when seen. This gives a rapid view of the duration of asthma, e.g.,

1 2 3 4 5 ~~6 7 8 9 10 11 12~~ 13 14 . . .

showing that the patient is now 12 years old and commenced asthma at 6.

Clinical History.—Suitable spaces are allowed below in which to write the clinical history of the case ; it should be elicited on the following lines :—

1. *The Personal History of the Patient.*—When and where did the asthma begin ? Why ? Is there any known cause or predisposing complaint, as whooping-cough, to which the patient can attribute his asthma.

Often the history alone may be sufficient to give us a good clue to the cause of the symptoms. More often one is unable to do so until after the dermal reactions have been completed, when the history may fit the protein sensitization exactly.

The following was an interesting history :—

Case 16.—A man, aged 53, had asthma in Australia up to the age of 9, when his father died and they left the estate. It has returned after an interval of forty years, while he has been staying at a hotel in South Kensington. He gave a large positive reaction to parrot-feathers, whereupon we are told that at the patient's house in Australia there were dozens of parrots. He does not think he has been in close contact with one until recently. At the hotel at which he is staying there is a lady who has a pet parrot which she carries about with her into the lounge and other rooms of the hotel.

Much depends upon the age at which the asthma started. The earlier it is, the greater is the likelihood of the patient being allergic. In children there is commonly a history of bronchitis, sneezing turns and recurrent colds before the diagnosis of asthma is made, often by a doctor new to the case, when the child is on holiday.

2. *Other Symptoms of Allergy.*—Questions must be asked about other symptoms of allergy. A history of *infantile eczema* is very common, occurring in 22 per cent of all cases, in 30 per cent of those hypersensitive, and in 35 per cent of those sensitive to foods.

A number of patients have had *urticaria.* Many people have had such an attack once in their lives ; the importance

here is a long continuance of the nettle-rash spaced over a number of years, and especially important is that affecting the lips, as from the taking of some food to which the patient is sensitive. A history of *hay fever* is common, and it may have been the starting-point of a seasonal asthma which has gradually extended for a longer time each year until, stretching on to the following hay fever season, it becomes permanent. Closely allied to this are *sneezing bouts* which are not seasonal, as hay fever. If they are forerunners of an attack of asthma, and especially if accompanied by lacrimation and itching of the eyes, it is certain that the patient is allergic and sensitive to some air-borne irritant. Many women of the menstrual age, who are plump with fine skins that bruise at the slightest touch, form the colloido-clasic type.

3. *Can the Patient take Aspirin?*—The question is one that must always be asked and the answer awaited with some anxiety. If the answer is negative, the patient belongs to the dread aspirin-sensitive type and the correct treatment must be accorded. This type is fully discussed in a further chapter; it will suffice to say here that in the nose of the aspirin-sensitive asthmatic one will usually find polypi.

4. *Nasal Examination.*—Inquiry must be directed to the nose. Does the patient suffer from catarrh? Is there a nasal history? Examination, transillumination, possibly a radiograph, and the assistance of a nasal surgeon may be required.

5. *What is the Nature of the Sputum?*—Is it the typical asthmatic sputum, only in evidence after the attack, or is it bronchitic? Is it green or yellow, and brought up each morning whether the patient has had an asthmatic paroxysm or not?

6. *Is the Patient subject to Colds?*—Firstly, we have to be sure that it is a real cold of the usual fourteen days' duration and not the kind that is more correctly a paroxysmal rhinitis. Another differentiation is between the cold that is caught, and one that may develop at any time when the patient gets chilled. In the first case there is an infection by an organism from an outside source; in the second the microbe is present in a tonsil or infected sinus, and starts activity whenever the patient's resistance becomes lowered.

Having caught a real cold, what is the effect upon the patient? If the infection travels down the trachea to the chest, the asthma will be made worse in those cases in which there is already some infection of the chest—the bronchitic type of asthma; furthermore, an inflammation of the mucous membrane of the respiratory tract will allow a modicum of protein to pass through and cause asthma, which to a healthy mucous membrane would be entirely ineffectual.

A cold therefore greatly increases the effect on the patient of the air-borne proteins. On the other hand, in certain rare instances patients say they are only free from asthma when they catch a cold. Probably the beneficial effect is due to some pyrexia which accompanies their colds, and a few questions may be asked on this score. Has the patient had any complaint that caused a high temperature, and if so, what was the effect?

One of my patients had periods of immunity after each attack of malaria. The beneficial results of a temperature are well known, and the production of a protein shock by an intravenous injection of T.A.B. or coliform organisms is a recognized and valuable method of treatment.

7. *At what Season of the Year is the Asthma Worse?*—Asthma may be simply a sequela of the winter cough. More commonly the spring and the autumn are particularly difficult seasons. Easter with its cold east winds chiefly harms the bronchitic types of asthma. Autumn with its growth of moulds and fungi chiefly affects the allergic types and those sensitive to dust and mould-spores.

8. *What is the Effect on the Patient of a Change of Air?*—In other words, can we obtain any evidence that one particular locality, house, or room is better or worse for the patient? Dozens of cases provide such information.

A cowman said the only time he was free from asthma was when on his week's holiday at the sea; he gave a large reaction to cattle hair.

A man always had asthma while staying at Weston-super-Mare. After giving a large reaction to feathers, he remembered that he always slept on an ancient feather bed when at Weston.

A governess was perfectly well at Brighton but ill directly after moving to an old house in Hawkhurst. She was very sensitive to house-dust.

The history of the case may make us suspicious of some protein sensitization and the dermal reactions may afford the explanation. On occasions when the history gives outstanding evidence that there is a cause of asthma present at one place and absent at another, the offending protein must be sought for with all the acumen possible.

A patient had asthma when he visited a friend's offices in Norfolk, and again when at a farmhouse on a fishing holiday. The friend was a cattle-food miller and the patient was found to be very sensitive to linseed meal. He then remembered dreadful experiences he had undergone when being poulticed in boyhood.

9. *What is the Patient's Occupation?*—A young man started work in a cotton-broker's in Manchester. Handling the cotton samples at once produced attacks of asthma. As he was very well-to-do and never had asthma elsewhere, he entered other employment.

A youth entered his father's business, that of a cattle miller. On certain days he had very severe attacks of asthma. When tested, he gave a very large reaction to beans. His attacks of asthma coincided with those days on which they were milling beans.

Several patients have been furriers and unable to work with specific furs. Wearing apparel may provide the cause of the asthma, as squirrel fur and, in another case, silk.

10. *When do the Attacks Occur?*—Are the paroxysms always confined to one season of the year, to one day of the week, to the day or only the night? Asthma which never disturbs the patient's sleep should make one suspicious, and suggest that we are not dealing with asthma in its truest form. On the other hand, when the patient wakes with asthma or is heard to be wheezing before he wakes, we have a very true form of asthma, and one that is surely beyond the pale of neurotic manifestations.

When the attacks recur each week-end, they commonly fit closely to the week-end type described by Adam of Glasgow. A week of hard manual work changes at midday Saturday to rest with an excess of food and perhaps drink, causing asthma and absence from work on Monday, in every way comparable with the 'Monday morning disease' of horses.

The athletic young man gets married, ceases exercise,

and becomes a devotee of the Sunday joint and Yorkshire pudding, leading to a similar type of asthma. If the asthma appears each week on the same day, some item of the day's routine, such as washing the dog, may be the cause. One patient had an attack each time the child's nurse had a day off. Having washed the child she powdered it profusely. A large reaction to orris-root explained this peculiar sequence.

11. *Are there any Prodromal Symptoms?*—The mother may know an attack is impending by an unusual hunger of the child, or by its becoming distressingly fractious before an attack.

12. *Is the Patient entirely Free in the Intervals?*—An extremely important point is the condition of the patient between the attacks. Is he entirely free from symptoms, or will exercise always produce wheezing? If free from asthma to the extent that he can take hard exercise, the attacks will most likely be due to some purely allergic cause. Incidentally this answers the oft-repeated question as to the heart being 'all right'.

On the other hand, the asthmatic turns may be so severe that the patient calls himself well and free from asthma when gross sounds can still be heard in the chest.

13. *Has the Type Changed during its Existence?*—Commonly an asthma that years ago was 'dry asthma' occurring in sharp spasmodic attacks with long periods of immunity has now become much less severe but far more persistent, a chronic bronchial type, or as we now classify it more accurately, the Group III type of asthma—mixed allergic and microbic.

14. *Menstruation.*—If the patient is a woman, the effect, if any, of menstruation on the asthma must be inquired into. Commonly the patient is worse for a day or two previous to the commencement of each period. Are the periods themselves scanty and painful? Have there been pregnancies, and did the asthma disappear during that time?

It is best to ask leading questions throughout, otherwise one may fail to obtain information of importance, and waste much time that can ill be spared. The patient should be encouraged to elaborate his case during the time that the dermal tests are being applied.

Family History.—The hereditary influence in asthma is very marked, as argued on page 37. In a series of

1000 consecutive cases, 521 gave a family history of asthma or hay fever in their immediate relations. Bray gives a figure that is a good deal higher, but his cases were mostly children.

In this present chapter we are concerned with investigations that will discover the cause of the patient's asthma, whether a sensitization or a microbic factor, or both; on this score the family history is of no practical value. Of 1000 cases sensitive to proteins, 567 gave a family history. Of 1000 cases not sensitive, 422 had a family history of asthma or hay fever in the immediate relations. Nor is there any likelihood of such information as we can gather about the parents' history in detail being serviceable.

Laroche, Richet, St. Girons[1] quote an instance of sensitization to egg running in the male line through four generations. Such cases are extremely rare, even from parent to child, and I have had very few examples. Most commonly the protein is pollen in these parent-and-child sensitizations.

Pollen and horsehair are such common proteins to which so many people become sensitized that the law of averages may quite well be enough to allow the child to be sensitive to the same protein that affects the parent.

Prenatal History.—In a great many cases we are obviously unable to get any information on this point, but when we do obtain a history it is often of great interest.

One patient's mother had seven children; her husband was a horse asthmatic. With one child, a boy, she had eczema throughout the whole course of her pregnancy: that boy is a horse and dog asthmatic, all the rest of the children being normal—a normal mother carrying the asthmatic child of an asthmatic father.

Another lady has had continuous and very severe asthma ever since she was married, excepting for nine months when she was pregnant. The child, a boy, is normal—an asthmatic mother carrying the normal child of a normal father. I have had a similar history with a migraine patient. This is in fact a common occurrence. One of my patients was entirely free during each of six pregnancies; another, a lifelong asthmatic, was free during seven pregnancies.

We may note here the altered likes and the poignant dislikes of pregnancy. Some women never look well or healthy except when they are pregnant. Others, cigarette

habituées to whom a week without smoking would be absolute purgatory, not only give up smoking within a week of becoming pregnant, but develop the greatest distaste even for the smell of smoke. In both sexes a slight temperature may be quite enough to give the recipient an immediate distaste for tobacco. All these things must be due to some alteration in the blood, and it may well be that the craving of the chronic alcoholic, the morphomaniac, and the drug addict might be controlled by some protein or other injection which would so alter their blood as to change a feeling of insistent craving into one of disgust.

I have had to stop giving an autogenous coliform bacillus because the patient complained that his power of writing fiction and verse was deteriorating. Maybe there is another claimant to the genius that produced the works of Shakespeare besides Francis Bacon and the great William himself —a coliform variant!

History of Foods.—By questions, we endeavour to discover any food that is known to upset the patient in an 'allergic' way, i.e., by producing asthma, sneezing turns, nettle-rash, sickness, or colic. Later such evidence can be substantiated by the dermal reactions. Commonly it is the other way round, and when asked about a food which is found to have produced a large wheal the patient will say: "Oh, yes, of course I have never been able to take that." People usually have an active dislike for the foods to which they are sensitive. The small boy who objects to cabbage might say with truth: "No, thanks, I'm anaphylactic to cabbage"! Our likes and dislikes may have some converse cause. Many patients know that big meals or late meals or mixed cooking will upset them. Pastry, which is a starch cooked in fat, is an article of food that they seem to avoid instinctively.

History of Animals.—Occasionally the patient is aware of some animal whose presence will make him sneeze or wheeze, and whose scratch will produce a wheal on the skin. A catalogue of the animals and birds with which the patient comes in contact is valuable, to refer to later when the results of the dermal reactions are known.

History of Treatment.—Reliance must be placed here on such information as is sent by the general practitioner. There will be a long list of drugs and medicaments that afford

temporary relief, such as those containing ephedrine, and powders and cigarettes containing stramonium. Occasionally a 'course of vaccine' such as peptone has been used. A point of considerable diagnostic value arises when a patient has had injections of microbic vaccines, either stock or autogenous, and has been worse after them. These cases are most certainly of the non-allergic microbic type, and will be cured by further vaccine in suitably small dosage.

The second page of the case-sheet contains a list of proteins where the results of the dermal tests can be recorded. These are considered in the following chapter.

REFERENCE

[1] Laroche, Richet, St. Girons, *Gaz. des Hôp.*, 1912, 1969.

CHAPTER X

EXAMINATION OF A CASE OF ASTHMA

(*continued*)

DERMAL REACTIONS

THE following quotation, given at length, shows that Salter in 1868 had already anticipated our latest work on sensitization to animal hairs and had described the dermal reaction. The italics are mine.

CAT ASTHMA

This singular phenomenon is, I imagine, almost peculiar to myself; I have never heard of a similar instance, except in the case of one individual, *a near relative of mine*, who is subject to the same affection in a lesser degree. The cause of this affection is the proximity of the common domestic cat; the symptoms are very similar to those of hay fever, and, as in the case of hay fever, are occasioned by some sudden influence inappreciable to the senses. I cannot recollect at what time I first became subject to the cat asthma, but I believe the liability has existed from the earliest period of life. I believe some asthma would present itself if I were sitting by the fire and the cat sleeping on the hearth-rug; but the effect is much greater when the cat is at a distance of one or two feet, or still closer; it is still further increased by the raising of the fur and moving and rubbing about, as is the habit of cats when they are pleased, also by stroking the fur; but most of all when they are in the lap just under the face. The influence seems to be stronger in kittens from two months old and upwards than in full-grown cats. Having been almost always accustomed to cats, I have had abundant opportunity of testing the peculiarities of this singular phenomenon.

With respect to the symptoms, I have only to say that they closely resemble those of hay fever with only such difference as might be expected from the near proximity of the cause, from its defined and local nature, and also from the facility for its entire and immediate removal. The paroxysm is consequently generally more violent than that of hay fever. The *asthmatic spasm is immediate and violent, accompanied with sneezing and a burning and watery condition of the eyes and nose*, and excessive itching of the chin, which may also extend to the chest and between the shoulders; the eyes are injected,

and instinctively avoid the light, and the caruncles are more or less enlarged. I believe, if the cause were suffered to continue, all or most of the other symptoms of hay fever would ensue, only with a more excessive and conspicuous asthma. After the removal of the cause the symptoms I have described begin immediately to subside, and if the paroxysm is not very severe, the cure is effected in five or ten minutes, leaving, as in all other cases of asthmatic spasm, a tendency to mucus at the top of the windpipe, which being repeatedly removed in the ordinary way, the last symptom disappears, and the lungs and throat resume their normal condition.

This includes all I have to say respecting cat asthma; but I shall here notice the evidence of the more general influence of cats on my system—of the existence of what I am disposed to call cat-poison. I mention this partly because of its singularity, and partly because the symptoms arising from this general influence are often coexistent with those of cat asthma, and are only occasioned by a different application to the respiratory surface, the asthmatic spasm. The symptoms of this poisoning are consequent on touch or puncture. The eyes, lips, and cheeks are susceptible to the effect of touch, but *a puncture of the claw affects equally any part of the surface of the body.* The eyes are more readily affected than the lips, and the lips than the cheeks. *I have often known the eyes and lips most painfully affected by being touched by the fingers after handling a cat.* That such a result may be produced by such means proves very strikingly the power and subtlety of the influence.

The eyes would at all times be affected by this means, but I do not think the lips would, unless there were some little crack or flaw in the skin, from cold or any other cause. The effect on the eye of rubbing it just after touching a cat is to produce a hot, stinging irritation of it, a profuse flow of tears, and injection of the whole eye, a tender painful swelling of the carunculæ (the sensation of painfulness and itching combined), and intolerance of the light.

If one eye only is touched the other merely exhibits the ordinary effect of sympathy. The result on the lips is an enlargement of the whole lip, and sometimes a sort of lump or protuberance at the part principally affected, together with a feeling of heat and irritation. The cheek is not influenced by this secondary touch, but is affected by the slightest touch of the fur of the animal. If the cat rubs against the face the cheek immediately becomes hot, a little swollen, and of a suffused red; sometimes there appears a defined little protuberance, something like a nettle-rash, which I imagine is produced by the puncture of a hair. *The wound from a claw, whatever be its form, is always surrounded by a white, hard elevation or wheal, very much resembling the appearance consequent on the sting of a nettle.* The pain, which is very much greater than attends ordinary scratches, is accompanied by

> a feeling of irritation and itching, like the pain of the scratch and sting combined. I must not omit to observe that I have never discovered any trace of such influence in any other animal, with one slight exception; a deep scratch on my arms with the claw of a rabbit has, in two or three instances, produced the same sensations as those above described, only less clearly developed. The saliva of a cat is perfectly innocent, and a bite with the tooth in no way differs from ordinary wounds of the same character; *in a word, I believe the influence is, in its source, exclusively cutaneous.*

This was written seventy years ago, and how the teaching of such an acute observer came to be practically lost is difficult to understand. Salter noted the wheal that followed the scratch of a cat, and that the effects produced were due to the epidermis of the cat. All that modern knowledge has been able to add to this has been to make it possible to elaborate these observations, and apply them to all other specific proteins that may affect our patients. Thus the elaboration of the proteins for testing, and their application to the skin, and the resultant observation of whether there is wheal formation or not, are exactly similar to those recounted by Hyde Salter in 1868.

For instance, in hay fever and in sensitization to horses, a large wheal will always be produced when pollen or horse-hair respectively is applied to an abrasion on the skin of the patient. Conversely, if the cause of the asthma is unknown, any number of proteins can be tested one after another, and the influence of each can be observed in any particular case.

A full discussion of experimental anaphylaxis is given in Chapter I. There seems to be no good reason for thinking that asthma and other allergic complaints are anything but anaphylaxis in man. Happily the complete syndrome ending in death is extremely rare, but it does occur. Many deaths from the injection of horse serum are to be found in the literature, also one from the injection of such a small dose of protein as was used during the procedure of an intradermal skin test. Freedman[1] states that a boy died after the intracutaneous injection of 0·05 c.c. of horse serum. Lesser symptoms are quite common during such testing, and sufficient may be given in the combined test injections to cause a sharp attack of asthma in a few minutes.

The Technique of Dermal Reactions

There are three methods of performing these satisfactorily: (1) The scratch method; (2) The intradermal method; (3) The puncture method.

1. The Scratch Method.—I use the following technique: Cleanse the anterior aspect of the arm and forearm with surgical spirit after seating the patient comfortably in a chair with the arm on a cushion, for it is a lengthy procedure. With a sterile scalpel, which should not be too sharp, make two tiny incisions close together about the size of inverted commas. These should be deep enough to show the red layer of the skin, the rete Malpighii, but should not draw blood.

With a platinum loop, cleansed in the flame, place a drop of $N/10$ sodium hydroxide solution on the scratches. Then with the loop still wet take up a little of the powdered protein and mix it into the drop of fluid on the arm. After cleansing the loop in the flame add another drop of the solvent.

When solutions are used, they can be transferred to the skin cuts directly by the loop. In this way some fifteen proteins can be applied to each arm even in thin people. They can be placed in a series at regular intervals down the arm in rows of two or even three on sufficiently large arms. If too near together, one test may influence its neighbour. According to Bowman[2] these tests should be placed $1\frac{1}{2}$ in. apart on either side of the arm and further apart vertically, as otherwise they seem to affect one another more easily. I have not found any difficulty in the scratch method, and if one thinks there is an interference it is easy to retest any doubtful protein reactions at situations some distance apart.

A control test can be made if wished by applying a drop of $N/10$ sodium hydroxide solution, but when doing a number of tests this is quite unnecessary.

2. The Intradermal Method.—The object here is to introduce the proteins into the skin. The all-important point is to inject them in equal quantities. The proteins must of course be in solution, and the amount injected must be gauged by the size of the immediate tiny wheal that is made, or by using a very finely graduated tuberculin syringe. Using equal amounts will allow the results obtained to be exactly comparable one with another. With the intradermal

method, a control injection of carbolized saline should always be used, as the patient's skin may quite well give a substantial wheal to any injury to which it is subjected.

The objection to the intradermal method is the fact that many patients will reply with a sharp attack of asthma in a few minutes if they are very sensitive to the proteins injected. Again, if they are sensitive to dust and many of the animal hairs, the sum total of the injections may cause an attack. The avoidance of these contretemps is a matter of experience and judgement. For instance, grass pollen must never be used for an intradermal test—it is far too powerful an antigen. Care must be taken that the injection is given into the skin and not beneath it, which modifies the result obtained very greatly.

3. The Puncture Method.—This is perhaps the safest and most reliable method to use. It gives us far stronger and more positive reactions than the scratch tests and eliminates the risks of asthma and urticaria of the intradermal method. It is also perhaps the least painful of the three.

A drop of the testing solution is placed on the skin, and the needle is then quickly pricked through it and vertically through the skin. On the thigh it is quite possible to do this without pain if the hair follicles are avoided.

Reading the Results Obtained.—If the patient is sensitive to the protein injected, the triple response of Lewis takes place. There is an immediate redness round the site of the injection and a wheal commences to form, which at the end of fifteen to twenty minutes will have reached its maximum, perhaps with pseudopodia running out from it, and always surrounded by an area of hyperæmia (*see* Frontispiece). Such large reactions are common enough; but should all the other tests be absolutely negative (00), then even such a small reaction as an area of hyperæmia around one test may have a considerable significance and must be duly recorded.

A very useful adjunct to the determination of small or doubtful reactions is to press down upon the site a clean microscope slide or similar piece of glass. The area of wheal formation may then not only be seen the more clearly, but by tracing round its edges with a grease pencil a definite measure of its extent can be made for comparison with other

tests done at the same time, and with the same test done at some subsequent examination.

For an exact comparison of the results obtained by different workers in this field it would be necessary for all to use the same proteins and an identical technique. Variations will therefore unavoidably occur. The essential, necessary for good work, is a considerable experience of the proteins being used. For instance, there was a fish protein on the market a few years ago which gave reactions on all tested.

What would be a normally large reaction to grass pollen would be a colossal reaction if milk were the protein being tested. Again, the normal reaction of different patients' arms to such a minor form of trauma varies a great deal. One commonly hears that the patient has been tested and gave a reaction to everything. This is of course absurd. Some experience is therefore necessary to know that a reaction to horsehair, whether used in the dry form by the scratch test, or in solution in the puncture or intradermal tests, always gives larger reactions, case for case, than does cat hair, which itself gives a reaction larger than dog hair; and similarly with all the other test proteins.

In the intradermal method one naturally gives the control test a nought, but the size of it must be deducted from all the other reactions before being certain that the latter are large enough to be worthy of counting as real reactions. Again, when the result of the injury is enough to cause a small wheal in the control, it is perfectly normal for the house dust to give a much larger wheal without in any way suggesting that the patient is really sensitive to dust. If on the other hand the control shows no sign of inflammation or whealing—what I record as 00—then all other reactions obtained are of importance.

Patients are more sensitive to testing by the intradermal method than by the scratch tests, but frequently their skins show too much reaction, so that on the whole perhaps the puncture technique gives us the most reliable results of all.

Lastly, it is always necessary to remember that the great objective is, not to obtain reactions, but to cure the patient; one reaction however large should not make us forget that there may be others.

With these provisos, understanding that patients may be expected to give larger reactions to pollens, to horse dander,

and to Brazil nut than to other proteins, a scale of reactions judged wholly by their size can be depicted by the following diagram (*Fig.* 11).

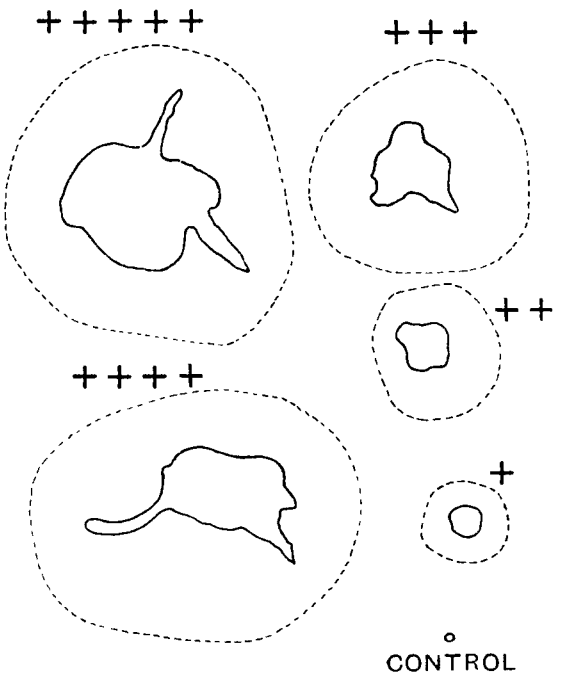

Fig. 11.—Diagram of the actual size of the wheal reactions.

Proteins Used for Testing

All proteins are antigens, to any of which the patient may be sensitive, so that the list of possibilities is a matter of hundreds. It is quite unnecessary to test each patient with all this list, and equally impossible to do so in the time usually available at an hour's consultation. The history may give us clear indications as to which to try.

An asthma that has recurred practically every night for a year will not be due to asparagus, tomatoes, or linseed meal; and a child who has a complete immunity from asthma while at school is not likely to be sensitive to the common foods: potatoes, bread, meat, or fish. To be ready

for all eventualities it is well to have as large a number of proteins as possible on hand, including the following :—

List of Test Proteins

Almond
Anchovy
Apple
Asparagus
Banana
Barley
Bean
Beef
Beetroot
Blackberry
Blueberry
Brazil nut
Brussels sprout
Buckwheat
Cabbage
Calf's brain
Carrot
Casein
Celery
Cheese
Cherry
Chestnut
Chicken
Chicory
Cinnamon
Clove
Cocoa
Coconut
Codfish
Coffee
Corn
Crab
Cranberry
Cucumber
Duck
Egg white
— whole
— yolk
Endive
Fig
Flour
Ginger
Goose
Grape
Grapefruit
Haddock
Halibut
Herring
Honey
Lactalbumin
Lamb
Lemon
Lentil
Lettuce
Lobster
Mackerel
Milk, cow's
— human
Mint
Mushroom
Mustard
Nutmeg
Oats
Olive, green
— ripe
Onion
Orange
Orris-root
Oyster
Parsley
Parsnip
Pea
Peach
Peanut
Pear
Pineapple
Plum
Pork
Potato
Prune
Radish
Raisin
Raspberry
Red-currant
Rhubarb
Rice
Rye
Sage
Salmon
Sardine
Shrimp
Sole
Soya bean
Spinach
Strawberry
Sugar
Tea
Tomato
Turkey
Turnip
Vanilla
Veal
Walnut
Wheat
— gliadin
— globulin
— glutenin
— leucosin
— proteose

Boxwood
Cotton
Cottonseed
Flaxseed
Kapok
Silk

Henna

Peptone
Beef serum
Horse serum
House dust

African monkey
Alaska seal
Beaver
Caracal
Grey fox
Hair, camel
— cat
— cattle
— dog
— goat
— guinea-pig
— hog
— human, black
— — white
— mouse
— rabbit
Hare
Horse dander
Hudson seal
Muskrat
Opossum, Australian
Raccoon
Red fox
Sheep's wool
Silver fox
Skunk
Squirrel
Wolf

LIST OF TEST PROTEINS—*continued*

Feathers, canary
--- duck
— goose
— hen
— parrot
— pigeon

Grass pollens

Yeast, baker's

Yeast, brewer's
— distiller's
— Fleischmann
- - lactose fermenting

Moulds—
Alternaria
Aspergillus fumigatus
— *glaucus*

Moulds—
Aspergillus nidulans
— *niger*
Chætomium
Monilia
Mucor plumbeus
Oyster yeast
Penicillium Camembert
— *chrysogenum*
- - *Roquefort*

PROTEIN GROUPS

Can time be shortened by using the proteins in groups?

If five or six proteins are used at one test, they must necessarily be diluted by the presence of the others, at any rate if used in the dry form. To this extent the size of the reaction and its value will also be reduced.

If prepared in the laboratory as 'group solutions', the material for use need not necessarily be a diluted form of each ingredient, but capable of giving a reaction of full value to each member of the group, which is of importance in the subsequent reaction analysis of any one single group by individual solutions of a strength equivalent to that present in the 'group solution'.

Groups with the animal hairs and air-borne dusts work very satisfactorily, and save much time, but must be subsequently separated; so that eventually one may be able to cure the asthma by the simple expedient of getting the patient to change her face-powder, instead of placing the cat, the dog, and the pillows under a suspicion that they have not deserved.

If the group contains five different foods, a subsequent test must be carried out to identify which of the group is at fault, and so obviate the giving up of five foods where only one need be avoided.

Methods of extraction of the various proteins are to be found in the book of Coca, Walzer, and Thommen. The relative strengths of the antigens are usually standardized by the amount of nitrogen they contain, although in many of them, particularly in pollen, it is a polysaccharide that is the essential ingredient, nitrogen-free specimens of which will give the specific wheal reactions.

With regard to bacterial allergy, Harley[3] summarizes his recent work thus :—

" Concerning the immunological relationships of cutaneous allergy to pneumococcus nucleoprotein, the specific polysaccharide, and vaccine: These three types of allergy are immunologically independent. Allergy to the polysaccharide is closely related to type-specific immunity. It seems likely that the manifestations of polysaccharide allergy and of type-specific immunity depend on a common basic mechanism, namely an antigen–antibody reaction between the type-specific antigen (or hapten) and its antibody.

" Allergy to nucleoprotein is dependent on the presence of circulating nucleoprotein antibodies, is unrelated to type or specific immunity, and is essentially an antigen–antibody reaction between the nucleoprotein and its antibody.

" Allergy to vaccine is independent of circulating antibodies and of type and species immunity. It appears to depend on an increased reactivity of the tissue cells as opposed to an antigen–antibody reaction.

" In conclusion, it is clear that no relationship of 'allergy' to 'immunity' is possible, with reference to pneumococci at any rate, in view of the complexity of the phenomena of bacterial allergy and their immunological relationships."

The subject of bacterial allergy is complicated but not impossible of solution, particularly if the differences between this allergy and generalized sensitization with free reagins in the blood is borne in mind (p. 18).

By making use of one's past experience and without any knowledge of the nitrogen content, the size and strength of the subsequent treatment dosage can be regulated by the size of the reactions obtained to the solution used for testing purposes.

Experience with Individual Proteins

There is no doubt that one does not see such a number of dramatic results as one did fourteen years ago from the skin reactions. The dissemination of the knowledge that animal hairs and other proteins can cause asthma has led doctors and patients to look out for such causes, and they

are eliminated before expert advice is sought. Sometimes the experimental avoidance of hairs and feathers is carried too far, and for the inadequate reason that they might be the cause of the patient's asthma. Cats, dogs, and feather-beds may be removed beyond return, with many unnecessary heartbreakings and no improvement in the patient's asthma. This wholesale slaughter of innocents should not be carried out without first subjecting the patient to a thorough test with the dermal reactions.

House Dust.—First recognized by Cooke in 1921, its potency in causing asthma has gradually reached the position of paramount importance amongst all causes of asthma.

House dust is found in all human habitations, more potently in the beds and bedding upon which we spend so great a portion of our lives. Its influence is air-borne, thereby reaching the nose and chest continuously with the greatest ease, gaining entrance to the cells when the mucous membrane is inflamed by any of the common respiratory infections. Occasionally patients give histories by which the time of sensitization can be determined.

Case 17.—A solicitor's clerk with asthma of five years' duration dated its commencement from an occasion when he spent a whole day in a cellar, hunting through books and bundles of papers while searching for a document; he felt himself smothered with the dust, to which later he gave a large reaction.

Of the gross number of reactions obtained, a large proportion agree closely with the clinical history of the case; others do not. With the single exception of grass pollen in hay fever, more reactions are obtained to house dust than to any other protein, and the percentage of such reactions in which the cause of the asthma thus found is proved to be correct is very high, as the subsequent clinical history, the effects of avoidance, and the results of desensitization demonstrate.

The quantity of house dust in any one home naturally varies, as also must its contents. Examined under the microscope, a kaleidoscopic collection of 'bits and pieces' of infinite variety may be seen. Among the ingredients mould spores can always be found. Exposure for half an hour in any room of a Petri dish containing a medium of so simple a nature as gelatine with a little peptone will always produce

luxuriant growths of moulds in a few days' time, as did the home-made jam of a previous generation. Mould spores continually fall down out of the air.

But if these moulds are prepared into a state convenient for use as tests, they fail to produce any reaction at all. There will be exceptions where the patient is sensitive to the mould as well as to the dust, but so rarely does this occur that it is perfectly certain that moulds *per se* are not the antigen responsible for house-dust asthma, although their growth on dust proteins, together with the enzymes they produce, may eventually demonstrate them to be an essential feature of this type of sensitization.

Interesting experiments have been carried out by Cohen et al.[7] in which new cotton, free from any value in giving dermal reactions, was found after an interval of two years to have become an active antigen, so that injections of it caused wheals in those sensitive to house dust. As the cotton was kept in hermetically sealed containers after being sterilized by heat at 120° for an hour it would seem that the only reason for this change must have been some chemical process occurring during ageing of the cotton.

The stuffing of furniture and of mattresses is particularly potent in the house dust factor, probably from this process of ageing. Wagner and Rackemann[5] find that kapok ages in the same way.

Storm van Leeuwen recovered the *Aspergillus fumigatus* from old kapok. Others place more importance on the mould content of dust than is presented here. Since mattress dust is so peculiarly powerful as an antigen, one's thoughts naturally turn to the human element of the sleeper on the mattress, remembering the potent extract of human hair in use by the late van Leeuwen. A very effective form of dust is that collected from theatres and cinemas, where again the human element is particularly evident.

Whatever may be the actual protein forming the antigen in house dust, it can be proved abundantly that, no matter whence it is collected, it may cause dermatitis, rhinitis, and asthma, and give correspondingly large dermal reactions in all these cases, so that there seems to be a single element at work, though distributed so widely amongst our habitations and their contents. No case of asthma can have been properly investigated without its use.

Case 18.—A lady, aged 69, asthma since the age of 45 of unknown origin. When she catches a cold it 'flies to the chest' and is followed by bronchitis and asthma. She gave a large reaction to house dust and then volunteered the information that her asthma first developed after she had cleaned out four rooms, since when she has done no dusting and avoids it whenever possible. A case easily missed without testing, on account of her considerable age.

Animal Hairs.—

Horsehair.—In these days of the ascendency of the motor car over the horse, the removal of the horsehair mattress and such other furniture as contains horsehair should leave the patient free from asthma from this source. Where the patient's work or pleasure is with horses it is not a difficult matter to be desensitized. The continual presence of horses then appears to keep up the immunity, which only returns after a long incubation period.

Case 19.—A young lady, a member of a hunting family, was unable to hunt owing to being extremely sensitive to horses. She was desensitized and could then hunt regularly and with comfort. She went for a trip to South America, and on her return found she was again sensitive, and had to have further injections until free. This occurred before the massive doses now given with adrenaline were possible.

Cat Hair.—Sensitization to cat hair is less common than to horse hair and more common than to dog hair. The normal full-sized reaction is also between the huge horsehair reaction and that to dog hair. For a full disquisition on the symptoms, reference should be made to the personal account by Hyde Salter of his own symptoms quoted at the beginning of this chapter.

The uncanny way in which those sensitive to cat hair can tell when one is present is remarkable.

Case 20.—A lady known to be sensitive to cat hair went to stay at a large hotel in Brighton. She felt stuffy directly she entered the bedroom and had asthma that night. It was the habit of a cat in the hotel to pass through her room and sun itself on the veranda, leaving sufficient emanation in the room to cause my patient to have asthma.

Dog Hair.—

Case 21.—A girl, aged 20. Asthma for two years. The attacks came on so suddenly and so badly that she could hardly get upstairs

to bed. Occurred chiefly in the winter time, mostly at week-ends, in the evening, and at night before she went to bed. Disappeared quickest with poultices. She had no attacks when once at work, and she was free for a month at Margate. There had been a collie dog in the house for nine years, and a cat for two. She also kept rabbits and chickens. Reactions: Dog hair + + + . Nothing else gave a reaction. She wrote eighteen months later: "Our dog was almost immediately, though very reluctantly, destroyed. I had one slight attack immediately after this—the following day I think—which was whilst the cleaning operations demanded by you were in progress. From that day I have only had one recurrence of the complaint, whilst in a house in which a dog was kept. . . . One more point I would mention. You will probably remember that we had a cat; well, this was not destroyed; we kept it and have it still, so that there is undoubtedly no ill effect emanating from this." There was no reaction from the cat hair when tried as a dermal test.

The treatment in such cases is to remove the animal, and it is very important to have the whole house thoroughly cleaned afterwards in order to remove every hair that may be left behind.

Unfortunately dogs are so prevalent in these latter days that persons sensitive to them are very restricted in the range of friends whom they can visit, and in spite of destroying their own pets, meet with frequent attacks of sneezing and asthma from the dogs of others.

Modern treatment consists of thorough desensitization with large doses of dog hair, by which means patients are enabled not only to visit their dog-loving friends but to keep dogs of their own, though perhaps at a distance.

Rabbit Fur.—Patients should be tested to rabbit fur as a routine measure. Most houses contain felt matting, as well as a multitude of other things, like pillows and mattresses, containing rabbit fur. One boy who came to see me was so sensitive that he could not carry a dead rabbit without getting nettle-rash on his hands. To avoid this he put the rabbit he had shot round his neck, the effect being naturally far worse.

Case 22.—A gentleman was subject to a great deal of asthma as a child on a farm in Ireland; this left him when he got about in the world, but always returned when he went home. Out of a considerable number of proteins tried he gave a + + + + reaction to rabbit fur, and to that alone. He then told me that the farm at his home is practically built on a rabbit warren, from which rabbits are sent to market by the dozen.

Cattle Hair.—Patients sensitive to cattle hair are usually farmers, milkers, and others in close contact with these animals.

Other Animals.—A patient may be sensitive to any animal, or to its fur. The same specificity of course occurs here, so that a lady unable to wear squirrel may have a large range of other furs which are harmless. I had a patient some years ago who only had asthma when sleeping in certain tents in Egypt: presumably he was sensitive to camel hair.

A few people will give reactions to human hair, but I have never had an experience of a hair which gave an almost universal reaction as did the specimen in use by van Leeuwen. It probably contained histamine, a product of hydrolysis of human hair protein. I have found sensitization to sheep's wool to be extremely rare, even when a potent product of the raw wool was used by the intradermal method.

Feathers.—In many instances the discovery was of the greatest importance to the patient. Happily the feather-bed is not very common now, though many of the poorer classes still take a great pride in the possession of one, even handing it down as an heirloom, as the following case shows :—

Case 23.—The patient, an asthmatic, was sensitive to hen feathers, and slept on a feather-bed which had been handed down to her by her mother, who also suffered from asthma. The latter in turn received it from her mother, my patient's grandmother, and she too had asthma.

I do not, of course, know if the mother and the grandmother were sensitive to hen feathers; most likely they were, and we have the accumulated wheezing of three generations as a sequel to the original purchase of this feather-bed.

The influence of feathers is extraordinarily powerful. Asthmatic patients often have six or more pillows which some kind friend will shake up for them before wishing them 'good night'.

Kapok is the common substitute, but I think wool is just as good. In any case, pillows should be renewed once a year at least, to prevent the effects of ageing.

Case 24.—A man, aged 22. Asthma nineteen years. Had practically none in the Army. Seemed to become worse at the week-ends, and then perhaps lasted until Thursday. Had to crawl about to his work. Reactions: Hen feathers + + + : Horse

hair + + : Pork + : Brazil nut + . He avoided feathers, and was practically free for ten months, having perhaps two slight turns from dietary indiscretions. He went for a holiday to the Lake District and had asthma the very first night—he was sleeping on a feather pillow.

I have had a few cases in which other feathers, those of parrots and pigeons, have been the cause of the patient's asthma, as witnessed by the reactions obtained to these proteins and the rapid recovery of the patient on their removal. I think it is better to have too much faith in the dermal reactions than too little. If a patient found to be sensitive to feathers does not improve after their removal, only one of two things can be possible. Either the feathers have not been completely removed from the house, or there is an additional cause for the asthma.

Other things being equal, the more intelligent a patient is, the more easily he may be cured. A patient was sent to me from the country by his board of guardians. He was found to be sensitive to feathers; he gave up his feather-bed, and returned to work. Three years later the silly fellow was sent to me again : he had returned to his feather-bed !

Orris-root.—This is a constituent of most face-powders, soap and tooth-paste, children's bath-powders, and, as I was told recently, of white peppermints.

Whereas the tendency is for a patient who is sensitive to one air-borne protein to give lesser reactions to many other proteins, orris stands by itself, either giving large reactions or none at all.

Reactions when they do occur are therefore striking and important. Avoidance of certain face-powders and the substitution of other brands that are free is a simple matter, but the lavish powderings of others that take place in the drawing-room and even at the dinner-table are so difficult to avoid that it is usually necessary to desensitize these people to orris-root as well as to review their own cosmetics.

All the proteins mentioned so far are air-borne. They are by far the most important group in their power to cause asthma, in the ease with which they can be tested correctly by the intradermal or puncture method, and in the value of the information obtained, excepting only the 100 per cent results with grass pollen in summer hay fever.

Foods.—Even when ample results are obtained with the air-borne proteins and when such are consistent with the clinical history of the case, it is best to test the patient as fully as possible with the common foods.

Tests should be made with eggs, milk, the cereals, the meats, fish, potatoes, and nuts. The rarer the food, the more likely is the patient to be aware of his idiosyncrasy before testing. It is easier to find foods to which the patient is sensitive than to make it certain or simple that he can avoid them.

Eggs provide the most difficult problem, as they enter into so many dishes. The glaze on the top of a bun, or soup which has been cleared with white of egg, may make the patient sick in a few minutes. Chocolates or a glass of port are taboo to those who are sensitive to egg. One patient even has to have his own frying-pan, as bacon cooked in the ordinary one used at times for cooking eggs contains enough of the latter to make him ill.

At one time and another I have obtained reactions to almost all these food proteins. Apart from eggs, there should be no great difficulty in their avoidance. In sensitization to milk the effective element is the lactalbumin, which is specific to each animal; casein is common to all milks, and patients are rarely sensitive to it. In infants, milk from other animals may be substituted for that of the animal to whose milk they are sensitive. If well boiled the lactalbumin appears to lose its specificity, rendering the milk harmless.

Patients sensitive to any of the starch foods—the cereals, potatoes, or rice—can usually find substitutes to take their place. Again, the more intelligent the patient the simpler the task, and the easier it is to break conventions and take potatoes for breakfast if necessary. Home-made rusks of milk bread baked brown in the oven are a useful addition to the diet of those unable to take bread. The harmful protein seems to be destroyed in the heat of the oven. Frequently it is possible to find amongst the patent foods some, such as Almata of Keen Robinson's, or other products, to which the patient is not sensitive, a welcome addition to a dietary that is becoming too restricted and monotonous.

Soya bean often gives a reaction. I understand from a Siamese patient that it enters into the composition of many sauces, apart from its more generally known uses.

Other Proteins.—One occasionally obtains a reaction to silk. This was so in the following case, the patient being sensitive to a great number of proteins.

Case 25.—A male, aged 40. He suffered from eczema always, urticaria at times, profuse sneezing in the presence of animals and dust. Asthma since the age of 2, except for two years in the Black Forest. + + + + + reactions to horsehair, cat hair, cabbage, pollen, goose feathers, silk, and holly. At Christmas time his hand would swell on touching holly. He had to have his dress clothes lined without silk—even a silk tie made his chin itch.

Linseed or flax seed is a fairly common cause of sensitization. One patient had much scarring of the skin of the chest, said to have been caused by poulticing.

I was once called out urgently to see a patient to whom I had given a dose of peptone at midday. The whole of her head and neck was covered in a coarse urticarial rash, the rest of the body being free. She had spent the afternoon at the hairdresser's and the rash was due to chemicals in the treatment of her hair, not to the peptone.

A patient can be sensitive to anything in his surroundings, and a list of proteins, no matter how long, is constantly being extended. Sensitization to tulips, to hyacinths, and to chrysanthemums is not uncommon amongst market gardeners, and is very materially benefited by preseasonal desensitization.

Grass Pollens.—Sensitization to grass pollens will be considered in a chapter on hay fever and rhinitis.

The Moulds.—Time and expense, and the fact that the patient has often come up from the country for the day, rarely allow sufficient opportunity for unlimited dermal testing; but I have been able to test a considerable number of patients with some 18 stock moulds in dry form. The results obtained have not been very satisfactory. An occasional late reaction is obtained.

Moulds are of such great number and variety that the best way is to send the patient a prepared dish for exposure in his home, testing him subsequently with such as grow on the medium.

The presence of moulds is occasionally reported in the patient's sputum. If a dermal test proves positive, the mould can be given in a vaccine to promote desensitization. Much work has been carried out in America on the subject.

Feinberg and Little[6] conducted a year's survey of the moulds in Chicago. A Petri dish containing Sabouraud medium was exposed for half an hour each day, one foot outside a closed window on the sixth floor of a medical school, special note being made of the mould *Alternaria*. An enormous increase in the amount collected from the air occurred in July. The whole mould-content increased at this time, and in all the warm months. Clinically it was thought that patients' symptoms followed this increase in July. As well as showing large reactions to the mould, the presence of reagins in the patients' blood was shown by passive transfer.

There is room for much work on this subject in England.

Moisture, heat, and food are the essentials necessary for mould growth. In England one would expect their greatest growth to occur in a warm September, when mushrooms and other fungi abound in the woods. The spores are smaller than those of pollen, and therefore still more easily air-borne. The great objection some asthmatics have to musty smells, to the air of damp woods, and to the neighbourhood of ponds may be due to the presence in the air of mould-spores. Certain patients are affected in their breathing the moment a train reaches a particular neighbourhood, and this is as likely to be due to a mould as to psychological causes. The centre of London is notoriously beneficial to asthmatics, and it may be noted that the trees in the London parks are free from lichen, the scaffolding erected by a mould.

Bacteria.—At one time I used to include scratch tests with dry bacteria in the routine examination of patients. My sense of their value was perhaps influenced unduly when first using them by a case I saw, in which the only two organisms that gave reactions were subsequently found, by the bacteriological report that came to hand later, to be the only two present in the sputum.

Experimentally it is possible to sensitize guinea-pigs by massive doses of dead bacilli, and to kill them with shock doses, but sensitization to the extent of anaphylaxis cannot be expected to occur in human beings, with the possible exception of the common cold in its earliest stage.

Whatever may be the cause of a cold, it apparently gives a very small and temporary resistance against other colds, but each cold may provide sufficient dead protein to sensitize

the patient, followed as it is by a well-marked incubation period before the next cold appears, with the initial symptoms so very like those of hay fever.

Rackemann's two daughters each had an attack of urticaria within forty-eight hours of catching a fresh cold.[7]

Probably many of the patients who have attacks of asthma following colds, often commencing forty-eight hours after the cold starts, are of a similar nature—a true anaphylactic response to proteins. Many other infections produce such a satisfactory immunity that the protection afforded guarantees the patient against subsequent attacks, as with the exanthemata.

The type of asthma which consists of four long attacks each year is of this true anaphylactic nature, with much sensitization but very little immunity. Certain fractions of organisms seem to be particularly prone to cause skin reaction—the nucleoproteins, and the polysaccharides.

Recently considerable research has been carried out by Stevens and Jordani[8] in which specially purified bacterial nucleoproteins were used for 5 organisms to test 100 patients intradermally, making 500 tests in all. Some very large immediate wheals (58) were obtained and many second-day reactions (108). Eleven cases were retested from time to time, and the reactions were found to vary considerably, depending upon changes of bacteria due to colds and other respiratory infections. Even if we allow that patients may become sensitized to bacteria, the whole process is so different from sensitization, say, to pollen that one would expect to see a very different picture in each instance, as indeed is the case.

In the ordinary sensitization to proteins the proteins are dead, as horsehair and egg-white, and if alive as pollen they have no life, even saprophytic, in the human body. Bacteria, on the other hand, not only affect the patient in virtue of their proteins, but by living and dying in the body they originate processes of sensitization. Anaphylaxis and desensitization may be taking place simultaneously, and, in the absence of an incubation period, sensitization will be of the allergic Arthus phenomenon type rather than that of the standard guinea-pig anaphylaxis. Reactions obtained to dermal tests with micro-organisms are often dependent upon the nature of the organisms used ; for instance Gram-negative

organisms tend to give reactions quite apart from any question of sensitization.

In short, I think that the reactions obtained to dermal tests with bacteria are so unreliable as to have no practical value in testing for the cause of the patient's asthma.

Reactions in Normal Persons.

The fact that reactions can be obtained on the arms of many normal persons, or rather, let us say, persons who are not afflicted with asthma or other 'allergic' complaint, need not deter us in any way from acknowledging the immense value dermal reactions afford in helping to unravel the cause of a patient's asthma.

A large number of those working as bakers or in wool trades have been found to give dermal reactions to wheat and wool respectively, but without having symptoms of asthma. This state of affairs may be inexplicable, but does not detract from the general value of such reactions. Grow and Herman[9] tested 150 normal patients and obtained reactions in 55 per cent. Against this the following criticism may be levelled: (1) 40 of these patients had had allergic symptoms, urticaria and so forth, in the past; (2) Faint reactions were taken note of, and we do not know how faint they were; (3) 32 per cent were found to be sensitive to lobster!—such an extraordinary result should make one suspect the integrity of the testing substance from one's own knowledge of fish and similar proteins in test sets; (4) All tests were carried out intradermally, the most difficult method of all from which to assess the value and size of reactions.

The effect of drugs on the dermal reactions is of interest. Adrenaline lessens the size of the wheals very greatly, either injected with the protein or elsewhere. This effect only lasts a short time, for an hour. The effect of ephedrine is much less marked, while atropine produced no inhibition at all. (Tuft and Brodsky.[10])

The application of a tourniquet to the arm was found by Furstenberg and Gay[11] to prevent wheal formation, only a purplish cyanosis being seen. On removal of the tourniquet the wheal appeared.

Diehl and Heinichen [12] found that under hypnosis the size of the wheal from an intracutaneous test injection can be increased by suggestion!

OTHER METHODS OF DETERMINING SENSITIZATION

The dermal tests by the scratch method, by the intradermal method, or by the method of puncture may be applied to any part of the skin, preferably that of the arms in children and men, and that of the front of the thigh in women. In America the back is used extensively for this purpose. It is usually too cold to make use of this site in England.

The Mucous Membranes.—The conjunctiva has been used to test sensitivity to pollen, but the skin is far more convenient. In certain cases in which it appears that the patient is suffering from some species of hay fever not discoverable by the skin reaction, the mucous membrane of the nose has been used. In America there are of course many more pollens causing hay fever than here, and the method may have some value.

In England, if a patient has hay fever in June he will without doubt give a reaction to a scratch test with grass pollen. In my experience there are no exceptions to this rule.

The Method of Passive Transfer.—In the scratch test the wheal is formed by an interaction between the applied protein to which the patient is sensitive and the circulating reagins specific to the protein applied. This interaction, perhaps with a local formation of histamine, produces an injury of the endothelium of the adacent blood-vessels, with an outpouring of lymph and eosinophil cells. The two essential factors are (1) the foreign protein, and (2) the reagin for it in the patient's blood and cells.

If the serum from a sensitized person is injected into another normal person and the specific protein then meets the serum injected, either by a scratch test over the site or by mouth, a reaction takes place. This is the Prausnitz-Küstner reaction. Küstner being sensitive to fish, injected Prausnitz with some of his serum. The next day Prausnitz ate fish and a reaction took place at the site of the injection.

Passive transfer consists of preparing a number of sites on the skin of a recipient, to which a variety of proteins can later be applied for testing purposes. Usually a 48-hour incubation period is necessary to allow the reagins to be fixed to the cells locally. One cannot see any great advantage of such a complicated procedure, except in those persons whose skin is in such a bad state, as from eczema, as to be useless

for the application of the ordinary dermal tests. The reagin present in the serum to be injected can be neutralized *in vitro* by a mixture of the specific protein. (Levine and Coca,[13] Coca and Kosakai.[14])

Taking blood from a hypersensitive allergic person, Sherrer[15] finds as previously stated that the plasma and serum are parallel in their reagin content. Apparently the fibrinogen of the plasma does not increase the reagin concentration. The serum dialysate and the albumin fraction contained no reagins. The globulins, particularly pseudoglobulins I and II, carried all the sensitizing substance. The euglobulins in all cases gave evidence of comparatively small amounts of reagins. In each instance the pseudoglobulin II was slightly more potent than the pseudoglobulin I.

Parlato[16] makes use of fluid from blisters to convey the sensitization to a third person. Neither tissue changes nor burning seem to affect the presence of atopic antibodies, that is, reagins.

The Patch Test.—This will be of use in such a case as that of a gardener who develops a dermatitis when handling chrysanthemums, or in a grocer who has a dermatitis of unknown origin. The protein is applied to the skin and kept in place by a piece of adhesive plaster. This allows of inspection from time to time. A control test should be carried out because of the number of people whose skin is unduly sensitive to adhesive plaster. If this should be of a high degree, the patch can be kept in place by a piece of cellophane stuck down with collodion. Eczema often antedates asthma, and I am inclined to think that it is a sensitization of the skin, an allergy, before full sensitization is developed with reagins in the blood, in which case wheal formation would not take place to the ordinary skin test, while to the patch test a reddened inflamed area at the end of twenty-four hours shows the significance of the protein under test.

The Elimination Tests for Foods.—These tests are tedious for the patient, but of great value in certain cases of migraine, urticaria, and colitis, in which the dermal tests are of little value.

The rationale of the treatment is to allow a diet containing a very restricted number of proteins for such a time as shall have made it obvious, by the absence of symptoms

while following the diet, that it is harmless. Having reached this point, other foods can be added to the diet and their effect noted.

For the first period the diet might consist of wheat in all forms, beef in all forms, butter, oranges, and marmalade, and one beverage, as tea, beer, or whisky, and of course water. Some skill and intelligence is necessary to arrange and cook these five proteins. Another diet of mutton or pork with four other proteins can be tried, or single additions can be made.

By this method the offending item can usually be discovered.

The Leucopenic Index (The Hæmoclasic Crisis).—This is based on the work of Widal, Abrami, and others, who noticed that after partaking of a protein to which the patient was sensitive the total white count fell instead of showing the leucocytosis which normally follows a meal. It is necessary to have the patient under observation while this procedure is carried out, in order to avoid excitement, exercise, and many other circumstances, apart from the food that is being tested, that may affect the blood-count.

In carrying out the test, after a night's fast the patient's white cells are counted and the food then given. As the exact time at which the rise or fall may show its maximum is variable, Rinkel[17] advises that three counts should be taken at 20, 40, and 60 minutes after the food has been eaten. Spangler[18] makes an interesting point and suggests that the leucopenia may show alterations in the differential white count. He says: "One patient came to my office last week with a marked urticaria of undetermined origin. Her total white count was 7400. The differential count showed 58 per cent lymphocytes, 41 per cent polymorphonuclears, and 1 per cent eosinophils. Ten minims of a 1–1000 solution of adrenaline were given hypodermically, and in about eight minutes the patient was practically free of clinical symptoms. Within another ten minutes a second white count was 10,600, and the range of the differential count changed to lymphocytes 26 per cent and polymorphonuclears 74 per cent, no eosinophils being counted in 200 cells."

The last point is especially stressed by Squier and Madison[19], who find that an eosinophilia accompanies the leucopenia after food to which the patient is sensitive and proves a very important additional factor in diagnosis.

Physical Factors.—In that group of patients whose symptoms are caused by physical disturbances—heat, cold, and light—appropriate measures may be taken to test them.

Heat.—Heat-sensitive people are quite common. They are closely allied, or at any rate not easy to separate, from others who have symptoms, especially nettle-rash, after exercise.

Cold.—It is well known that placing the hands in cold water may be sufficient to produce hæmoglobinuria in those suffering from paroxysmal hæmoglobinuria. Another patient may have the arms covered with nettle-rash in a few minutes. These patients are not at all uncommon. Immersion in cold water, as sea-bathing, may lead to a severe degree of syncope.

Light.—Many people sneeze in a strong light, but this is an eye–nasal reflex. Those sensitive to light will have to avoid the sun in every possible way. If a piece of cardboard with a hole in it is placed on their arms, a few minutes of ultra-violet light applied through the hole is sufficient to produce a large wheal in another ten minutes.

A leucopenia accompanies each of these physical 'allergies'.

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CHAPTER XI

EXAMINATION OF A CASE OF ASTHMA

(continued)

BACTERIOLOGY IN ASTHMA

IT has become increasingly evident during recent years that bacterial factors play an important part in many cases of asthma and allied 'allergic' complaints. The part they take in the causation of the various syndromes is of a more general and diversified character than the very specific reaction of the foreign proteins discussed in the last chapter. Although it is the purpose of this book to be essentially practical, it is necessary to discuss shortly the part played by bacteria in the different types of asthma, in order to give full rational coherence to the practical procedures described. It is not proposed to discuss the intimate biochemical and serological research work now in progress on the specific biochemical factors of various micro-organisms. These investigations have as yet no immediate bearing on the practical examination and treatment of cases of asthma.

Bacterial infections in asthma may be classified into (1) *primary*, and (2) *secondary*, a distinction of the utmost importance. It is at times extremely difficult to assess the relative value of each, as often both primary and secondary infections are present together. One must keep steadfastly before one the basic fact that asthma occurs as a spasmodic condition of the bronchial musculature consequent upon some intrinsic hypersensibility of that organ. Primary bacterial factors are therefore those infections which have an actual causative relationship to the induction of such a bronchial spasm. Secondary bacterial factors are those infections occurring subsequently to physiological changes brought about by the continuous attacks of bronchial spasm, induced primarily by some allergic or other factor. Many such secondary infections originate thus as a condition following attacks of asthma, but later become more closely allied to the primary division in their symbiotic effect in association with the original primary cause.

1. **Primary Bacterial Infections.**—In order to review this complicated subject, and obtain a clearer conception of their importance in one's own mind, one may subdivide these factors. Nevertheless such a tendency to infinite academic subdivision plays a relatively small part when the asthmatic patient presents himself for treatment. It serves, however, as a logical basis for discussion. Primary bacterial infections in asthma, then, may be classified as: (*a*) Direct bacterial allergy; (*b*) Direct local irritation; (*c*) Reflex irritation; and (*d*) Toxin-histamine spasm.

a. Direct Bacterial Allergy.—Full hypersensitiveness to bacteria is not in our opinion a common cause of asthma; nevertheless the possibility of its occurrence must be reviewed. In the same manner as an asthmatic patient may be reactively sensitive to the specific protein of a duck's egg, he may also be hypersensitive to the whole or an intrinsic portion of a bacterial micro-organism. Owing to the very nature of bacterial infection the course of events likely to produce a state of hypersensitiveness is extremely rare, and is comparable to the rarity of food 'allergies' in patients fed with the same diet from day to day—so regularly that the intervention of an incubation period necessary for the production of full sensitization cannot occur. Not only is it theoretically possible for a hypersensitivity to a pathological organism to be present, but in an analogous way to the fact that an asthma patient may be sensitive to a very ordinary food substance such as milk—harmless to others—so one may imagine that a state of hypersensitivity to a micro-organism which is otherwise non-pathogenic is possible. That such can occur or be induced in the experimental animal is shown by Zinsser.[8]

The allergic relationship in tuberculous infections has been mentioned, and that of rheumatism, according to some authorities, may be another example; but these would be allergy in the true von Pirquet sense: a cellular sensitization without there being free reagins in the blood, and this may well be present in the bacterial forms of asthma. As already stated, we believe full sensitization to be extremely rare as a cause of natural spontaneous asthma in man, and would perhaps go so far as to state that there is no clinical evidence to support it as occurring at all, with the single exception of the intermediary class of life represented by the moulds,

yeasts, and streptothrices; but with these, intervals necessary for the incubation periods will occur.

b. Direct Local Irritation.—Bacteriologically this type may be classified as chronic infections of the bronchial tubes. The presence of bacterial micro-organisms continually multiplying and dying in situ leads directly to an inflammatory irritation. Furthermore, the continual coughing consequent upon this inflammatory irritation gradually leads on through many bouts of chronic bronchitis to a time when a real asthmatic spasm of the muscles will occur. Such a case is therefore the direct result of a local infection, although this infection may itself have had a more remote ancestry in an attack of pertussis, or a bronchiectasis or fibrosis as the result of an unresolved pneumonia. After the separation of cases of asthma by means of the differential sedimentation test into Types I, II, and III, the primary bacterial asthmas are all found to be in Type II, which is essentially the only one determined as a pure infective type of asthma, and should be regarded as an entity unassociated with a general cellular hypersensitivity to a foreign protein, as in all other types. By this serological test we see the state of the serum to be exactly similar to that of other persons responding in a natural way to other infective invasions of bacterial origin, whether a boil, a pneumonia, or a simple bronchitis. This Type II has therefore no association with the typical allergic group, Type I, described in other chapters; consequently its treatment must be similarly dissociated. Treatment has to be on the lines of a respiratory infection, and results of treatment by vaccines fully confirm the hypothesis in regard to its causation as outlined in this section.

c. Reflex Irritation.—The importance of the balance of the tonic stimuli between the vagal and sympathetic nervous systems in maintaining the normal function of the bronchial muscles and the tendency to bronchial spasm and asthma with the preponderance of the vagal stimuli has been discussed on page 33.

Furthermore, the significance of the sensitive surface in the post-nasal area described by Brodie and Dixon has been alluded to on page 34. Apart from cellular hypersensitivity to foreign proteins in that area, such as dust, pollen, etc., which may cause an irritation and congested state and so reflexly stimulate the vagal nerve-endings, with subsequent increased vagal tonus and bronchial spasm, there is an equal possibility

that this irritation may be wholly or partly bacterial in nature. Some doubt has been expressed as to the actual occurrence of a reflex bronchial spasm from the Brodie-Dixon area, because it has been found in laboratory animals that the degree of stimulation required to bring about contraction of the bronchial muscle in these animals would seem to be greater than could possibly occur in a patient. Against this it must be remembered that during the routine examination of patients it is quite common to find that touching the septum lightly with a probe will produce a cough, a spluttering, or a wheeze in many of these asthmatics, showing most plainly a high degree of sensitiveness in the nasobronchial reflex.

Infections in the post-nasal space may therefore not only cause a direct vagal stimulation by inflammatory irritation, but the mere fact that such an infection is present will lead to an inflamed, congested, and œdematous condition in the tissues, which is so much more suitable for allowing the inhalant antigens to gain access to the body and affect the bronchial spasm by the general allergic cellular sensitivity.

d. Toxin-histamine Spasm.—This is the commonest and most important of the four groups of primary bacterial factors in asthma and its allied conditions. The significant basis of this group is the production by bacteria, or bacterial products, of histamine or some closely allied 'H' or histamine-like substance. This group falls naturally into two further subdivisions, depending on whether the bronchial spasm is caused (i) by the distant production of 'H' substance away from the lungs, or (ii) by its local production in the lungs. That is to say, while an organism may produce in the gut or urinary system a histamine derivative by digestion of proteins, there are other organisms whose toxins or digestive by-products are not themselves histamine-like in their physiological action, yet when they reach situations rich in histamine, such as the skin and lungs, they will liberate the histamine-like substances in these situations, with the consequent spasm in the hypersensitive bronchial muscles, or the urticarial patches in the hypersensitive skin. This latter effect, i.e., the local production of histamine-like substances by toxins, is of great importance; and although we have been aware of the fact from a clinical point of view for many years, this working hypothesis has only recently been proved experimentally by Feldberg and Keogh.[1]

In view of this significant piece of work it becomes very probable that all bacterial factors in asthma have as a basis the toxin-histamine spasm relationship, since it appears improbable that there could be a direct production of histamine-like substance in a situation distal to the hypersensitive reacting area sufficient to produce symptoms without the histamine being detoxicated by the organs through which the blood must pass. Histamine introduced artificially into the blood-stream disappears with remarkable rapidity.

To re-emphasize the point, then, it appears that toxins of bacterial origin may circulate in the blood or lymph, and on reaching the special organs rich in histamine they may liberate that substance in quantities relative to their content, the two most important being the bronchial muscle and the skin. *A reasonable explanation is thus given of the importance of distal foci in asthma.* When it so happens that the infection is in the post-nasal space, there is the toxin production of histamine added to the additional stimulus by reflex vagal causes; so that one is led to regard, as a result of the recent experiments as well as from practical clinical experience, that focal infections in the post-nasal space are of paramount importance in bacterial asthma: and even more so than the more local bronchial infections determined by examination of the sputum.

2. **Secondary Bacterial Infections.** — A nasal mucosa continuously œdematous and congested from 'allergic' causes is an excellent pabulum for the growth of micro-organisms, while a sluggish circulation hinders processes of natural immunity and impedes the course of phagocytic procedures. Such indeed is true of the whole respiratory tract. These infections are easily acquired as a result of the altered physiological and anatomical state of the tract consequent upon a long history of asthma. Indeed, as has already been stated, it is a practical fact that nearly all cases of persisting pure allergic asthma will sooner or later become secondarily infected. Whether this secondary infection will develop into a partial primary factor will depend (*a*) upon the anatomical situation of the infection, (*b*) upon the type of protein hypersensitivity already present, and (*c*) upon the type of the infecting organism and its power to manufacture toxin producing histamine.

Secondary infections therefore acquire their importance mainly in relation to the possibilities of their becoming primary

ones. While as yet our knowledge of the bacteria producing toxin-histamine is extremely limited from a purely scientific point of view, we learn much from the practical experience of the specific micro-organisms isolated in these cases. The recent experiment on the production of histamine distally by toxins was carried out with staphylococci, and we find it extremely significant therefore that it has been our experience for several years that the very highest importance must be attached to certain varieties of staphylococci isolated from the posterior nares in cases of asthma.

Experience in clinical bacteriology in asthma would lead one to postulate that there are only certain organisms isolated from distal foci which are of importance in the mixed allergic-infective type of asthma (Type III), while practically the whole gamut of bacterial micro-organisms may be found to be of significance in the local bronchial infective types. For it is in the latter group that the mere fact of irritation and inflammation is the promoter of the spasm, while the former group naturally depends on the specific toxins to produce histamine.

In concluding a theoretical consideration of bacterial factors in asthma, one must make a note of the intestinal flora. While there may be organisms in this situation which are fundamental toxin-histamine producers, there are in addition other points in evidence. Constipation, achlorhydria, faulty or necessarily abnormal diets may lead to the excessive multiplication of bacteria and absorption of their toxic products. This burden falls upon the detoxicating mechanisms of the hepatic and reticulo-endothelial systems. Continued over a period of time this gradual overburdening leads to a poisoning and deficient function, or at least a deficiency in the reserve powers. Such a state has repercussions when bacterial foci take their hold and become evident in other situations. The diminished general resistance and detoxicating functions lead to the unchecked advance of such foci, which in a patient with a tendency to asthma may prove just the necessary additional burden to overbalance the threshold value and provoke an asthmatic spasm.

THE BACTERIOLOCAL EXAMINATION OF A CASE

Practical matters in regard to the bacteriology of asthma must now occupy our attention, and must aim at answering

the fundamental question: Is there an infective element in the case that must necessarily be treated in order to effect relief? In other words, the practical aspect must deal with the thorough bacteriological investigation of a case with a view to the production of a reliable, potent, and comprehensive vaccine. The technique of the clinical administration is set out in Chapter XVII. While it may be reasonably held that the investigations are more properly part of a routine text-book on bacteriology, it will be helpful at this stage to emphasize one or two points of major interest and importance, while to complete the picture a few additional references to technique are appended at the end of this chapter.

The main general features which lead to the decision for bacteriological examination are those cases in which the asthma or allied symptom has started after adolescence, often associated with an acute infective complaint; those cases where there is a purulent or muco-purulent post-nasal discharge; those in which the attacks last for several days without remission; those in which no positive dermal tests are elicited; those that are sensitive to aspirin; and such cases as are indicative of infective conditions as a result of the examination by the differential sedimentation test.

The special case of urticaria, where this is not due to a specific foreign-protein antigen, has been found to yield to treatment on bacteriological grounds as a toxæmic state of the bowel. Extremely heavy cultures of fæcal streptococci have been observed in such patients, who later have responded very satisfactorily to vaccines and the control of the intestinal flora by drugs, diet, and physical methods. In cases, therefore, in which these conditions are present, vaccine therapy is indicated to be advantageous, and bacteriological investigations have to be instituted. Such a practical examination consists in routine bacteriology.

On general principles a complete bacteriological examination repays the labour entailed, and in such a case includes specimens of fæces, urine (catheter in women), vaginal swab (only with the pathogen-selective blood-culture), post-nasal and throat swabs, and the sputum. Antral washings, teeth, turbinate swab, boils, sinuses, and other pathological foci may have to be examined from time to time. Reduced to a minimum, we may consider the examination of the posterior

nares and fæcal specimens as the two most important, and those that should never be overlooked.

A great number of papers have been written concerning ' bacteriology ' in asthma which report solely on the flora of the sputum. This specimen we regard as of comparatively little importance. Direct microscopical examination of stained slides of sputa may give one useful information from the histological and cytological structures in them, but when culture is considered the specimen is, in our opinion, of lesser value. On the other hand, the post-nasal swab may be taken easily and be a pure culture of the part examined, and we have never yet met a specimen which does not contain all the relevant organisms that may be found in the sputum from the same patient. The sputum (usually mixed with saliva) contains masses of bacteria of many varying types. The important varieties can almost always be isolated from the posterior nares, the specimen from which is uncomplicated by the large number of unimportant normal commensal micro-organisms.

If the theoretical factors discussed earlier in this chapter are held in mind, the obviously greater importance of the post-nasal bacteriology is recognized. The sputum may be held to be of greater import only in those cases of asthma belonging to Type II where a primary bronchitis or other local intra-thoracic infection has paved the way to the development of a spasmodic bronchial musculature, in which case there is no general cellular allergy.

A considerable number of cases have been examined in conjunction with the pathogen-selective blood-culture methods, the modified technique (Crowe[2]) of the original (Solis-Cohen[3]) being utilized. Without giving any details, the principles may be briefly referred to. An emulsion of the bacteria of each specimen is mixed with a fresh specimen of the patient's own blood. In the quantities used normal blood has an immediate lethal action and kills all the organisms present. It is found in certain cases, however, that on culture of these mixtures, one or two varieties of micro-organisms may continue to grow and multiply. Such organisms are termed ' pathogen-selective positive ', and are necessarily a function either of a deficiency factor in the blood, or a ' specific stimulator ' substance in the blood, acting in the same manner as an ' aggressive ' factor of the organism. The exact significance is as yet not fully understood. Hæmolytic streptococci tend

always to be pathogen-selective positive, pneumococci, *Staph. aureus* and *Staph. E*, and certain enterococci have a greater tendency to be positive, while all Gram-negative organisms may be said to be very rarely positive, although varieties of *B. coli*, Friedländer's bacillus, *M. catarrhalis*, and Pfeiffer's bacillus have from time to time been observed to be truly positive.

While the significance of a positive pathogen-selected organism remains obscure in its relationship to the pathological condition under investigation, one cannot postulate that the performance of such tests is in any way essential to the examination of asthmatic conditions, or that the results obtained bear any greater value than the ordinary methods in demonstrating the causal organisms of primary importance. From a research point of view the results may eventually lead to some better understanding, but the real and valuable assistance of such tests is from the aspect of technical manipulation. Where there is a very numerous and mixed type of bacteriological flora, such as in sputum, or throat and gum swabs, the elimination of the large numbers of commensal and other relatively unimportant organisms by exposing the emulsion of the specimen in question to the lethal action of fresh blood becomes a practical performance of much assistance. By such methods the examination and isolation of the more important bacteria is made materially easier and thus more efficient. This manipulation is made use of in rendering the routine examination of the cervix in women a rapid and practical procedure. By taking a swab of the cervix and fornices through a narrow glass cannula passed into the vagina, the flora of that region is determined together with the organisms of a cervical discharge in a quick and easy manner, without necessitating the expert and more elaborate technique of the usual gynæcological methods. If the vaginal swab is examined by the pathogen-selective culture methods, all the normal organisms of the vagina are killed and the important streptococci, staphylococci, etc., grow satisfactorily (the gonococcus being of no importance in asthma).

The following table shows the result of examining 347 specimens by the pathogen-selective culture method from 100 consecutive patients. Under each specimen heading there are two columns, the first or left-hand one indicating the predominant organism, while the right-hand column shows

those that are pathogen-selective positive. A further analysis of the staphylococci and streptococci is given in the second and third sections of the table.

PATHOGEN-SELECTIVE CULTURES IN 100 CASES OF ASTHMA

	POST-NASAL		THROAT		SPUTUM		FÆCES		URINE		VAGINAL		NASAL
Number examined	100		10		70		88		39		36		4
ORGANISM	O.*	PS.	O.	PS.	O.	PS.	O.	PS.	O.	PS.	O.	PS.	O.
Staphylococci ..	28	10	2	1	8	3	5	2	4	7	–	3	3
Streptococci ..	73	21	9	5	62	30	28	4	–	2	–	8	1
Pneumococci ..	16	9	2	1	18	14	–	–	–	–	–	–	–
M. catarrhalis ..	25	4	2	0	12	1	–	–	–	–	–	–	–
Friedländer's B.	7	1	–	0	9	0	–	–	–	–	–	–	–
Pfeiffer's B. ..	5	1	1	1	3	0	–	–	–	–	–	–	–
M. tetragenus ..	1	0	–	–	3	1	–	–	–	–	–	–	–
Hofmann's B.	3	0	–	–	–	0	–	–	–	–	–	–	–
Others ..	17	2	–	–	10	4	4	1	–	3	–	1	–
Non-lactose bac.	0	0	0	0	1	0	12	1	0	0	–	0	–
Enterococci ..	–	–	–	–	–	–	23	29	2	5	–	2	–
S. fæcalis ..	–	–	–	–	–	–	13	3	–	0	–	0	–
S. zymogenes ..	–	–	–	–	–	–	2	3	–	0	–	2	–
Sterile ..	4	37	0	10	0	14	0	39	12	21	–	20	0
Staph. A † ..	3	2	1	1	3	2	2	2	0	0	–	0	0
Staph. E ..	11	5	1	0	3	1	0	0	1	2	–	2	0
Staph. D ..	5	2	0	0	0	0	1	0	1	1	–	1	0
Staph. albus ..	9	1	0	0	2	0	2	0	2	4	–	0	3
Str. hæmolyticus	2	1	1	2	0	0	0	0	0	0	–	5	–
Str. viridans ..	68	20	8	3	62	30	23	3	–	1	–	2	–
Str. anhæmolyticus	3	0	–	0	–	0	5	1	–	1	–	1	–

* O = Number of times organism particularly noted in ordinary culture.
PS. = Number of times organism determined as pathogen-selective positive
† *Staph. A.—aureus*, mannite +, milk clot 48 hours.
Staph. E.—E type, ,, +, ,, ,, 5 days.
Staph. D.—deformans, ,, –, ,, ,, 48 hours.
Staph. albus—albus, ,, –, ,, ,, negative.

It will be noted that there is an occasional anomaly in that there are more specimens pathogen-selective positive to a certain organism than there are specimens containing that particular organism. However, this is only an apparent anomaly, since the organisms are noted in the respective left-hand columns only when they are present in sufficient numbers as to be considered abnormal. It may often occur then that a few enterococci are observed in a fæcal specimen; indeed this may be so in the majority of normal people. They

would not be noted under such circumstances in the left-hand column, but might nevertheless be pathogen-selective positive. Cronin Lowe[4] even goes so far as to suggest that an organism may be revealed as pathogen-selective positive when it could not be isolated from ordinary culture. To sum up, the pathogen-selective method is a useful laboratory procedure, and is of very considerable interest; but the correlation of the observed results and the clinical significance is as yet not fully appreciated.

There is no one single organism that can be specifically associated with asthma as a causative agent, such as is the *B. typhosus* in enteric fever. It follows, therefore, that from a purely bacteriological point of view we have to review the occurrence of the various kinds of bacteria more frequently associated with the different primary and secondary infective types of asthma. In an analogous manner the pneumococcus may be said to be closely associated with, though not a specific cause of, pneumonia, for experience has led to the knowledge that the pneumococcus may also be the primary organism of importance in other conditions totally unrelated to pneumonia, and at the same time pneumonia itself can occur as a typical clinical entity but due to an organism in no way related to the pneumococcus.

While the general trend of research advances in that direction, it is as yet too early to postulate that the essential factor in asthma is not the organism, but the production of a bacterial by-product capable of producing bronchial spasm by the toxin-histamine link. The proof of this lies in the animal laboratory, and practical clinical bacteriology can concern itself no more at present than with the observed organisms in the various foci, which is, however, the aspect—the production of a means of treating the patient—that we are essentially concerned with in this chapter. Provided, as indeed is the case, that the results are satisfactory from the patient's point of view, the empiricism of the method can have no adversaries, while the intimate biochemical links can be joined together slowly and surely in the research laboratory in the course of time.

The whole range of micro-organisms associated with catarrhal conditions in the pharynx and respiratory tract may be isolated from time to time from asthmatic cases of infective type. We can note, however, the greater frequency of certain

organisms, and remark upon the question of the staphylococci. Before specializing on particular organisms, it is as well to emphasize our belief that specific autogenous vaccines of one or two organisms are inferior in their therapeutic effect to the extensive and comprehensive vaccine mixtures here advocated. The vaccine to be effective must be comprehensive and potent. Potency is accomplished by the use of rich and suitable media together with the avoidance of multiple subculturing. Comprehensive vaccines are produced by the careful acquisition of each type and variety of each type of organism present, which procedure is made more rapid and easy by the direct macroscopic differentiation methods by colony characteristics on solid 75 per cent blood media. Crowe[5] differentiates some seventy varieties of non-hæmolytic streptococci, while Thomson[6] gives characteristics of the organisms other than streptococci. The comprehensiveness of the vaccine is further maintained by the combination of a polyvalent stock mixture, consisting of all the varieties found in cases of asthma and catarrhal infection of the respiratory tract. An anaerobe may also be included, the *Anaeromyces bronchitica*, which has been isolated from the sputum of asthmatic cases by Thompson,[7] who places some stress upon it.

Investigation of Particular Foci.—Dealing with the organisms isolated from particular foci, which do of course form the essential constituents of any autogenous vaccine, the features of each locus usually dealt with in a routine examination may be briefly reviewed.

a. The Posterior Nares.—The area examined by the (West's) swab of this region is of primary importance. It should be examined in every case of asthma where microbic factors are suspected. Normally a few streptococci and other commensal mouth organisms are always present; even a few pneumococcal colonies cannot be considered as evidence of a pathological focus. In asthmatic cases, heavy cultures are, however, obtained. Where the infection is a 'primary' one, that is to say, a direct casual factor, the cultures tend to show large numbers of one or two morphological types, as opposed to secondary infection, where there are considerable numbers of many different types. In primary infections, certain catarrhal types of *Str. viridans*, pneumococci, *M. catarrhalis*, Friedländer's bacillus, and Pfeiffer's bacillus are those most frequently present and often in almost pure culture. In

addition there may be present the important staphylococcal organisms. The proved significance of staphylococcal toxin in the distal production of histamine has already been emphasized. Corroborative evidence from clinical examinations has been our experience for many years. The occurrence of staphylococcal infections, especially with the E type coccus, is to be considered of great importance, and a type of case which yields most satisfactorily to vaccine treatment. As an integral factor in the aspirin-sensitive group of asthma it reaches the height of its asthmatic pathogenicity. With the exception of the *Staph. albus*, therefore, all staphylococci isolated from this region should not be discarded as irrelevant contaminants, but, on the contrary, as a potent source of histamine-producing toxin.

b. The Fæces.—The fæcal specimen often shows an abnormal type of flora due probably to digestive abnormalities. Very heavy streptococcal growths, however, are of much importance in urticaria and the allied allergic complaints. In a simple asthma it is infrequent to determine a very abnormal fæcal flora. Excessive quantities of normal bacteria and numerous bacillary organisms capable of producing much toxic material may be present, thus tending to add an unnecessary load on the liver function.

c. The Urine.—Very occasionally, but more particularly in urticarial cases, a coliform, streptococcal, or enterococcal infection may be determined. In one very striking case, a man from whom a fæcal streptococcus (*zymogenes*) was isolated responded to an injection of the vaccine of this single organism by a sharp and severe attack of asthma.

d. The Cervix.—As examined by the pathogen-selective test on the vaginal swab, streptococci are most usually isolated, often of the true hæmolytic variety.

e. The Throat.—This is examined in many cases, but more particularly in the younger patients in whom the tonsils are enlarged and inflamed. From their situation it may well be understood that all manner of different organisms may be isolated, but the examination is carried out with particular reference to the isolation of a predominant organism, or for the presence of staphylococci or hæmolytic streptococci.

f. The Sputum.—Bacteriological examination of the sputum becomes of importance only in those cases where a bronchitis or other acute respiratory disease precedes an asthmatic state

in a person who has no general cellular hypersensitivity or allergy; that is to say, in those cases where a subacute or chronic infection persists locally to the eventual production of a muscular spasm. Examination in these cases may produce a fairly pure culture of a single variety, but when persistent for any length of time, the bacteriological flora more usually approximates to that of a secondary infection and shows multiple varieties of streptococci, together with any of the whole range of organisms that may be similarly isolated from the post-nasal space.

The morphological differentiation of bacteria in asthma presents therefore a mixed and to some extent an unsatisfactory picture in comparison with the importance of such bacterial infections in these particular types of asthma. The absence of any specific action in any single organism complicates a satisfactory understanding of the biochemical or physiological mechanisms at play, and one is left with a wide variety of morphological types to consider, to isolate, and to prepare for vaccine therapy. In the staphylococci alone is there any direct relationship to be seen between the experiment of the physiological laboratory and clinical experience, but one may venture to take a longer view into the future, and envisage a more direct relationship being demonstrated, not so much with any individual organism, as with the products of their symbiotic metabolism in effecting a biochemical and distal production of H-substance in the hypersensitive locations of either the bronchial muscle or the tissues of the dermis.

Technique.—The following points of interest in the technique may be referred to :—

All specimens are immediately emulsified in sterile normal saline to a suitable dilution. These are then plated out on solid 75 per cent blood-agar medium. (Chocolate medium, Crowe.) In addition fæcal specimens are plated on McConkey's medium, post-nasal and throat swabs on blood-agar, and sputa on mould medium.

After some forty hours' growth, single colonies are picked off and grown for a further twenty-four hours in a 1 per cent glucose trypsinized ox-heart broth, at a *p*H of 7·3; in which a very copious growth will have occurred. These organisms are then emulsified in 0·5 per cent carbol-saline, sterilized by

heat at 60° C. and standardized by opacity tubes, and suitably diluted to a therapeutic strength.

Further morphological differentiation is determined by subculture by the usual routine methods.

Successful catheterization in women is a simple matter if after an antiseptic wash the whole area is thoroughly dried in a sterile manner, the catheter being dry and then lubricated with oil.

A specimen of sputum is examined by washing a piece of mucus twice in sterile saline and then emulsifying the washed plug in a sterile pestle and mortar.

Medium for examination of moulds and yeasts is an acid medium of *p*H 5·3 containing lactose or maltose with acid potassium tartrate.

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CHAPTER XII

EXAMINATION OF A CASE OF ASTHMA

(continued)

THE CYTOLOGY AND BIOCHEMISTRY OF THE BLOOD

WITH such definite evidence before us as the infallible passive transfer of the essential factors in hypersensitivity by the Prausnitz-Küstner reaction, it becomes an easy deduction to determine that in the blood, separated from its host, must lie some biochemical factors of the greatest importance to the further understanding of the allergic phenomena. That we are as yet far from a complete understanding of these facts is also patently obvious. In this chapter we review the various significant points that have been investigated in the cytology and biochemistry of asthma.

Taking one step back from the fundamental deduction just made above, the sum total of 'allergic' asthma and every portion of it depends upon the presence in the blood of reagins against those proteins to which the patient is sensitized. When these reagins and the foreign proteins to which they are specific meet in the blood, there is from a cytological point of view the constant occurrence of a hæmoclasic crisis with a leucopenia, a relative lymphocytosis, together with a fall in blood-pressure, and all the other anaphylactic symptoms. Such a syndrome —the hæmoclasic crisis—can, however, occur in so many other conditions that its diagnostic value is thereby impaired.

Our new work entailed in the differential sedimentation test is referred to in the next chapter. As will be seen from the results of the investigations by these methods, there emerges a serological classification of asthma.

This classification into Types I, II, and III by the differential sedimentation test agrees so consistently with a clinical classification of the same cases into I—allergic, II—bacterial, and III—the mixed type, that we feel there must be much to be learnt from these facts.

If from the serum alone a case can be placed in its correct clinical group, it holds as a corollary that the serum of a

patient of the allergic type differs in some essential way from that of a patient of the bacterial type; and as a consequence not only is an interesting field of research offered in explaining how and why they differ, but real biochemical advance is possible in such research.

The same classification is possible in other allergic complaints, as in urticaria. The differential sedimentation test has proved perhaps of the greatest value in determining that the important factor in the aspirin-sensitive group is a double one—a real hypersensitive state or allergy as well as a microbic infective element—and thus with the proper understanding of this as a result of the serological tests, much of the prognostic gloom of these particular cases has been eradicated.

The factor of an increased eosinophil count, capricious though it be, is so intimately concerned with the presence of foreign proteins in the blood that it suggests again that the explanation of the whole problem of sensitization will eventually be found in the blood and the colloidal constituents of the sensitized cells.

The colloidal particles in the blood, as seen under the microscope with the dark-field illumination, give further evidence of blood-changes in asthma.

Reference will now be made to a number of points in greater detail with regard to the pathology of the blood in asthma. The majority of the observations have been extracted from the literature; and as they refer to asthma as a whole and not to the individual groups which differ so essentially from one another, it may be that anomalies occurring in the results obtained by different observers have been due to the type of case examined by one being different from that of another.

A further cause of variance is possibly the fact that there is usually no information given as to whether the observation was made on a patient during an attack of asthma or at a time when he was entirely free.

Blood Calcium.—No definite abnormality in the amount of blood calcium has been demonstrated. The more recent findings thus contradict the original claims that a deficiency exists, and deny that calcium therapy in any way influences the blood or the course of the complaint by producing any permanent change in the blood. Claims that patients suffering from asthma and hay fever have shown improvement after the injection of calcium must also pay some discount from

the fact that many other forms of intravenous injection are likewise followed by benefit, neither should substances such as peptone be forgotten, with which these colloids are often suspended.

Criep and McElroy,[1] examining the blood of 160 allergic cases, found the average amount of serum calcium to be substantially the same as in 40 normal persons, namely, 10·43 mg. per cent.

The whole subject of the calcium in the blood has been for many years a very complicated one, and none the less so as a result of the recent work of McLean and Hastings.[2] Up till this time there had been the teaching that calcium in the blood was dependent upon a large variety of other constituents —phosphates, carbonates, glucose, vitamins, and hormones. With the recent demonstration by McLean that there exists a simple mass-law equation between the serum proteins and the calcium—even to the extent of the proteins and total calcium alone determining the all-important ionic calcium—the whole question is again, so to speak, thrown into the melting-pot. By this work the amount of ionic and thus active calcium is determined entirely by the quantity of protein present and a glandular factor influencing the total calcium. To say that this glandular factor depends on the balance of activity of the parathyroid glands is but to bring in the whole gamut of glandular balance, and involves the possibility of any one of them being ' out of balance '. One of us (H. C.) has, however, determined the ionic calcium on these lines in a number of cases. No abnormalities of ionic calcium could be determined in the serum from asthma patients, and where quite gross changes occurred as observed by the differential sedimentation test, these calcium determinations were always within the limits of normal. This, if the teaching of McLean is to be accepted, would eliminate, not only the possibility of calcium, but more importantly ionic calcium, from having any bearing on the allergic state.

Again, it has recently been suggested that the calcium-potassium balance has to be considered as of importance in asthma. From the laws of colloidal chemistry one might very well expect that such a balance might be of the very greatest importance in a colloidal solution so perfect as is serum. Probably similar active and inactive states of the cholesterol will also have to come into the consideration of

the balance, but we may refer to the important work of D'Silva.[3] While this work is still in the experimental stage, the preliminary deduction, that 'the quantitative liberation of potassium by adrenaline . . . in the liver suggests that the liberation of the base may parallel the destruction of adrenaline in the liver cells', would appear to be of the greatest importance.

The rationale of calcium therapy was based on the assumption that by its use vascular permeability was decreased, nervous irritability allayed, blood-pressure—notoriously low in asthma—raised, and the peripheral blood-vessels contracted. According to the findings of Curphey and Solomon,[4] large doses are necessary to produce results. They suggest that 30 c.c. of a 20 per cent calcium gluconate solution should be given intravenously. This intravenous dose of some 90 gr. (7·6 gr. of calcium) may be compared with the usual 10 or 15 gr. of calcium lactate (2·74 gr. of calcium) commonly given by the mouth, or with the dose of 3 gr. of calcium chloride given intravenously in which there is only 1·08 gr. of calcium.

What little benefit has followed using calcium has been, I have thought, from the intravenous injection of collosol calcium, an infinitely smaller dose, but effective from its large surface and its colloidal nature. Both Ramirez[5] and Cohen and Rudolf[6] find no value from giving calcium in the treatment of allergy; nevertheless there is much in the medical literature of praise for its effect.

Blood-sugar.—This is also found to be normal both during and between attacks in allergic and non-allergic cases, as was the sugar tolerance (Wagner and Rackemann[7]). Beckman[8] only saw 6 cases of asthma in 6000 diabetics, and only 2 cases of diabetes in 3000 asthmatics.

Blood-counts in Asthma.—In asphyxial conditions and in asthma, especially when accompanied by cyanosis, there tends to be a high count of red cells and a proportionately high hæmoglobin count.

Pepper and Farley[9] state that the white count may rise to 15,000 or 20,000 towards the end of a paroxysm. Apart from the presence of an eosinophilia, there would seem to be little abnormality in the blood cytology of an asthmatic.

The Arneth Blood-count.—Acton and Dharmendra[10] noted that the Arneth blood-count generally registered below 70 in allergic asthma and above 70 in bronchial asthma. For

this purpose the white cells are classified into five groups in accordance with the number of nuclei that they contain. The Arneth index is the sum of those containing 1 or 2 nuclei plus half of those containing 3 nuclei. Napier and Dharmendra[11] found that the shift to the left in the bronchial cases was reduced in the cases favourably affected by treatment with vaccine, and they consider a marked improvement in the Arneth count after treatment to be a good prognostic sign.

Blood-pressure in Asthma. There is no variation in the blood-pressure of asthmatics from the normal, according to Witts.[12] His 'normal' figures are those given by Alvarez and Stanley[13] of the warders and inmates of a large state prison, who are, as Alvarez quaintly puts it, "freed from the hurry and strain and fatigue incident to earning a living".

The Clotting Time appears to be normal, while in some instances the clot-retraction is remarkably small.

Clot-retraction.—While some observations have been recorded suggesting that there is a deficiency of clot-retraction in certain cases of asthma, the results suffer in an identical manner to those of the sedimentation rate. These faults are two—firstly, a lack of primary classification of the clinical cases with which the results are to be correlated; and secondly, the essential physical characteristics of the process of clot-retraction and its measurement. There would appear to be a probability that the Type I asthmas may show a 'real' deficiency in clot-retraction, and it is a question well worth investigating. In order to establish this, however, various simple principles must be held in mind, for which principles we are indebted to Dr. R. G. Macfarlane, from whose original methods of measurement the observations and deductions were formulated. Briefly summarized they are as follows:—

1. The clots formed by fresh and recalcified citrated blood contract with a smoothly diminishing velocity, losing from 40 to 60 per cent of their original volume.

2. This process is practically complete in an hour at 37° C.

3. Up to 45° C. increase in temperature is accompanied by an increase in retraction; above this point retraction is inhibited.

4. Retraction is not sensitive to alterations in *p*H, or salt or calcium concentrations.

5. Below a certain number (probably from 60,000 to 100,000) reduction in the platelets is accompanied by a decrease in retraction. This relation is not due to the actual number of platelets present

in a given volume of plasma, since dilution of the plasma with saline does not reduce the subsequent retraction, though it reduces the concentration of the platelets. However, dilution by 'platelet-free' plasma does result in a reduction of retraction, so that the relation must be between the number of platelets and a fluid constituent of the plasma.

6. Normal cell-free plasma produces clots that retract to approximately 10 per cent of their original volume. Adding cells to such plasma reduces retraction, the cells themselves being retained within the fibrin-mesh of the clot, and being of a semi-rigid nature they naturally enlarge its final volume, so that it now retracts only to its original degree plus a volume equal to approximately 0·7–0·8 of the cells added. It is possible therefore to apply a simple correction to the observed clot-retraction for the actual corpuscular volume or hæmatocrit value.

7. Cell-free plasma with a deficiency of retraction is not affected by addition of cells until the volume of cells added is larger than the volume of the cell-free retracted clot. Consequently the correction factor applicable to normally retracting blood will not apply when retraction is deficient. Its use, however, will reveal a deficiency which might be marked by anæmia.

Eosinophilia.—Much has already been said about eosinophilia (*see* pp. 76, 77). Probably an eosinophilia is a normal reaction to the entrance into the blood of a foreign protein during the course of allergy or from some live parasite growing in the body. The presence of reagins does not produce it. Burrage[14] in a group of hay-fever patients examined before the season found no eosinophilia.

In a graph showing daily counts, Spangler[15] found that during two months when the patient had asthma the count was 10 to 15 per cent. This continued until the asthma ceased, when the eosinophilia dropped to 2 per cent. The only indication of value to be deduced from an eosinophilia is that the patient is probably of the allergic protein-sensitive type, or rather, that he is suffering from the entrance into the blood of a foreign protein.

Hæmoclasic Crisis.—This has been considered on p. 23.

The Colloidal Particles of the Blood.—This may be one of the most important questions in the whole body, but it has not received a tithe of the research that it merits. The work of McDonagh is well known, but the *Nature of Disease* and other writings are so difficult to read that there would appear to be ample scope for some one else to commence again at the beginning and build afresh, explaining and proving each statement as he goes.

Reports by Gage and Fish,[16] Peters,[17] and Fraser and Stewart[18] more recently published are beginning to throw some light on the subject.

The original definition of colloidal particles by Graham in 1861 determined them to be of such a size as to pass the ordinary form of filter, but not to pass through a semipermeable membrane, as do the more simple inorganic compounds. Since this the whole scientific study of colloidal chemistry has arisen. I refer here, however, to colloidal particles in a way not so well defined, but of a more comprehensive character for the practising physician.

By observing a drop of serum under a microscope with the most powerful lens systems we can conjure into being, it appears to be the clearest of solutions. The air of our consulting-rooms appears perfectly empty under ordinary circumstances; in the light of a powerful beam of sunlight through the window we are soon led to believe otherwise, and we are amazed to see the almost 'solid' nature of the air we breathe; myriads of small particles are brought within our powers of vision. Similarly, if we arrange an optical apparatus with a microscope and a powerful right-angled beam of light, the previously clear serum can be seen to contain a host of small particles darting about in all directions. To these particles observed in the dark-field ultra-microscope I am here applying the term 'colloidal particles'.

Some slight skill is necessary to manipulate the apparatus and to focus the beam of light in line through the dark-field condenser, the slide, and the microscope, but this accomplished, the particles are very easily seen. I have examined many hundreds of specimens of fresh blood and serum, and though the main problems are as yet untouched certain observations have been noted.

The technique must be so perfected that any specimen of freshly shed blood can be under examination before it has time to clot, and so standardized that variations seen in different bloods cannot have been caused by alterations in the method of examination.

With a very thin film of blood the colloidal particles can be seen between the red cells, but the film must be sufficiently deep so that the field may be reviewed while neither the upper surface of the slide nor the under surface of the cover-slip comes within range of the focus.

The following features are to be noted :—

1. *The Number of Colloidal Particles Present.*—These are counted through a small pinhole in a disc placed in the eyepiece of the microscope, and may vary from one or two to many hundreds.

Fraser and Stewart[18] find that the number of colloidal particles in the blood increases after a meal containing fat; they find that the blood fat increases and falls with the number of colloidal particles present. There is no increase in the number of particles after meals containing pure carbohydrates or pure protein; in fact, after the pure carbohydrate there may be a fall from the basal number present in starvation. In my own blood the increase in number is some 30 per cent after a mixed meal.

2. *Their Movement.*—The particles are knocked about by the kinetic energy of the molecules in solution in the plasma or serum. Roughly speaking, the smaller the particles the greater the Brownian movement in a fluid of standard viscosity and temperature.

3. *Their Size.*—Sometimes all the particles appear to be of the same size, but in most bloods larger and smaller particles are to be seen. Sometimes very large round white particles may be noted, other particles diminishing in size to invisibility. Beyond this there are still myriads of particles present of even smaller size; invisible either because the resolving power of the optical apparatus is insufficient to show them or, if of a larger size, because their refractive index differs so little from that of the surrounding medium that the light fails to refract off them and so define their outline.

4. *Aggregates.*—Aggregates are rarely seen in normal bloods. They consist of two or three particles joined together.

5. *Clumps.*—More rarely, clumps may be seen, that is some twenty or thirty particles massed together, or more still when flocculation occurs.

6. *Rouleaux* formation and the contour of the red cells is beautifully shown. Crowded particles jostle one another in the white cells and glisten in the light refracted off them.

7. *Clotting.*—The process of clotting can be seen. The colloidal particles take no part in this. Tiny stiff strands appear connecting points together until the whole field is a meshwork of tightly drawn filaments, between which the particles move unconcernedly.

8. *Crenation of Red Cells.*—The slightest pressure on the cover-slip causes crenation of the red cells and their appearance as large gooseberries. With greater pressure still they appear as wizened cells empty of contents and of low refractive power.

9. '*Worms*'.—In many specimens are seen what one may call 'worms'. They have the thickness of large particles, some short and stubby, others as long as the diameter of three red cells. Being entirely flexible and being hit at various points by the molecular movement around them on all sides they have a peculiarly lifelike wriggling movement, without of course any progression. They may be seen in fresh blood before it has clotted. The ends appear to be bulbous and slightly frayed like the cut ends of a piece of string; possibly they are extrusions of white cells.

10. *Inclusion Cells.*—About one quarter of the size of red cells, they show the barest of outlines. The envelope is but poorly refractive, the contents are quite clear except for one or two colloidal particles undergoing very active movement, as though exercising a great effort to find a way out from their prison. Other cells of the same size and outlines have an occasional particle firmly adherent to their surface.

In cases of asthma the outstanding variation is the great difference to be seen in specimens in the number and size of the colloidal particles. Their arrangement into aggregates and clumps is more obvious in specimens of serum a day or so old. In some specimens of serum large masses of equal size appear as snowflakes.

In many asthmatics during the attack there may appear to be no particles present at all, and I have noticed them to return after the attack has subsided, though their return is possibly due to the taking of food. The number of particles is usually increased by a meal, especially a fatty one, but very little from day to day in a normal person under standard conditions.

No obvious correlation could be established between the colloidal picture and the findings of the differential sedimentation test in 300 cases. The particles are visible because, being of a different refractive index to the continuous phase in which they are suspended, sufficient light can be reflected off them to allow their outline to be seen. Other constituents of the

serum, as perhaps viruses, may be invisible because they are of the same refractive index as the medium in which they float.

But however different one serum may appear from another, little can be hoped to evolve from merely noting these differences until some fundamental knowledge of the underlying causes—electrical, physical, and chemical—is forthcoming to suggest the basis and laws on which these changes in size and number occur.

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CHAPTER XIII

EXAMINATION OF A CASE OF ASTHMA

(continued)

ERYTHROCYTE SEDIMENTATION RATE (E.S.R.)

(Red Cell Suspension Stability)

THIS widely used clinical test has been applied to cases of asthma by many investigators with rather negative results, which in general we would confirm from several hundred estimations. The value of this test has suffered like many other biochemical manipulations from a complete lack of correlation with a clinical type-classification of asthma. The observations have been recorded in relation to asthma regarded as a single general entity, instead of realizing practically, that asthma is a clinical symptom subject to activation by various entirely separate and different primary pathological factors.

In the erythrocyte sedimentation rate, the rate of fall of the patient's red cells in their own plasma is measured. There are many techniques for performing this, varying essentially in the apparatus in which the rate of fall is observed. The two methods we have used are the Westergren[1] technique and the Wintrobe.[2] In the former the rate of fall is observed in a specimen consisting of four parts of blood diluted by one part of 3·8 per cent sodium citrate. A column 200 mm. long and approximately 2·7 mm. diameter is measured. In the Wintrobe technique, the coagulation is prevented by solid potassium and ammonium oxalate, and a column 3·5 mm. in diameter and 100 mm. in length is measured. In the special tube devised by Wintrobe and Landsberg[3] the rate of fall is measured and then the whole tube spun in a centrifuge to pack the cells, by which means the percentage volume of the whole blood occupied by the cells is measured, since the size and number of the red cells naturally affect the rate of fall. By means of a special graph, a correction may thus be made which is not obtainable by the Westergren technique.

In general the results in asthma have shown that despite the extreme severity to which the asthmatic condition may ascend, many of these bloods show perfectly normal sedimentation rates. There have been several reports that the allergic asthma patient does, generally speaking, show a tendency to a very slow rate of fall. Schulhof's[4] conclusions are of particular interest. He writes :—

> A very slow sedimentation rate of the erythrocytes is a constant symptom of allergic individuals unless they show evidence of a complication, especially infection, which tends to accelerate the sedimentation. As an infection may mask the expected slow rate, so may an allergic individual show a slow rate even in the presence of a serious infection of short duration, such as a gangrenous appendix. The interaction of the two opposite tendencies should be taken into consideration in the diagnostic and prognostic evaluation of the sedimentation rates. Besides the patients with known allergic conditions, a very slow sedimentation rate seems to be fairly common in lumbago.

Ellis[5] seems to support the idea of an increase. These observations are, however, usually based on the direct uncorrected Westergren method, and do not take into account its errors ; more especially none of them have allowed for the very important cell-volume factor of the blood, which modern research has shown may completely mask an abnormal rate of fall, or accentuate to abnormality one that is really normal (Gibson,[6] Wintrobe and Landsberg[3]), particularly in view of the cell-volume change in the pulmonary insufficiency of a chronic case of asthma, with compensatory effects in the blood, both in the size and numbers of the red cells.

Naturally where the cell volume approximates to the normal (42 per cent for women, and 47 per cent for men), and especially where the volume lies between 42 per cent and 32 per cent and allows of a free rate of fall for the cells, then the effect of primary and secondary infections in asthma will be reflected in the sedimentation rate as in other disease conditions of an infective nature. There is much room for further investigation in these cases, but unfortunately, as our knowledge increases from the technical aspect one has to discount many previous observations ; and perhaps more unfortunately still one has to admit that very little is as yet known from the serological aspect of the pathology of an increased sedimentation rate, though clinical observations of a similar nature date back to Galen and even Hippocrates.

As in other disease conditions, such as rheumatism, the inferences that may be drawn from estimations of the erythrocyte sedimentation rate are few and simple; and it must be borne in mind that such inferences are derived from a purely empirical clinical test, and no great weight can be put upon the actual figures so derived. Further, in all cases, especially where there is chronic pulmonary insufficiency, the inferences are subject to the consideration of the hæmatocrit value (or percentage cell-volume), and this in asthma should receive special attention and be allowed for in every result.

The inferences that may be drawn may therefore be summed up as follows:—

1. Where the cell-volume or hæmatocrit approximates to normal, the average normal rate of fall is given as 3·7 mm. in one hour for men, and in the same time 9·6 mm. for women.

2. Cases of asthma, however severe, show no increase in rate where the primary origin lies simply in hypersensitivity to a foreign protein. Taken over a very large number of cases of this type, the average rate of fall is slightly less than normal, more especially in the younger patients.

3. Cases where infection plays either a primary or secondary part show varying degrees of increased rate of fall roughly proportional to the severity of the infection, especially where this is bronchial. In general, however, it is not permissible to make a comparison of the severity of one case with another by their comparative sedimentation rates. Serial estimations in the same patient give a guide to the progress of the case, provided always that the correction for gross changes in cell-volume is allowed.

4. A normal rate of fall is never to be regarded as proof of the absence of infection. It frequently happens that cases may have an all-important primary infection in the posterior nares or bowel and yet show no increase in the rate.

These facts suggest therefore that the observation of the erythrocyte sedimentation rate affords little practical assistance in the problem of asthma and its treatment. However, with the passage of time and much further research work on the colloidal systems of plasma, together with more accurate methods of effecting corrections to the observed rate of fall, more light may be thrown on the subject and more practical assistance made available.

DIFFERENTIAL SEDIMENTATION TEST (D.S.T.)

We now pass to the consideration of the findings of the differential sedimentation test. The general technique and biochemical rationale of this test have been discussed *in extenso* elsewhere (Coke,[7] 1937), but owing to its particular application into the investigation of a case of asthma a full consideration of the differential sedimentation test must be set out here, both in regard to the elements of the technique and to the facts of its derivation.

Before proceeding one must reiterate a basic fact that we have attempted to put forward throughout this book, that in any discussion on asthma as a clinical syndrome it is absolutely necessary to be aware of the three main types of that condition. We then are able to interpret and corroborate such an essential step by laboratory findings, and enhance the importance of such a foundation from an entirely separate angle.

In the discussion on the erythrocyte sedimentation rate in the previous section it was seen that one of the essential difficulties of deriving any practical results was the fact that measurement of the conditions in the plasma is attempted with an agent (the red cells) which is in itself never standard, and with which the variation from standard may lie in several entirely different factors. By eliminating from such observations the red cells as a measuring agent, and replacing them by an absolute standard colloidal solution, a far more accurate determination of the actual conditions in the non-cellular portion of the blood is obtained, and thus changes of greater significance can be noted. While it is generally held that the fibrinogen in the citrated or oxalated plasma plays a part in the rate of fall of the red cells, it is equally held in most countries nowadays that it does not play the essential part. This gains even greater confirmation in that from the differential sedimentation test a reading is obtainable, known as the ' serum sedimentation ', which is in every way comparable to the erythrocyte sedimentation rate, but is a reading derived entirely from the interaction of serum and a standard colloidal agent, in which there is neither fibrinogen nor the variations of the red cells.

In the serum sedimentation the figure for a normal serum lies between 0 and 10 per cent, as in the erythrocyte sedimentation rate, and shows the same degrees of increase, according

to the severity of changes brought about as a result of infection, hypoproteinæmia, neoplastic disease, tuberculosis, pregnancy, etc., as with the erythrocyte sedimentation rate. The differential sedimentation test has, however, the additional improvement of being able to register observations of an abnormally small sedimentation by allowing readings in the reverse direction beyond the normal line of 0, which are empirically noted as minus quantities—a finding which has only been observed to any great extent in the true and uncomplicated allergic diseases, to which reference will be made immediately.

The first step in the differential classification of asthma can now be referred to in association with a demonstration of the correlation of the serum sedimentation with the erythrocyte sedimentation rate. This is seen in the following table :—

CORRELATION OF ERYTHROCYTE SEDIMENTATION RATE WITH DIFFERENTIAL SEDIMENTATION TEST.

NORMAL		TYPE I ASTHMA		TYPE II ASTHMA	
E.S.R.	D.S.T.	E.S.R.	D.S.T.	E.S.R.	D.S.T.
2	2	15	−14	31	26
3	6	9	− 5	30	29
3	3	13	− 2	28	32
4	1	5	− 3	87	52
9	1	6	− 1	25	19
2	2	5	− 4	13	16
7	8	4	−13	13	17

From such a table it becomes immediately obvious that two completely divergent types of asthma present themselves. The increased sedimentation which differentiates Type II from both the normals and Type I has exactly the same significance as an increased erythrocyte sedimentation rate, and is brought about by the same causes which, in the case of asthma of this serological and clinical type, are almost invariably referable to bacterial infection. Whether the infection is bronchial, post-nasal, urinary, or otherwise is of no consequence to the serum, since it is merely reflecting the basic fact that the patient's general system is responding to a bacterial infection.

In the minus sedimentations of the Type I case we have a significant and unique observation ; this type of allergy being

the only pathological condition in the human body so far determined that gives this particular result so constantly and to such a degree. Minus sedimentations are, however, recorded as a result of certain therapeutic measures.

For the moment it must remain a recorded observation, and one that, given a case of asthma, is peculiar to one particular type. It is, as we shall see immediately, associated with other even more typical observations in the differentiation with the heating and ether effects.

The most important and fundamental fact is that it has become evident, from the examination of 332 sera from asthma cases out of a total series of 2700 tests, that all cases of asthma can be grouped by this method of differentiation on purely serological grounds into one of three main groups. That these groups so defined can be correlated so closely with a similar clinical classification is the important corollary feature, and one by which we believe that the assignment of a case to a particular group has led to advances in the understanding and treatment of asthma in general. That we regard such a basis of classification as of the greatest import may be realized since it is the one on which this second edition of the present book has been arranged.

Having digested the previous chapters, the reader will have determined the clinical type of classification of asthma, but to reiterate in general terms it is found that cases of asthma fall into three groups, which are briefly:—

Type I : The Simple Allergic Group.—Those straightforward cases of asthma due to protein hypersensitivity uncomplicated by bacterial factors of either primary or secondary nature. The sensitivity to foreign proteins is demonstrable by dermal reactions. They occur as a pure type more frequently in the first two decades of life (Chapter VI).

Type II : The Pure Bacterial Infection or Microbic Type.—Those in which primary bacterial infection is the essential factor in the stimulation of the asthmatic paroxysm, and in which there is no general cellular hypersensitivity demonstrable by dermal test or history, other than an inherent 'allergic' bronchial musculature in asthma, or 'allergic' skin in cases of urticaria.

Type III : The Mixed Type of the Foregoing Two Groups.—This is the type most commonly met with in later years, and especially after the second decade, when nearly every case

of the first group becomes secondarily infected; or if the asthma has only started at a late age it has done so only as a result of the two factors—protein hypersensitivity and bacterial infection—acting together to provide a sufficient stimulus to effect a bronchial spasm.

Passing to the second and more important step of the classification of asthma by the differential sedimentation tests, we shall have to consider the actual technique of the test in slightly greater detail.

To derive the serum sedimentation a volume of the serum is mixed in a series of small test-tubes with the standard colloidal agent—orthovanadic acid in a buffer acetate solution being the most convenient, though by no means the only one available. The mixtures are so arranged that each tube varies from the next one by being slightly more acid. It is then observed that the neutralization of electrical charges between the positively charged serum proteins and the negatively charged standard colloidal acid leads to a precipitation of the two substances together; furthermore, that with increasing acidity the quantity of precipitate becomes less and less, until there is finally none. Again, it is found that in general a relative low albumin/globulin ratio in the serum increases the amount of precipitate, while a high ratio decreases the amount of precipitate at any given degree of acidity: though this is not by any means the sole factor operating.

It thus becomes obvious that it is possible to draw a graph, with the amount of precipitate as a result of the reaction as the ordinate, and the initial degree of acidity as the abscissa, such as the line A in *Fig.* 12. Comparing this line A from a normal patient with that obtained from a Type II asthma (line B), a marked difference is immediately observed. To measure this difference in absolute terms, a horizontal and empirical line is drawn representing a certain quantity of precipitate of 40 units (actually 2·7 mg.). It is then seen that the position of line A may be numerically compared to line B by reference to the abscissa line. This abscissa is divided into a scale whose figuration corresponds to the erythrocyte sedimentation rate, i.e., from 0 to 100 per cent. The normal line A is then crossing this horizontal line at a position between 0 and 10 per cent, while the line B from a bronchial infective asthma crosses at a position corresponding to 45 per cent. This, then, is the method of deriving the serum sedimentation

as the first step in the differential sedimentation test. Line C in the same figure is from a typical Type I asthma; it demonstrates the method by which minus sedimentations are derived, and explains their occurrence, as opposed to their impossibility with those observations of red cells falling in plasma (E.S.R.).

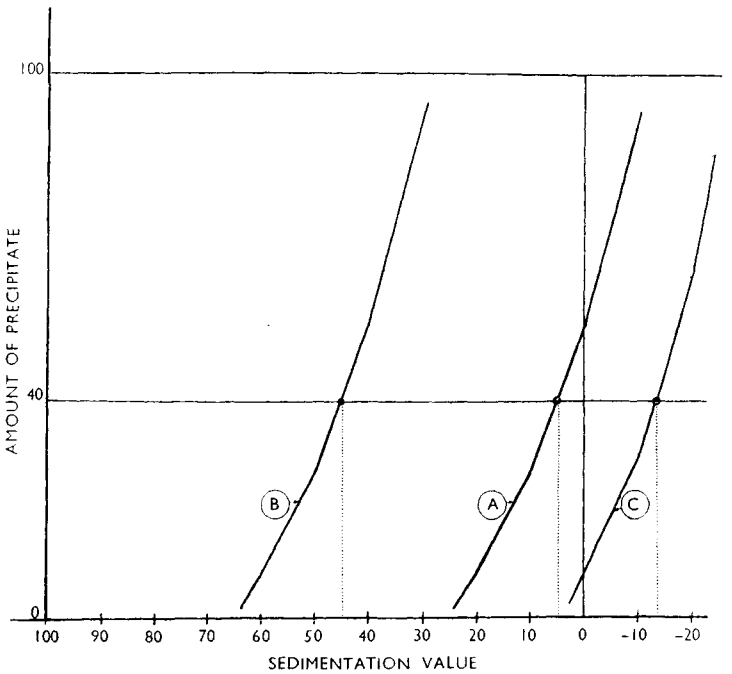

Fig. 12.—Sedimentation value. A, Normal; B, Type II; C, Type I.

For each individual serum a curve may be drawn in this manner. If, however, we now denature the same serum by heating it for 30 minutes to a temperature of 56° C. and perform exactly the same test again, it is observed that the line thus delineated on the same graph falls to the lower side of the normal untreated serum; i.e., for every specified degree of acidity the precipitate with the heated is less than with the untreated serum. Referring then to *Fig.* 13, we have the line D representing the untreated serum, while the line H represents that of the heated serum. The changes thus brought

about may be referred to as the heating effect. In an exactly similar way a third curve may be determined with the same serum (line E) representing an increased amount of precipitate for the same degrees of acidity. Such a curve is drawn as a result of performing the same test a third time with the same serum after it has been treated with ether. The changes thus induced may be again referred to in this case as the ether effect.

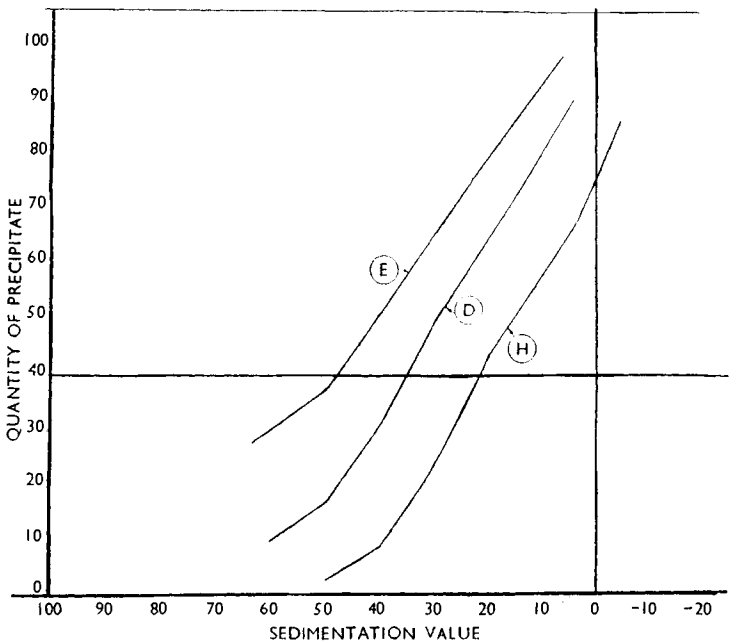

Fig. 13.—Sedimentation value. D, Untreated serum ; H, Effect of heating ; E, After ether.

For every serum coming for examination the serum sedimentation is derived from the initial curve of the unheated serum (*Fig.* 12, A, B, C, and *Fig.* 13, D). Further differentiation is subsequently obtained by the estimation of the two further curves as a result of the heating and ether effects respectively. To assist visual understanding and interpretation of such curves the intervening space is coloured red and green for the ether and heating effects respectively, so that for simplification these effects may be more conveniently referred to as the

red field and the green field for each particular serum, as in *Figs.* 14–17. The figures given under 'Result' in these charts are the sedimentation value of the untreated serum followed by the red/green ratio.

The biochemical and biophysical factors inherent in the changes in the red and green fields are not a matter for elaboration here, as they are fully dealt with in the *Charterhouse Papers.*[7] However, before differentiating the groups of asthma by the changes in the two fields a very brief survey of the clinical factors involved will materially assist our interpretation of the charts from cases of asthma, our knowledge being gained from the correlation of clinical conditions to the results obtained by examination of the serum from many hundreds of cases of asthma and other pathological conditions.

The Green Field.—The *green field* is intimately connected with a patient's response to infection. It may be expressed numerically, and in the normal person has a value of approximately 15 units. As soon as an infection occurs the general metabolism responds and is reflected in the serum by an enlargement of the green field. The more acute and active response is not necessarily equal to the degree of infection. It must be emphasized that this figure represents the *response* and not the *infective process*, so that it may occur that an infection in a patient severely debilitated, in whom there is no responding power, is not accompanied by an enlargement in the green field. In the same way, where a chronic infection has been present for some considerable period of time, this gradually leads to a diminution in the response or general resistance of the patient, which fact is shown by a diminishing green field, until this may be well below the normal. In addition to these simple responses, there are, however, certain pathological states, of which the Type I allergic asthma is a typical member, where there is a much diminished green field, caused not by a lowered resistance as a result of infection, but possibly by a combination of inborn metabolic errors in the serum proteins and certain important prosthetic substances such as calcium, potassium, and the sterols.

The Red Field.—In a like manner the *red field* may be referred to as the toxicity factor, emphasizing again that this should more accurately but less simply be spoken of as a deficient detoxication. This may be due to either, a primary deficient detoxicating mechanism, or the production of excessive

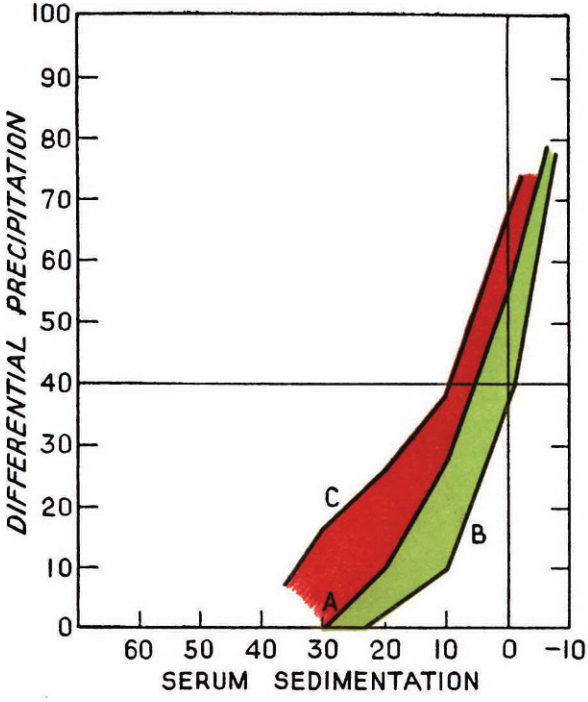

Fig. 14.—Normal serum.
Result: 5%; 12/15 = 0·8.

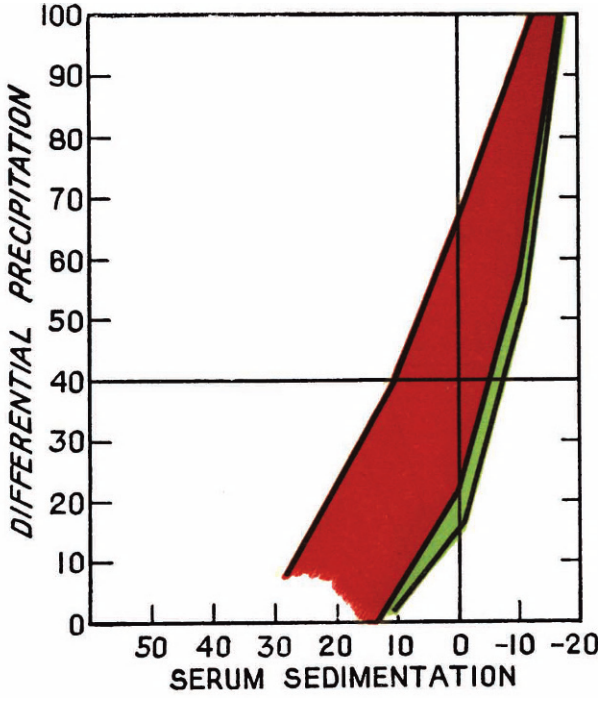

Fig. 15.—Asthma, Type I. Simple and uncomplicated protein hypersensitivity.
Result: −5%; 41/6 = 6·9.

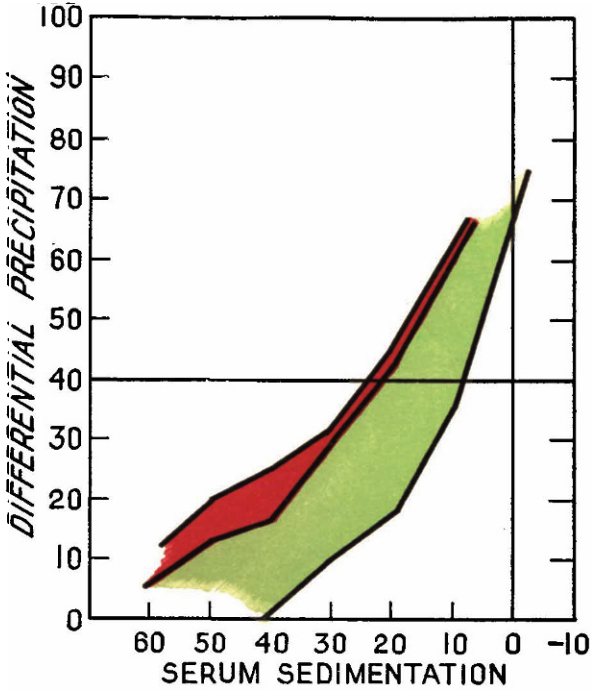

Fig. 16.— Asthma, Type II. Microbic infective type with no protein hypersensitivity.
Result: 21%; 3/24 = 0·12.

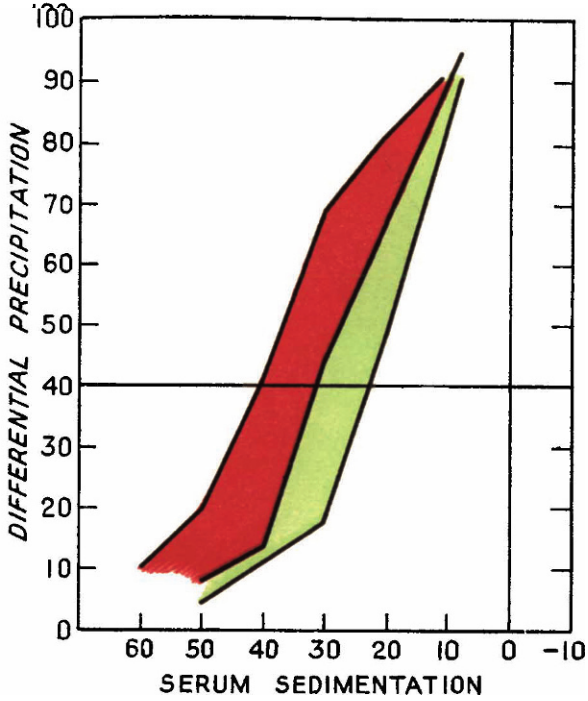

Fig. 17.—Asthma, Type III. Mixed microbic and protein hypersensitivity. Post-nasal infection.
Result: 31%; 27/22 = 1·2.

amounts of toxic material. Both may and frequently do occur together, and form a vicious circle. *The red field* is increased clinically in all those cases where there is toxæmia from the bowel or a closed toxic focus, in which the actual infective element is perhaps small, but the continuous absorption of toxic material leads to the vicious circle just mentioned. It is increased artificially by toxic drugs, and is a useful guide to the dosage of such substances as gold.

Referring now to the specific case of asthma, we find that each of the three major clinical groups or types has a further differentiation in the red and green fields. We have seen a

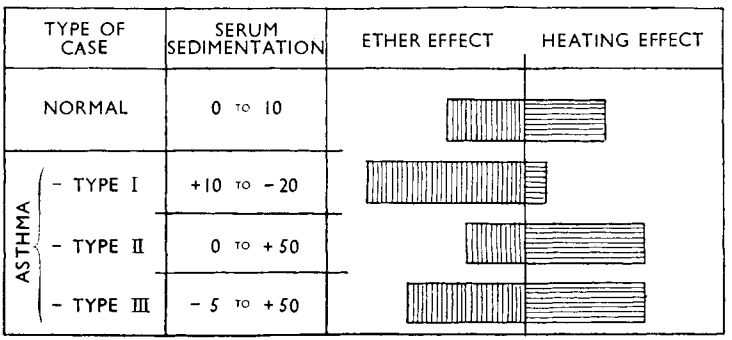

Fig. 18.—Sedimentation value. Diagram representing typical findings.

preliminary differentiation in the sedimentation, by either red cells or the serum sedimentation, and this can now be taken to a second stage for completion. *Fig.* 18 represents diagrammatically the typical findings in the normal person and the three types of asthma, representative charts being shown in full in *Figs.* 14 to 17. The main features are therefore:—

Type I Asthma.—The simple allergic type uncomplicated with primary or secondary bacterial infection. A sedimentation that is always normal and frequently a minus reading. A much enlarged red field and a much diminished green field.

Type II Asthma.—Simple primary bacterial infective asthma. An increased sedimentation. A normal red field and a definitely enlarged green field. This is a typical picture of a case responding to bacterial infection of any description,

and not necessarily associated solely with asthma. The bronchial spasm is the specific response of an allergic muscle to the toxin-histamine spasm syndrome, while the changes in the serum are those of response to infection alone.

Type III Asthma.—The mixed allergic-infective type. This group has become differentiated in recent years largely as a result of these investigations. It will be readily understood that, superimposing the enlarged red field of the Type I on to the enlarged green field of Type II, a type of chart is obtained that shows the characteristics of both groups, and hence it may rightly be called the mixed type.

Included in Type III are the aspirin-sensitive cases.

Three series consisting of ten cases from each group are shown in the following tables :—

ASTHMA : TYPE I

No.	SEDIMENTATION	RED FIELD	GREEN FIELD	RED/GREEN RATIO
	per cent			
1	5	22	4	5·5
2	−3	20	9	2·2
3	0	19	1	19·0
4	−6	39	4	9·8
5	13	27	9	3·0
6	−3	17	7	2·4
7	10	31	1	31·0
8	6	27	10	2·7
9	−1	13	7	1·9
10	−3	31	5	6·2

ASTHMA : TYPE II

No.	SEDIMENTATION	RED FIELD	GREEN FIELD	RED/GREEN RATIO
	per cent			
1	10	1	26	0·02
2	24	18	22	0·8
3	17	8	19	0·4
4	15	21	28	0·75
5	16	9	24	0·4
6	37	15	25	0·6
7	15	21	27	0·8
8	17	8	25	0·3
9	25	22	26	0·8
10	10	11	25	0·4

ASTHMA: TYPE III

No.	SEDIMENTATION	RED FIELD	GREEN FIELD	RED/GREEN RATIO
	per cent			
1	31	27	22	1·2
2	20	34	24	1·4
3	18	31	25	1·2
4	52	27	24	1·1
5	16	23	18	1·3
6	7	13	11	1·2
7	8	37	13	2·2
8	7	32	20	1·6
9	5	30	18	1·7
10	14	27	21	1·3

A brief summary of the first two cases in each of the three groups is as follows:—

TYPE I

Case 26.—Girl, aged 17. Commenced asthma after a bronchial attack when 6 weeks old. Was free for many years, but was always sensitive to eggs. Dermal tests showed an extremely positive reaction to egg white and yolk and a remarkable negative result to all the other usual allergens.

Case 27.—Girl, aged 16. Eczema as a baby. Asthma commenced when 7 years old. Has been better, but relapsed again. Has had urticaria and paroxysmal rhinorrhœa. Asthma associated with exercise and colds. This is a case that would have progressed to a Type III if allowed to proceed unchecked.

TYPE II

Case 28.—Man, aged 56. No history of asthma until this age, when he had recurrent colds and bronchitis. Wheezing at night progressed to real asthma. Three days after test he developed 'status asthmaticus' and a frank bronchopneumonia, from which he later recovered. Dermal tests negative.

Case 29.—Man, aged 58. A gardener. Never had any trouble until rheumatic fever during the war. Developed pleurisy in 1924 after which wheezing commenced with bronchitis. This led to a florid bronchial asthma following a bronchopneumonia in 1933. Dermal tests negative.

TYPE III

Case 30.—Man, aged 58. No symptoms until a year ago. Asthma commenced following a cold and bronchitis, and persisted severely with little sputum. Polypi were then removed from the nose. Bacteriological investigation showed a heavy infection that was positive on pathogen-selective blood-culture to a type of *Str. viridans* from the posterior nares. The sputum showed a comparatively smaller number of organisms of a mixed nature common to respiratory catarrhal conditions.

Case 31.—Woman, aged 55. Suffered with asthma many years. now has it practically continuously and very badly during night, necessitating six to seven injections of adrenaline per day. Has has polypi removed. Cannot take aspirin without being severely ill. Bacteriology showed a heavy infection of posterior nares with four varieties of *Str. viridans* and a *Staph.* '*E*'. Pathogen-selective blood-culture showed a heavy positive reaction, the staphylococcus growing out in pure culture.

Reviewing these serological results in the light of the general classification of types the close correlation is significant.

Consideration must now be given to the application of these charts to the practical aspect of diagnosis and treatment.

In the first place the peculiar and typical features of the Type I asthma form a picture that is the complete antithesis of the microbic or infective Type II group; so much so that if a patient presents one or other of these two types, one can be assured of the fundamental cause of the asthma, allergic or microbic, and, in consequence, of essential and effective methods of treatment.

Where a patient shows a typical Type II chart, there is absolutely no necessity to enter into a multiplicity of complicated dermal tests and detective histories, since from the chart of this particular type one is clearly shown that bacterial infection is the factor of primary import, and that vaccine treatment is the method of choice. Similarly in a case presenting a Type I chart, vaccines have no part to play in treatment, but an offending antigen to which the patient is sensitive must be sought with diligence. More particularly are the D.S.T. charts found of use in the urticarial group.

If, as our experience has demonstrated, the serological findings in these primary groups correspond closely with the clinical evidence, the importance of the test determination of a Type III case becomes more enhanced. In the first place, a large series of cases examined by the differential sedimentation test have proved the comparative rarity of a pure Type I in the later years of life, and hence that at some time practically all cases of this group become secondarily infected. It affords a reasonable explanation to the problem of the patient who develops asthma or an allied condition in the later years of life, and yet who shows by positive dermal tests an inherent protein sensitivity that must have been present for very many years. The degree of hypersensitivity cannot have been sufficient by itself to produce the typical symptoms of asthma, and it has

only been with the additional burden of a toxin-histamine product from a bacterial infection that the necessary impetus has been produced to effect a true bronchial spasm.

From the therapeutic point of view this mixed group naturally calls for treatment of a mixed type to afford relief. The method has been perhaps of the greatest benefit to the aspirin-sensitive group of asthmatics, a class of patient with a relentless and severe form of asthma previously most unamenable to any form of treatment, passing from one consultant to another trying every means of relief. The examination of many sera from this group showed in every case a typical and severe Type III case, i.e., a mixed allergic and infective condition. The extremely sensitive 'allergic' part is obvious in their tragic relations with aspirin, though the mechanism is perhaps not fully understood. Their asthma persists in an intense form despite long periods of complete abstention from all drugs containing salicylate. Their sera demonstrated quite definitely that there was an additional 'infective' element, and thorough bacteriological investigations were instituted. Important micro-organisms, usually staphylococci or pneumococci, were found in the posterior nares in every case, and the very satisfactory results of vaccine treatment with these organisms is referred to in Chapter XVIII on this class of case. Suffice it here to point out with emphasis that this is just one instance of how the deductions from these serological observations have led the way to an understanding of this particularly difficult type, and have shown the way to investigations of primary importance, with resultant satisfactory methods of treatment.

One further demonstration may be mentioned as an illustration of the application of the differential sedimentation test to these questions. A clinical observation has frequently been made that many 'allergic' cases of asthma are much improved during the occurrence of pregnancy or even a minor infective complaint. It has been seen that the typical 'differential' serum picture of a Type I asthma has an abnormally small or subnormal green field. In pregnancy or an infective condition we know by observation that the normal person responds to these two states by increase of the green field. Such an occurrence when superimposed on the subnormal green field of a Type I allergy naturally tends to bring the sum total back to normal. Such are the actual biochemical observations which empirically so closely parallel the clinical facts; but the

proper understanding as to why they should produce these results remains purely a matter of conjecture. Nevertheless as with all these observations they are a starting-point to enable light to be thrown on these previously disconnected phenomena.

By serial estimations in the same patient the progress of the case may be assessed, particularly those in the Type II class. In the Type I group and to a lesser extent in the Type III, the changes as a result of treatment are not always so well marked serologically as the clinical result might suggest. This would appear to demonstrate that the allergic state is an inherent part of the patient's make-up, and that although specific desensitization has lowered the reactivity of the patient below the threshold point, there is still present a degree of fundamental cellular allergic sensitivity. It must be emphasized that when speaking of a typical allergic or Type I group, these remarks apply strictly to the subject of asthma and do not necessarily include hay fever, Large numbers of blood examinations have not been made in hay fever partly because hay fever, when it is reviewed logically, is not a typical allergic complaint, since symptoms are only local to those mucous membranes in direct contact with the offending antigen.

These results open up a new and interesting aspect of the subject. The numbers investigated and the consistency of the results do at least form a very firm foundation. The exact meaning of the observations recorded must emerge with study in due course of time and experience, but that they open up a new vista should be apparent.

The biochemical problems associated with these investigations have been dealt with extensively in the earlier publication mentioned.[7] The space here available, where the whole problem of asthma in all its aspects has to be dealt with, only allows the differential sedimentation test to be touched upon very lightly as it affects the patient suffering from asthma or a clinically allied complaint.

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CHAPTER XIV

TREATMENT OF THE ACUTE PAROXYSM

IT is not unusual for an asthmatic to pass many years without seeing his doctor. When assistance is required it is either to subdue the intensity of an individual attack or in the hope of finding some treatment that will prevent the occurrence of further paroxysms.

When called in for emergency treatment we find the patient sweating profusely, with dishevelled hair and cyanosed face, perhaps unshaven and minus dentures. With head sunk low between his heaving shoulders the patient presents a caricature of his normal self, suddenly aged in a losing fight to get his breath.

ANTISPASMODIC TREATMENT

1. Adrenaline.—The first indication is to break the spasm of the bronchial muscle. Having inquired what drugs, if any, the patient has taken recently, we can proceed at once to give an injection of adrenaline. A miraculous change in the patient's condition may be expected with some confidence, except in very severe cases, which merit the description of the *status asthmaticus*. *Adrenaline* ($C_6H_3(OH)_2CHOH.CH_2NHCH_3$) is the trade-name for the active principle of the medulla of the suprarenal gland known as epinephrine in America. It was first produced as a crystalline substance in 1901 by Takamine.[1] The form commonly used is the 1–1000 solution of the hydrochloride. A dose of 5 to 10 minims of adrenaline (1–1000) should be injected hypodermically in the upper arm. Massaging the site helps to hurry the injection into the blood-stream.

In the case of great emergency, adrenaline can be given by the intravenous route. The objection to this is the fact that it may cause an intolerable headache, such as occurs at times in patients who inadvertently give themselves an injection into a vein.

The good effect of adrenaline may last but one hour, when the dose can be repeated. Hurst[2] advises leaving the needle in the skin and injecting the dose slowly over half an hour.

Locally adrenaline causes so much contraction of the blood-vessels that the injection must always be given well below the surface; if not, some necrosis of the skin may occur. Not uncommonly one sees a patient whose forearms are a mass of round scars from such faulty administration.

Experimental work and clinical observation has produced much knowledge of the action of the suprarenal glands. Life is impossible without them, death occurring a very short time after their removal, with coma and convulsions.

The production of adrenaline is confined to the medulla, and in many animals lower than the vertebrates the two portions, medulla and cortex, are anatomically separate. Loss of adrenaline tissue causes the whole metabolic rate to be decreased, the blood-pressure falls, and muscular asthenia, so prominent in Addison's disease, is well marked. But in Addison's disease there is no asthma, nor do its symptoms appear in the asthmatic, with the exception of the low blood-pressure. Excess of secretion as witnessed in hypernephroma may produce a hairiness in women, and other trends towards a masculine psychology and outlook, which have been known to subside on removal of the tumour.

The presence of adrenaline in normal blood is probably of the nature of 1–1,000,000,000. It mostly disappears in the capillary circulation. A considerable store of adrenaline exists in the medulla, to be liberated during asphyxia, rage, pain, excitement, and other forms of emergency. The adrenaline thereupon causes a cessation of activities in the alimentary canal and a shifting of blood to more important places, as the lungs and the heart; there is increased cardiac vigour and abolition of muscular fatigue, and the mobilization of sugar-production—all designed to bring the individual into the best fighting condition possible.

The pallor and tremor seen after an injection of adrenaline and the increased heart-beat are the same as occur when trembling with rage, pale with fright, or with one's hair standing on end, and are activated by a similar sympathetic-nerve excitation.

During pregnancy there is a great increase in the activity of the suprarenals, especially the cortex, continuing during lactation. Strychnine causes a marked increase of output of adrenaline, perhaps explaining the favourable action often followed by its use.

Case 32.—An asthmatic patient going down a steep hill was aware that he had not enough strength available to operate his somewhat ineffective brakes, and ended in the ditch. Getting out of the car he found his asthma had disappeared. The emergency had produced automatically an outpouring of adrenaline.

The low blood-pressure of asthmatics, the disappearance of asthma during pregnancy, and other points gain interest when discussing the action of the suprarenal gland. I do not remember seeing an asthmatic lady of the hirsute masculine type.

2. Pituitrin.—Preparations of adrenaline in combination with an extract of the posterior pituitary lobe seem to be of even greater value. This is rather surprising considering that the hypophysis contains histamine, an active substance in causing contraction of the bronchial muscle.

In fact, pituitrin is given to cause contraction of the uterus during the second stage of labour, as is ergamine biphosphate, in virtue of the histamine that it contains; the latter gives the large histamine wheal when applied to the skin scratch. In spite of this there can be no doubt as to the value of adrenaline-pituitary preparations—asthmolysin (German), evatmine (French), pitrenaline (Parke, Davis & Co.), and others.

3. Atropine.—The tone of the bronchial muscle is balanced between sympathetic and vagal control, and if upset, as in the spasm of the bronchial muscle in asthma, it may be corrected through either the stimulation of the sympathetic by adrenaline or the depression of the vagus by atropine. The latter course is not so likely to prove effective, because spasm of the bronchial muscle is not always dependent upon stimulation of the vagus.

In an animal sensitized to horse serum, anaphylactic spasm of the bronchial muscle will take place if horse serum is perfused through the lungs after their removal from the carcass of the animal, and so shorn of their nerve-connexions.

Atropine would therefore seem to be confined in its use in asthma to those cases in which a reflex vagal stimulation is an essential causative factor.

Marjoric Gillespie[3] suggests that it might be used as a diagnostic method to differentiate between cases of asthma of vagus nerve origin and those from other biochemical causes. Experimentally atropine will stop bronchial constriction from pilocarpine but not that from histamine.

4. Morphia.—The next step to take in cases in which adrenaline is without effect is to give an injection of morphine. I think it is important to give enough morphine when this drug is used, and should suggest one-third of a grain, but morphine sulphate, $\frac{1}{4}$ gr., with atropine sulphate $\frac{1}{150}$ gr., is usually sufficient to break the attack. When the spasm begins to abate the patient can be given a good rub-down and a clean pair of pyjamas; he may fall asleep and awake relieved. Failing this, care must be taken that he does not get chilled, bathed as he so often is in perspiration.

The breaking of a paroxysm, especially after adrenaline, is signalized by a few short coughs: a pledget of mucus is expectorated and one airway is cleared, allowing more air to be taken into the lungs and coughing to become more effective in clearing other bronchi.

5. Oxygen.—The patient's endeavour is to obtain sufficient oxygen to supply the blood, this demand being much increased by the physical effort required to force air in and out past the obstructions in the bronchi. If the oxygen content of such air as does enter can be increased, the shortage of available oxygen in the alveoli will be materially relieved.

An excellent apparatus for this purpose can be loaned from the Inhaling Drug and Apparatus Company. It provides a closely fitting face mask with a sufficiency of easily manipulated cocks and gauges, allowing as much or as little oxygen to be inhaled as is required. The oxygen passes at high pressure through a phial containing adrenaline, and can be breathed in a fine smoke capable of reaching all parts of the lungs.

Its value is particulary obvious in those cases where myocardial weakness adds an extra demand for oxygen, and in those who have had asthma more or less continuously for some days. Such relief gives the patient confidence with which to stop attacks at their commencement, and so avoid the fighting for breath otherwise so inevitable.

These enfeebled people, to whom the least exertion is a trial, find the severe physical exercise demanded in an attack of asthma to be fraught with the greatest danger and alarm.

6. Inhalation Therapy.—A convenient method of giving drugs to asthmatic patients is to produce by mechanical means such a fine subdivision of the drug in the air that it can be inhaled into the lungs with each breath. For the atomizing cloud effect to be produced, oxygen or air must be pumped at

high pressure on to a nozzle containing the drug in solution or in suspension. With an active person a small hand-operated rubber pump may suffice, but an electrically driven air pump or gas from a cylinder at high pressure is more convenient. A face-piece allows the patient to derive the fullest measure of the vapour and prevents waste. Unless the subdivision of the solution is as fine as a smoke, much of it will fall upon the mucous membrane of the nose, mouth, fauces, and trachea, and will not reach the finer bronchi.

Various antispasmodics can be used in these machines. The oldest perhaps is cocaine. As the usual strength is 5 gr. to the ounce and as that may last the patient for a month or more, it shows the minuteness of the dose required to prove effective by the inhalation method.

More recent solutions contain adrenaline, ephedrine, atropine, papaverine, and the cocaine substitute anæsthesine. Some of the newer instruments, electrically driven, are extremely efficacious and helpful.

7. Chloroform.—The lengths to which the physician may be led is illustrated by Garber,[4] who states that he gave a woman 1 oz. of adrenaline, ¾ gr. of morphia, besides luminal and chloroform, during twenty-four hours, in the endeavour to subdue an attack.

Experimentally it has been found that anaphylaxis can be prevented in animals by anæsthetizing the animal prior to the injection of the exciting dose. The minimum amount is given, as in childbirth.

In these very severe cases the patients literally do not mind whether they live or die, and the psychological effect of knowing that they are going to become unconscious and free from asthma may be visible immediately.

8. Ether.—I have had several patients sensitive to ether, some so affected by the smell that they have been unable to qualify in medicine and have found other work. There is little danger of this fact being unknown to them.

A method of treating severe cases of asthma that appears to be useful and easy of accomplishment is to anæsthetize the patient with ether per rectum. The dosage advised by Kahn[5] and used by him successfully is a mixture of ether and olive oil. For children, 1 to 2 oz. of each is injected, for adults 5 to 7 oz. After this the patient may be expected to sleep and to awaken relieved of the asthma.

He also advises that for the general treatment of asthma, the maintenance of 20-minute anæsthesia by inhaling ether has excellent effect. This is repeated two or three times in the intervals between attacks.

Not unusually the patient says he has been told that he could not have an anæsthetic, perhaps to have a tooth out, because he has asthma. In my experience this is entirely wrong. While not advising a prolonged ether anæsthesia in bronchitic subjects, nitrous oxide and oxygen can be given to any asthmatic even when the degree of asthma present is considerable. The bronchial spasm will disappear as anæsthesia becomes established. I have seen urticarial wheals disappear under ordinary gas given for a tooth extraction.

9. Avertin.—Fuchs[6] describes the successful use of avertin (tribromethylalcohol) by the rectum, 50 to 70 mg. per kilo weight or 1 gr. per $2\frac{1}{4}$ lb. or 6 gr. per stone weight. The avertin is dissolved in 120 c.c. of cold distilled water, and is instilled very slowly through a funnel. Relaxation of the bronchial muscle follows, the patient sleeps, and awakens well.

Feldweg[7] issues a warning against the use of evipan on the asthmatic, having seen a fatal case with this drug.

Of these various measures available in treating severe emergency paroxysms, none is of greater general use than adrenaline. Its immediate effect is extremely rapid, its after effects nil. Next in importance is morphine. This offers a longer period of relief, but is apt to cause sickness in some, and in most some feeling of nausea and heaviness on waking. Heroin, $\frac{1}{12}$ gr., is extremely useful, but as the only drug addicts I have seen among my many asthma patients have been those taking heroin, the greatest care must be exercised in preventing the patient from becoming too fond of this drug or in making it available for his own use.

Papaverine, another alkaloid of opium, is less powerful in its action, and it does not create a habit. It is a constituent of many proprietary asthma cures.

ANCILLARY MEASURES

Having gained control of the spasm and mitigated the distress consequent upon the forced unnatural breathing, what more can be done to help the patient in his immediate discomfort and to prevent a return of the gross symptoms ?

Diet.—The patient is in the condition of one who has had to undergo very severe physical exercise, such as might occur in running some miles across country, often without any previous training, and starved for hours in the process.

The indications are to provide a large fluid intake to replace the water lost by sweating, and to give such nourishment as will most rapidly be absorbed into the system.

A pint of barley water containing an ounce or more of glucose should be sipped and repeated as soon as possible. Half a wineglass of whisky or alcohol in any other form acceptable to the patient should be taken, so diluted as to prevent the patient coughing. As the natural tendency is for the patient to avoid all food and to be entirely devoid of any appetite, some coaxing may be necessary to get him to take even drinks.

Purgatives.—Directly an attack becomes imminent by the appearance of recognized prodromal symptoms a sharp purge should be given, of which castor oil is undoubtedly the best.

In children and in many cases of a liverish nature, constipation is itself a prodromal symptom and must be dealt with at once.

A weekly dose of grey powder for children and a blue pill for grown patients often proves a prophylactic measure of great value.

Counter-irritants.—A mustard blister on the pit of the stomach repeated along the lower edge of the ribs will help to loosen the spastic condition of the diaphragm and adjacent muscles.

Posture.—Each patient will take the position which he has found by experience to be the most comfortable. One will be on his side, another sits bolt upright in bed, while a third will get into a favourite chair. Others stand up holding on to the mantelpiece, or go to the open window for more air; but the latter demand seems to be uncommon in pure asthmatics. Further assistance is now afforded in the chosen position. The pillows should be firm, capable of being piled up to give support even when the patient sits upright. The mattress should be tightened up so that the patient does not sink into a hole in the middle of the bed, away from his pillows and supports. The hands or elbows must have sufficiently firm support to assist the patient in fixing the shoulders and afford a *point d'appui* so that even the pectoral muscles may take their share in the respiratory struggle. Many like a broad chesterfield, the

back of which gives them something to lean sideways against when they doze. Those who stand are often stout and emphysematous; this position allows the abdomen and its contents to fall away from the heart and diaphragm while giving the abdominal muscles greater play.

Drugs.—In the acute paroxysm emetics are often of great use, especially in children. A teaspoonful of ipecacuanha wine, or the tincture as it is called now, is the common household remedy in such cases. In the earlier part of the paroxysm it will empty a distended stomach of much food and wind, while in the later stages a generous quantity of mucus will be loosened and expelled from the bronchi. We may note the relief given by vomiting in many cases of migraine. In fact, a number of these patients are not satisfied if their headaches subside before they have been properly sick, as they know the pains in the head will return again and again until they have emptied their stomachs of a certain amount of bile. They and the asthmatics will make use of their fingers or a feather to produce the desired effect. Drugs other than those already mentioned are of little use in the acute paroxysm, but a mixture of sodium iodide, with ammonium carbonate and chloride, may help to loosen the thick phlegm with which the tubes are blocked.

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CHAPTER XV

GENERAL TREATMENT BETWEEN THE ATTACKS

BEFORE considering the treatment specific to the allergic type, or that due to microbic infection, certain fundamental rules with regard to diet, exercise, and treatment will be mentioned.

Strict observance of these rules is necessary for all types of asthma, and not uncommonly suffices to cure the case without further help.

DIETARY

There is not the least doubt that the majority of us eat too frequently, too fully, and too fast, with little or no exercise to assist the general metabolism and to work off the excess. Superfluous food becomes superfluous fat: with very few exceptions all fat people eat or have eaten too freely. The problem can be attacked with mathematical precision by making the patient count in calories a weekly intake of food and drinks and then undergo such a diminution as will keep him well within limits. Not uncommonly "just ordinary food" may total to 4000 or more calories per diem, whereas 2000 is probably enough for the asthmatic until cured of his asthma.

If the patient is above the ordinary weight a short spell of 1000 calories a day may be necessary. Patients who are too stout tend to be short-winded in virtue of the extra amount of work the heart is called upon to undertake in the exertion of carrying the extra weight about with possibly some fatty degeneration of the heart in addition.

The 'Ruthin Castle' diet, or some slight modification of it, of 1000 calories may be used as a basis, as explained in Beaumont's *Medicine*.[1]

Breakfast.—Grilled fish (4 oz.); or grilled fish (2½ oz.) and egg (1); or bacon (2–3 oz.) and tomatoes (3 oz.); or cold ham (2 oz); or bacon (½ oz.) and egg (1); or eggs (2) boiled or poached. Toast (½ oz.); butter (⅙ oz.); sugarless marmalade (½ oz.); milk (1½ oz.); tea.

Lunch.—Roast beef or mutton, hot or cold (2 oz.); or grilled steak, boiled beef, grilled chop, boiled mutton, roast turkey or chicken (2½ oz.); or veal (3 oz.); or grilled sweetbreads (3 oz.) with bacon (½ oz.); or liver (3½ oz.). Green vegetables (4 oz.), or salad (4 oz.). Stewed fruit (3 oz.), or fresh fruit (4 oz.); toast (½ oz.); butter (⅙ oz.).

Dinner.—Fried fish (2½ oz.) or meats as at lunch, or eggs (2) boiled, poached, or made into an omelette. Vegetables, fruit, toast and butter as at lunch. Toast may be increased to 1 oz. if the vegetables are omitted. Tea.

If this diet is doubled in quantity a diet of 2000 calories will be taken. Many patients like to have diets written out in great detail as above, and will follow them closely. For those who have not time to carry out the instructions so punctiliously a 2000-calorie diet consists roughly of a good quarter of a pound of meat, eggs, or fish, at breakfast, lunch, and dinner, with toast or Ryvita biscuits and a little butter. No bread or potatoes are to be taken, but green vegetables, salads, and fruit are allowed in practically any quantity.

Reliance on measured calories in food is, however, irksome to the patient and makes him a sorry guest with others. It is simpler to forgo the evening meal altogether, or, more easy still, to have one fasting day a week, it being understood that he is not to be overfed next day to make up for his fast of the day before. One of the commonest fallacies, especially dear to the child's nurse, is that he wants 'feeding up'. Milk at eleven in the morning and superfatted at that, with cream and cod-liver oil at other times, and a veto on exercise because it makes him wheeze, is not only the wrong treatment for asthma, but oftentimes the actual cause of the complaint in children.

Late Meals.—Late meals are particularly harmful to the asthmatic. As Hyde Salter said, "the patient should go to bed with the lacteals empty."

The chief difficulty arises with those people who cannot have a substantial midday meal, either because of the expense or because it makes them unable to work in the afternoon. The evening meal then becomes the chief meal of the day. If the patient cannot finish it three hours before bedtime it must be an extremely light meal. Particularly harmful is a cup of something before going to bed, usually of a farinaceous nature in hot milk. The night-starvation slogan, so rife in the advertisement columns of the newspapers, suggests a pathology entirely wrong for the asthmatic, as indeed for all normal people.

If the patient becomes unduly hungry during the evening, a cup of weak bovril may be taken, or better still, a drink of glucose or a few barley-sugar sweets. In general, notoriously indigestible foods, as cucumber and pork, had best be avoided, especially in elderly patients, but for the most part the choice of individual articles of food can be left to the patient's own discretion. What must be avoided are dishes containing two or more of the three main classes of food—proteins, fats, and carbohydrates—so intimately mixed in the cooking as to be inseparable in the course of digestion.

Each class of food requires digestion in different places by different enzymes and by different methods of absorption from the gut. Starches cooked in fat, as pastry, batters, pancakes, fritters, muffins, and crumpets, must be omitted entirely from the diet in all cases. Heavy cakes, thick soups, greasy dishes are best avoided. A slice of cold meat is preferable to a curry or other ' done-up ' dish ; a dozen of oysters is less harmful than a mixed mess of hors d'œuvre. Even a rice pudding if well made is starch cooked in fat and taboo for the same reason. With starvation towards the end of the day, the patient will require a good breakfast and lunch, thus shifting the main intake of food to an earlier period.

The Földes Diet.—Whilst almost contrary to the rules that have just been laid down, one must consider shortly the question of the water-retentional states discussed at length by Földes,[2] since by means of the anti-retentional diet advocated by him several remarkable cases of improvement in asthmatic patients have been noted. Such a scheme of dietary is necessarily subject to the proviso that the patient in question is of the water-retentional type. For the complete details reference should be made to his book, but there appears little doubt that a state of water-retention is so often a factor in many cases of asthma that reference must be made to it here, though I would not go so far as to suggest that all hay fever and allergic asthma is of the water-retentional character.

The patients so affected are usually overweight, with poor, overburdened hearts. The subcutaneous tissues, though not truly œdematous, are thickened, as can be determined by pinching the skin up anywhere (this is not painful as in panniculitis). They tend to drink quantities of fluid per day, and their diet is usually the antithesis of that to be immediately recommended. They are ' flabby ' people, often women at or

about the climacteric. On inquiry it is frequently ascertained that they pass large quantities of urine per day, and usually have to get up one or more times during the night. The essentials of the diet recommended by Földes follow. With strict adherence to such a scheme, an extraordinary amount of weight as water is immediately lost, and this loss proceeds hand in hand with the improvement in the clinical condition, provided that there is at the base a true water-retentional state.

The main features of the diet are :—

To be Avoided.—All salt, if possible even that in cooking. *Fats* in every visible form—meat fat, butter, fried things, eggs.

To be Limited.—Water intake, which should not exceed one quart per day, but it may be taken at any time and in any form. *Carbohydrates*: No white bread, root vegetables, sweets, sugar. *Proteins*: Simple proteins, cheese, peas, beans, etc. in moderation.

To be Taken.—Proteins: Especially nucleoproteins must be taken. Liver, kidneys, sweetbreads, brains, tripe, etc. Next in perfection are lean meat, fish and game. *Carbohydrates*: Small quantities, preferably Ryvita, Energen, or as toast. One ounce of pure cane sugar per day (brown coffee sugar). Take plenty of fresh fruit and green vegetables, tomatoes, salads, oranges, grape-fruit, etc.

Two illustrative histories will show the effects produced in suitable cases.

Case 33.—A young woman, aged 30 years. An annual sufferer from hay fever sufficiently severe to make her life the usual misery during the pollen season. A very strict adherence to the Földes diet during the season relieved the symptoms almost completely —to the extent that she was able to go about the country where she lived without discomfort. Attendance at a typical summer function proved her downfall, where the temptation of strawberries, sugar, and cream followed by luscious creamy pastries overcame her, and the next day the hay fever was as bad as ever, whereupon she returned to her diet a prodigal daughter.

Case 34.—A woman, aged 32. She weighed 13 stone and this was far too much for her build. The tissues were all tight and waterlogged, the skin the typical white soft type. She had continuous wheezing with attacks of asthma, mostly in the early morning, which she had since the age of 18. The condition was associated with a fibrositic type of rheumatism as so frequently happens. Serologically a typical Type II case. Dermal tests all negative—vaccines were not satisfactory owing to her being extremely hypersensitive. Other treatments proved valueless. She commenced a very strict dietary régime of the Földes type. The asthma was relieved almost immediately and gradually left

her, and later the continuous wheezing, so that it now only recurs after unusual exercise. During the four months of treatment she lost 37 lb. weight. For the last year the strictness of the diet has been modified to the extent of allowing more and more of the 'things she likes', but calling a stop whenever the symptoms tend to relapse. Vaccine in the later stages has consolidated the very definite improvement initiated by the Földes diet.

EXERCISE

The manual labourer requires more food than the sedentary clerk to supply the fuel for his greater output of physical work, measured in foot-pounds; therefore no better way of using up superfluous food can be found than exercise.

If one wishes to become a 'strong man', individual muscles must receive attention; but if the desire is to keep fit, the liver must be exercised by the jolting of movement and by deep breathing, while the circulation of the skin is increased by 'getting hot' or by the friction of rubbing. It is said that Alexander the Great made his soldiers exercise to the extent of reaching the sweating level once a day.

With very little inconvenience it is possible for all to obtain good sweating exercise once a week. Skating, especially out of doors, offers an excellent medium for this. Dancing and indoor Badminton are not so good. If a small courtyard can be found, singles at deck quoits will produce a state of perspiration in the shortest time possible. The paraphernalia required consists of one rubber quoit, one badminton net, or a piece of tape stretched 5 feet from the ground, and such rough markings of a 'court' as are convenient.

An asthmatic whom I had never seen wrote to me saying that he agreed on the value of exercise; having been an asthmatic all his life, he bought a small house and garden and found that as he dug so the asthma left him. He now keeps a small portion of the garden in which he alternatively digs a deep pit and fills it up again; this sweating exercise keeps him fit and free from asthma. These dicta may sound trivial, but upon them depends much of the success or otherwise in treating asthma. The main theory has formed part of the teaching of Adam of Glasgow for the past twenty years in explanation of what he has called the 'week-end type' of asthma.

Amongst working classes, a week of hard manual labour ends at midday on Saturday and gives place to a day and a half of extra feeding and perhaps drinking, with no exercise

to work it off. If the worker reaches Monday morning safely the return to hard exercise saves him; but quite often on Sunday night or sooner a bad attack of asthma develops and he is an absentee on Monday morning—hence the soubriquet, 'the week-end type'.

The fullest use should be made of Sundays. The hot joint with Yorkshire pudding is anathema.

Case 35.—A stout flabby man came to see me from the country. He worked the whole week in London at clerical duties. On Sunday morning he went to church, had a large lunch, and slept in the afternoon, waking with asthma, which he had on and off all the week. On changing this régime he lost his asthma. He took walks on Sundays, gradually lengthened to 15 or more miles in the day, summer and winter, and with the aid of a pair of field-glasses he became an authority on the bird life in his neighbourhood.

As a daily morning exercise nothing is better or easier than marking time at the double; commencing with ten or twenty jumps the number is increased until some 300 can be accomplished without shortness of breath.

Of muscle and joint movements, all the time available should be devoted to the spine and chest. While still in bed, commencing at the occipital ridge on one side and continuing the whole way down the spine, the muscles close to the spine should be kneaded with the fingers or knuckles of the other hand. Special attention should be given to any tender spots which are found. By getting the elbow against the pillow the spine can be reached from the top to about the middle of the dorsal region; continuing from below, the whole spine can be massaged to the sacrum. Each portion of the spine should then be moved, flexed, extended, and rotated to the fullest possible extent, first the cervical spine, then the dorsal, and lastly the lumbar, the other portions being kept fixed meanwhile. On standing up the pelvis can be rocked in the same way as the negro tribes do in their many excellent dances.

Breathing Exercises.—On listening to the chest of an asthmatic, even when free from all asthma, the vesicular murmur though heard loudly in the upper portions of the chest is almost absent at the bases.

This is due to an entire lack of movement of the diaphragm, and indeed it is surprising how very little control the ordinary person has over the movements of that muscle.

Those who saw the film, *One Night of Love*, will remember the astonishment of Grace Moore in the character of a budding prima donna at the fact that for the first four months of her training she was not asked to sing a note: she had to be taught first how to breathe. It takes no less time to teach the asthmatic.

Abdominal breathing must be combined with thoracic breathing. There is: (1) The raising of the upper portion of the chest wall; (2) The expansion of the lower portion of the chest; and (3) The depression of the diaphragm. If the walls of the chest expand with the diaphragm working as a piston rising, as it usually does in the asthmatic, very little air enters the bases of the lungs. The initial movements are perhaps little more than a trick, and once proper control is gained, subsequent perfection is easy.

The exercises devised by Goldthwait et al.[3] as essential for the correct posture and maintenance of proper balance or 'body mechanics' have the advantage of being both simple to perform and eminently suitable for teaching the asthmatic patient the exercises for development of the thoracic and diaphragmatic muscles of respiration. Extremely complicated as they are to read in the book quoted, they may be simplified in the following manner (Crowe[4]), so that even a child may soon pick them up properly.

Exercise A.—The patient lies on the back on the floor or other hard surface. The hands are clasped behind the head, and the elbows pressed downwards and outwards until they touch the floor. This expands the upper part of the chest. A deep inspiration is then taken, and the whole chest wall lifted to its fullest extent. It is then held in that position. With the chest wall thus held, deep breaths are taken using the diaphragm and the abdominal muscles only. With the inspiration the abdomen is pushed out, and with expiration it is pushed in. This is sometimes the most difficult thing to educate the patient to do in the correct sequence. Not only is the diaphragm thus exercised to its fullest capacity, but the whole splanchnic venous system is massaged, and the liver literally shaken up. Some twelve of these deep breaths are taken, and the fixed chest wall then relaxed again in a long deep expiration. After *Exercise B* it may then be repeated; fifteen to twenty breaths every morning on rising, and again on going to bed, should be ample for anyone.

Exercise B.—This exercise is aimed at improving the poor costal angle seen so frequently in asthmatical patients. The patient again lies on the floor. The right hand is placed on top of the head, with the elbow on the floor. The left arm lies down by the side.

As a deep inspiration is taken, the arm pivoted on the head is raised —even dragged upwards, drawing out the whole of the right side of the chest wall, and widening very considerably the narrow costal margin. The left hand is then placed on the head, with the right one by the side, and the same process repeated on the left side. Several breaths are taken on each side, and the only difficulty is to teach the patient the proper extent of raising the arm and dragging on the chest wall. Six to ten breaths on each side should be sufficient for this exercise.

In one or two lessons the main essentials of these exercises can be learnt. As simply told to the learners: when they breathe in, the stomach must come out; when they breathe out, the stomach must go in.

All asthmatics can breathe in and out at their fullest for a very long time before having to stop in the condition of apnœa that soon overtakes the well trained breather.

Before 'marking time' for three minutes at the rate of 100 per minute, two minutes must be given to deep breathing, as rapidly in and out as can be accomplished while maintaining the fullest gamut of inspiration and expiration. In this way the patient learns how to breathe; he keeps the diaphragm at its maximum efficiency; he gives the bronchioles at the bases of the lungs a scouring with fresh air, during which the patient will commonly cough up phlegm; and lastly, if the deep breathing is effective, every cell in the body will be able to receive an ample supply of oxygen from the superoxygenated blood.

When the deep breathing exercises are fully mastered the air should be heard entering the bases of the lungs in its full volume and with a loud vesicular murmur.

Once a patient has learnt to breathe properly, exercise can be taken without producing an attack, and in fact many people find that the asthmatic attacks can be stopped by exercise.

DRUGS

Treatment of asthma is so rarely by one method alone, that the value of any prescription may be hidden by other lines of treatment. On the other hand, patients having prescriptions have had so many years in which to try them out that their information should be valuable. But whereas we so often find they have a prescription which they get made up from time to time, the contents vary in almost every case. There

is no specific drug treatment for asthma, nor do I know of any experimental work that has been conducted on the value of drugs in asthma.

The three following prescriptions are of use in certain cases. The sodium iodide is a mixture for those cases in which there is much sticky phlegm; the second is a routine medicine for asthma; while the third is of value in more acute cases.

℞	Sod. iod.	gr. v
	Ammon. carb.	gr. iv
	Ammon. chlor.	gr. x
	Syr. tolu.	℥ xv
	Aq. chloroformi	ad ℥ss
	Every four hours.	
℞	Ferri et ammon. cit.	gr. x
	Pot. iod.	gr. ij
	Pot. cit.	gr. x
	Sp. chloroformi	℥ x
	Inf. gent. co.	ad ℥ss
	Three times a day.	
℞	Caffein. cit.	gr. vij
	Tr. stramonii	℥ vij
	Tr. hyoscyami	℥ xxv
	Liq. ext. glycyrrhizæ	℥ x
	Aq. destill.	ad ℥ss
	A dose at teatime and another during the evening.	

The iodides have a long-established reputation in treating asthma, together with arsenic. Digitalis has seemed to me to have almost a specific value in certain cases; working as it does through the vagal nerve-endings this might well be so. Belladonna, hyoscyamus, stramonium, and lobelia all find their way at one time or another into prescriptions. Most of these drugs, even the iodides, have some toxic effect, and should not be taken except under medical supervision. Arsenic in particular requires careful usage, and should only be taken for a short time.

Ephedrine is used in an enormous number of cases, and usually without any medical control. Its value lies in the fact that it can be taken by the mouth. Though slower in taking effect than adrenaline, the easement which ensues is of longer duration. Hence it offers great help to those patients who, though able to do their work, are at times caught with an attack of asthma possibly at inconvenient times, as when about to attend a board meeting, or other function of business. No reliance can be placed upon it to cure asthma, and when

taken three or four times a day ephedrine may lead to depression, a weakening of the heart's action, and insomnia. In elderly patients, owing to the action of ephedrine on the muscular wall of the bladder, there may be temporary retention of urine. It forms a constituent of numbers of the proprietary cures for asthma that have so recently flooded the market.

Patients commonly resort to the burning of asthma powders and cigarettes. Pulvis stramonii co. *B.P.C.* is stramonium 50 per cent with lobelia, anise, and tea impregnated with potassium nitrate. Though giving temporary ease to the spasm, its effect upon any concomitant bronchitis is to increase the chronic inflammation.

COLONIC LAVAGE

Having attempted to improve the patient's metabolism by careful dieting, by exercise, and by deep diaphragmatic breathing, we come to the question of the elimination of waste products and such toxic elements as may be forming in the lower bowel. As it is theoretically possible to pass daily refuse from food taken some days previously, a hastening of the food through the bowel and its ejection should be assisted with regular and sufficient purgation, as by a blue pill once a week.

Colonic lavage washes out the contents of the lower bowel thoroughly and completely, emptying the numerous diverticula that may protrude from the colon, and which may hold their contents while the main stream of the contents passes slowly by. For this purpose colonic lavage is often of great value.

To provide the maximum elimination from the kidneys, the normal water intake by the mouth should be increased by two or more pints of fluid per day.

Such methods of dietary and of metabolic hygiene may be sufficient to cure patients who are not too greatly affected by other allergic and microbic causes, and in all cases will help to overcome the asthma.

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CHAPTER XVI

TREATMENT OF THE ALLERGIC TYPE (TYPE I)

In discussing the treatment of the various types of asthma, with their very complicated aetiology, a point is soon reached where sharp distinction between the types breaks down, making it difficult to label each correctly. Some conform so closely to type as to be purely allergic or purely microbic, but the separation must not be pushed too far.

The typically allergic child, sensitive to animal hairs with clear-cut spasmodic asthma, will in the course of years become secondarily infected with micro-organisms, until in the forties or fifties he has become a chronic asthmatic with a large daily output of sputum, and otherwise conforming to what would appear to be a purely microbic type. Nevertheless he still belongs to the allergic type and as such requires treatment specific to that type, no matter how pronounced the microbic element may be. He is, in fact, a 'mixed' case, or type III.

Similarly the separation of all cases of asthma into the three types—I, allergic; II, microbic; and III, mixed—by the differential sedimentation test, will fail to show an absolute cleavage between the types in exact proportion to the number of cases in which the actual causes of asthma show graduations from pure allergy to pure microbic origin. Treatment, then, must vary from measures designed to combat the allergic nature of the case to those aimed at the purely bacterial influence.

A certain amount of overlapping will commonly be present, and the treatment here given, although separate for each type, may at times necessitate modifications to fit a particular case. The treatment specific for each type described therefore will be that necessary supposing the case to be an unmistakable example of that type, and experience alone can make the modifications.

Many of the non-specific forms of treatment that are given, such as the treatment by X rays, are available for many forms

of asthma ; we should observe that they have been given and reported on cases without proper classification or grouping by either clinical or serological procedures.

The treatment available for a patient sensitive to a foreign protein is : (1) Avoidance of the protein ; (2) Specific desensitization ; (3) Non-specific desensitization ; (4) Other methods.

1. THE METHOD OF AVOIDANCE OF PROTEINS

Much has already been said on this subject when dealing with sensitization to foreign proteins (Chapter X).

Foods.—Foods which are rarely taken can be avoided with some ease, but difficulties may arise even with them. For instance, any one who is sensitive to mushrooms must be continually on guard to avoid their presence in hors d'œuvre, soups, fricassées, in sauces served with fish or entrées, the penalty of taking mushrooms inadvertently being sickness or an attack of urticaria before the evening is out.

A patient of mine took a chocolate unthinkingly during the play in a theatre ; it contained brazil-nut to which he was sensitive, and he spent that night in a nursing home with gastro-intestinal symptoms, only less severe than poisoning from bad food in that he had recovered by the next morning.

With the common carbohydrate foods—bread, potatoes, rice, and the legumens—not only must care be taken to avoid those foods to which the patient is sensitive, but ingenuity is required in finding substitutes. So specific is the sensitization that each of the cereals—wheat, oats, barley, and rye—should be separately tested, not only by the dermal reactions but also by clinical tests to see if convenient substitutions can be made between them. I have had patients who could not take wheat but could take oatmeal. Others again can take cooked wheat but are sensitive to raw flour, clinically and by test. Sensitization to meat is extremely rare in my experience.

The majority of foods give rise to other allergic symptoms besides asthma, such as eczema, urticaria, migraine, and gastro-intestinal upsets.

Air-borne Dusts and Animal Emanations.—These provide the commonest cause of asthma, and, being inhaled, cannot be avoided except by residence away from the cat or dog, or by the removal of these animals from the house, supplemented by a considerable spring-cleaning to remove the hairs left behind.

One of the greatest trials for those sensitive to horsehair is the clothes of other people who have been hunting, giving them asthma without even seeing the horse that has caused the trouble.

Patients can be kept from foods, but the animal hairs and feathers must be kept away from the patient until such time as desensitization is sufficiently complete to admit of their return. Breeches, habits, and other clothes worn while riding must be kept outside the patient's bedroom.

The aim must be not only to get the patient better, but to get him perfectly well. In the case of a child found to be sensitive to house dust, feathers, and some animal hairs, the advice given will be to let him sleep alone as soon as old enough in a room free from anything that will hold dust, such as thick carpets, curtains, and hangings. All heavy upholstery should go, and the bedroom made as lightly furnished as a hospital. Kapok should take the place of feathers, and as we know that even kapok becomes altered by the process of ageing, it should be changed every year. Of all places in the house the dust from bedrooms is most potent, that from the bedding being particularly harmful; therefore the bedding should be sufficiently beaten on the line once a month.

Patches of mould in the ceiling, cupboards, or walls should be sought out and removed. The actiological significance of moulds is very marked in some cases, and in the mattress and bed furniture, kept warm and moist by the body, we may particularly expect a luxuriance of growth.

If the slightest reaction is obtained to dog hair, the animal had better be removed; half-measures are of no avail, because unless the dog is a kennel dog or a sporting dog and never admitted to the house, its presence rapidly covers the whole house with its hair. The nursery should be quite free of all animals and birds such as canaries and budgerigars.

Air-conditioned Rooms.—If the patient is placed in a room free from those air-borne proteins to which he is sensitive, and if all air admitted to the room is passed through mechanical filters so as to be free from these proteins, he will be able to live and sleep in that room free from symptoms.

This is rational, but appears to have no other advantage; that is to say, the patient does not thereby become desensitized to the air-borne proteins, or gain anything other than a temporary cessation of symptoms.

When the degree of asthma from which the patient is suffering is so severe that it is imperative to give relief and at once, these air-conditioned rooms are of great assistance.

Originally in use by Storm van Leeuwen, full descriptions of rooms and more or less portable air-filters are to be found in the American literature. (Criep and Green.[1])

2. THE METHOD OF SPECIFIC DESENSITIZATION

In an animal sensitized to a foreign protein, a state of anti-anaphylaxis can be produced by injecting the animal with doses of the protein to which it is sensitive, starting with minute doses and increasing the size until in twenty-four hours a lethal dose can be given with impunity, the anti-anaphylaxis of Besredka. By this mechanism the specific reagins in the blood and cells are gradually used up and neutralized. At the end of a further incubation period the animal will again become sensitized.

Having discovered by the dermal reactions to which proteins the patient is sensitive, it only remains to discover the correct dose with which to commence treatment.

Attempts have been made to standardize the testing solutions by noting their nitrogen content, but as the active portion of the antigen which causes the sensitization, and the dermal wheal, is often a carbohydrate, and as nitrogen-free solutions are still potent, this method appears to be of little value except to make a fresh solution of a protein and to make it of the same strength as the last, a matter of consequence to the manufacturing chemist rather than the individual practitioner.

The first rule in using desensitization successfully is that the solution used for treatment and that for testing the patient shall be from the same bottle and therefore of the same strength.

On testing the patient by the puncture method, if a solution gives an enormous reaction it is too strong for commencing treatment, and another test puncture must be made with a weaker dilution. Finally, that solution is chosen which gives a faint but distinct reaction against a control. What the solution contains—that is to say, its strength—is of no importance so long as it has been proved by the dermal reaction to be correct for the patient under treatment. This is the second rule : to select the strength to be used for treatment by means of the dermal reactions and without regard to any measurement of strength on the bottle.

Less care is required in selecting the initial dose than was necessary some years ago, because adrenaline is given with each dose, isolating it and making its absorption very gradual, and safe from the production of such symptoms as urticaria and asthma.

The initial dose of a protein is 0·1 c.c. of that solution to which the patient gives a slight dermal reaction. Each subsequent injection should be increased by a similar amount, 0·1 c.c.

Injections can be made as frequently as is convenient. Daily injections can be given to patients in nursing homes or hospitals. When the patient has to visit the doctor, injections are given once, twice, or three times weekly as may be convenient. It makes no difference to the ultimate state of the patient how often the injections are given, except that the more frequently injections are made the sooner the patient's asthma is under control.

Each patient keeps a record on a special asthma chart of his attacks. As soon as the attacks disappear, the intervals between the doses can be extended until he is having a dose of such strength as is found to be necessary to control the symptoms, being continued once a month for a year.

At the end of a week of daily injections he should be symptom-free and remain so during the remainder of the treatment, nor should the asthma return, although it is never possible to give any guarantee of this. Two patients came to see me again recently on account of a recurrence of their asthma, each of them having been entirely free from asthma for twelve years until this summer. Both responded very quickly to further injections of the proteins to which they were sensitized.

Group Proteins.—I have always endeavoured to avoid the use of proteins in groups, and have thought that every attempt should be made to isolate the protein actually at fault. Those commonly grouped are the air-borne dusts, and a skin test may be made with the one solution instead of six or seven separate solutions, a matter of great convenience in children. Tested and treated by a group solution in this way proves very effective in removing the asthma ; if the patient wishes to know whether it is the dog or feathers or face-powder that really affects him, this can be discovered by separate tests ; and I think it is very well to know, because of the additional

help that can be gained by the avoidance of such proteins when possible. Probably the injection of those ingredients of the mixture to which the patient is not sensitive acts in a non-specific way to help treatment.

Groups of proteins other than the air-borne dusts are of much less use. It is impossible to get a more closely allied group than the cereals, but when one knows that a patient may be sensitive to wheat and not to oats, or vice versa, discovering that the patient is sensitive to the cereal 'group' debars him from taking both. Individual tests are essential in such a case.

Groups of foods based on strict botanical relationship, especially those more rarely taken, as the currant tribe or certain of the Umbelliferæ, prove quite useful, and evidence exists that desensitization to one of the group materially assists desensitization to the other closely allied antigens.

Baldwin and Benedict[2] found that mixing the serum of a sensitized patient with one member of a group, as carrot, lessened the reagins in the serum, when tested by passive transfer, to others of the same group—namely, celery, parsley, and parsnips. With apples, quinces, and pears the same interchange held good. Experiments in the fish group and the cereals also proved the close relationship of antigens of similarly related proteins.

With foods the usual way to attempt desensitization has been to give the food by the mouth. In those cases in which the patient is very sensitive, as to egg, minute doses must be given to start treatment, accurately measured and parcelled into pills for this purpose. But apart from the fact that foods often give rise to gastro-intestinal symptoms after they are eaten, the cause of all symptoms of sensitization lies in the fact that there exist reagins against the food in the patient's blood.

Desensitization is therefore best carried out by injection against foods, just as it is against pollens in hay fever. One knows then exactly how much protein is being injected into the system, and sufficient adrenaline can be given to counteract any temporary symptoms from overdose that might follow.

This method of giving adrenaline with the therapeutic doses of protein to which the patient is sensitive, was first suggested by the work of McDowall,[3] and brought into practical use by Bray.

McDowall and Thornton[4] describe the method by which the effect of drugs on the bronchial musculature can be measured. Water passed down the trachea and out through scarifications on the lung surface at a constant rate can be read by a manometer and recorded on an ordinary kymograph paper on a revolving drum. A permanent record can then be made of the flow, together with any fluctuations that may occur. Contractions of the bronchial muscle will lessen the calibre of the bronchioles and make the passage of the water through the lungs slower, as demonstrated by the increased pressure of the water passing into the trachea.

The drugs or antigens to be tested are passed through the blood-vessels. Perfusion of the antigen—egg-white, etc.—to which the animal is sensitive causes the bronchial muscle to contract; if adrenaline is perfused at the same time the contraction of the bronchial muscle is controlled. This finding is so obvious that it may be thought not to constitute a discovery of any great merit, but it has led to a great advance in treatment, in that doses some ten or more times as strong can be given to the patient as compared with those formerly considered possible.

The duration of the course of injections is greatly reduced and the control point reached far more quickly.

In the voluminous literature in America no mention of this use of adrenaline with the antigens has appeared so far. There is no suggestion of a neutralization of the antigen or reagins by the adrenaline, as the latter may be given in another part of the body with similar effect.

In brief, the treatment of a patient hypersensitive to protein consists of testing the patient intradermally with the solutions to be used in treatment, selecting that strength of protein which gives a reaction noticeably larger than the control. Injections of the selected strength are given two or more times a week with adrenaline. When the record chart shows the symptoms to be under control the intervals between the doses are extended, until a large dose is given once a month for a year.

Desensitization by Means of Oral Administration.—If the blood of a fish-sensitive patient is injected by passive transfer into a normal person, an inflamed irritating swelling will be formed at the site of the injection if the normal recipient then eats fish. This is the Prausnitz-Küstner reaction, and it

shows that fish protein or some constituent of it enters the blood in normal people.

An experiment I heard Dr. Freeman mention some years ago bears this out. A hay-fever patient and a patient not subject to hay fever were each given a considerable dose of pollen to drink in a glass of beer. Shortly afterwards the hay-fever patient developed a sharp attack of hay fever.

This being so it is quite rational to expect desensitization to be possible by doses of proteins given by the mouth.

Barksdale[5] describes the successful use of house dust and pollens given by the mouth. The solution used contained 1 mg. per drop of the soluble constituent of the original house dust, made by extracting 5 g. of dust in 200 c.c. of water. The pollen used contained 1 mg. of pollen granules per drop, the drop presumably being a minim.

Dosage commenced with 5 to 20 drops, three times a day, increasing to 2 or 3 fluid ounces of the extract. He claims 70 per cent cures. I have not used this method, but it should be quite easy to carry out and convenient for use in children, except that comparatively enormous doses of the dust and pollen are required.

3. METHODS OF NON-SPECIFIC DESENSITIZATION

Almost every change that takes place in the blood of an asthmatic patient will be liable to have an effect upon the complaint, whether the change is brought about by an infectious disease, by pregnancy, or by the injection of some foreign protein.

After the discovery by Pasteur of the existence of bacteria, certain species became identified with certain diseases. Most notable was the discovery by Koch of the *B. tuberculosis*. Koch enunciated certain postulates which had to be satisfied before any microbe could be considered as the certain cause of any complaint. These discoveries of specific organisms for specific diseases, obeying all Koch's postulates, naturally led to a wave of opinion that neither looked for nor admitted the possibility of any bacterial action which was not specific in character.

It was not only discovered that the presence of the causative bacteria was essential; but it was also found that the toxins formed by these microbes and the antitoxins formed by the patient were also of an extremely definite and specific nature. The whole of Ehrlich's work and theories consolidated the

idea of the specific nature of these reactions. Bacteria which did not produce obvious poisons or exotoxins were looked upon as being outside the picture and of no consequence, merely saprophytic and non-pathogenic. Where organisms produced obvious effects, but no exotoxin could be demonstrated, the term endotoxin was coined to describe the effect produced.

The discovery that there was a reaction on the part of the patient to these bacteria and their various toxins, by the formation of antibodies, led to the wholesale injections of dead cultures of specific organisms obtained from the patient and thought to be the cause of his complaint. This is a method of the greatest utility where it is wished to raise the specific antibody titre against organisms that are troubling the patient, such as some abnormal inhabitant of the nose or bronchi.

Next it was attempted to make animals provide a strong solution of these antibodies for use, by injecting horses with the bacteria and obtaining their serum when fully charged with antibodies, for reinjection into man. Typical examples of the successful application of this method are to be found in the use of antidiphtheritic and antitetanic sera. With other organisms this method has failed, because the animal has become sensitized to the organisms that were being used, and further injections of them have had to be stopped, short of full immunity.

All such methods are entirely specific, both in theory and in actual practice. The infecting organism is identified, a vaccine is made from it, this is injected into the patient, and a specific response by the formation of specific antibodies results.

It gradually began to be noticed, however, that other results took place after the injection of these vaccines besides the specific reactions which it was intended to provoke. The general mortality amongst large bodies of men, such as those employed in mines, was reduced not only in typhoid fever but in other diseases by the prophylactic injection of antityphoid vaccine. Sir Almroth Wright[6] described the general well-being that was noted after the inoculations, and stated that many chronic complaints, such as eczema and so forth, disappeared or showed improvement. Thus there appeared to be a non-specific action resulting from the vaccination. This was at first disregarded, because it did not fit in with the craze for specificity then in vogue. When it had at last forced itself into recognition, experiments began to be made to discover

how far this non-specific collateral effect of a vaccine was of value.

Whilst the profession was still biased by a belief in the 'specific' nature of all reactions, only such bacteria as were of close morphological relationship to the original microbes were used, and the only result that was looked for was an increase or otherwise of specific antibodies to the original organism. Soon it became obvious that in using the various antitoxic sera the protein of the horse serum was not the least important part of the injection. From the injection of this protein it was a short step to the injection of other foreign proteins such as white of egg, or more particularly milk. Next it was discovered that many of these proteins produced a shock soon after their injection into the patient. It was found that some patients, suffering from such acute bacterial infections as pneumonia and typhoid fever, would, after this protein shock, end their complaints at once by crisis, and enter into a state of convalescence the next day. Treatment on these lines is known as non-specific protein therapy. Excellent work on the subject has been published by Petersen,[7] and the reader is also referred to articles by Gow.[8]

The Method of Dansyz.—In my experience, over a great many cases, nothing is so effective in non-specific therapy as the method of Dansyz, or the injection of the mixed coliform vaccine.

Dansyz's[9] theory was that these allergic complaints were caused by "*l'anticorps en excès*", that is, the presence of too great an amount of reagins in the blood and cells of the patient; and he interwove this with theories by which he claimed effective cure of all such allergic complaints and many other disabilities by the injection into the patient of his own intestinal flora.

My own theory would rather be that on the injection of any foreign protein into the blood, reagin formation takes place against the protein injected. As there is no reason to suppose that there is more than one mechanism by which this is brought about, new reagin formation takes place at the expense of the old reagins in the blood, so that the latter become desensitized in specificity to former proteins.

The method of Dansyz was to make a vaccine from all those organisms found to be growing in the intestine, obtained by culture from the stool on ordinary sloped gelatin, beef, or

peptone media. The various pure cultures were mixed together in the proportions in which they were found to be growing in the bowel. They were dried and weighed, mixed with normal saline, and sterilized with heat at 70°. Vaccines made on similar lines may be called mixed coliform vaccines. For hypodermic injection Dansyz used $\frac{1}{500}$ to $\frac{1}{50}$ mg. of the bacteria. He also used the vaccines by mouth in doses one hundred times as strong. I have employed the latter method in children, thus avoiding the slight pain necessary to a hypodermic injection.

With regard to the dosage of vaccines, asthmatics are a law unto themselves. It is impossible to state standard doses, except to say that patients can be cured by *one-thousandth* of the dose used in ordinary cases, or even smaller. The amount fitting to each individual case must be discovered by trial doses.

Dansyz claimed cures in a large range of chronic complaints, and I have been able to duplicate all his cases, except in psoriasis. Several of my cases were ordinary seasonal hay fever, giving the large reactions constant to the grass pollens, and they were cured without the use of pollen. This has always seemed to me the best form of non-specific treatment that exists, and I have only one criticism to make. Should the asthma return, as it may, after an interval of a year or two, a second course of treatment is not so effective as the first.

An additional value of the mixed coliform vaccine is that the patient's general condition is greatly improved, to the extent that he will be able to pass through the following winter without catching a cold. This occurs after many series of injections, in patients who have had a desensitizing course of dust or pollen.

The same immunity from colds has been observed by Strenberg,[10] who has noticed that after a course of pollen injections patients who had previously been unduly susceptible to colds had no colds during the succeeding winter.

There may be some malaise following these injections of mixed coliform vaccine, but there are never any symptoms of an anaphylactic nature on the one hand, or of protein shock on the other. This is an additional advantage in their use.

Tuberculin.—I used 'old tuberculin' at one time, but only half-heartedly, as I could never see any advantage in using such a potent not to say poisonous remedy, when the

mixed coliform vaccine fulfilled every concept of the perfect non-specific remedy. Storm van Leeuwen[11] spoke well of tuberculin. In any case the treatment is a matter of some months, and the results obtained do not seem more satisfactory than by other non-specific means.

Peptone.—There are three ways in which peptone is used to treat asthma: (1) by injection; (2) by mouth; and (3) by the production of protein shock.

1. *Injection.*—I have given hundreds of injections of peptone, especially in children, but specific desensitization has quite displaced it in my present work. Originally brought into use by Auld, many improvements have been suggested by him to obtain the best results from its use. I have always used the 5 per cent solution for intravenous injection or the $7\frac{1}{2}$ per cent solution for intramuscular injection, as made by Martindale. Treatment is commenced by an injection of 0·1 c.c. and increased to 1 c.c. or 2 c.c. at weekly intervals. A great many cases respond very well.

Towards the end of a course, patients are apt to complain of some nausea immediately after the intravenous injections. When this occurs treatment can only be continued by the intramuscular route, as once a patient starts this sickness it will recur after all subsequent doses.

Except for one single experience out of the many hundreds of injections which I have given I should have said that its use was entirely without danger or alarm.

Case 36.—A lady about 30, who had had very severe asthma for many years, came to me and I commenced a course of peptone with a dose of ℥3 of the 5 per cent solution, intravenously. Within a minute a tremendous spasm of the bronchial muscle developed. She became unconscious, passed water, and presented a truly alarming anaphylactic state. Her pulse was strong and regular throughout. An intravenous injection of adrenaline brought her round gradually, and she was eventually carried to a nursing home, where she rapidly became perfectly well. Next morning on calling to see her, she had gone to work, she felt so well. The asthma disappeared entirely for five weeks afterwards, but I did not repeat the dose.

2. *Oral Administration.*—In France the experience has been that if a small dose of the food to which the patient is sensitive is given one hour before a meal at which the food is to be eaten, the leucopenic crisis is avoided, and the patient will be free from symptoms. Much use is made of peptone to effect the

same purpose. A dose of ½ g. (7½ gr.) is given in a cachet one hour before each meal. Subsequent desensitization is claimed for this method. I have used it successfully on certain patients who have had an increase of asthma after each meal.

3. *The Production of 'Protein Shock'.*—A third method of using peptone is to give a large dose intravenously to produce a protein shock. I have never used it for this purpose, nor shall I ever do so after my experience with the case mentioned where ℥3 of a 5 per cent solution produced such a grave condition. Doses of 8 to 10 c.c. of a 10 per cent solution of Witte's peptone have been used for this purpose to produce a protein-shock reaction. The majority of these peptones contain a certain amount of histamine, and one may think it is that which produces the curative effect.

Autohæmotherapy.—Blood is taken from a vein in the patient's arm and reinjected subcutaneously elsewhere before it has had time to clot. A No. 15 or 16 needle should be used when injections of 5 to 10 c.c. are to be given, otherwise the blood may clot in the syringe with disconcerting rapidity. For those who are not accustomed to much intravenous work a little glass adaptor fitting between the needle and the syringe is useful. Directly the vein is punctured a spot of blood appears and can be seen through the glass. This adaptor was invented, I believe, by Blair Bell. I used it when giving intravenous injections of lead for cancer. Nothing less 'foreign' or less likely to prove provocative could be imagined than the patient's own blood; nevertheless an occasional patient is upset by autohæmotherapy, a dose of a few minims being enough to cause a temperature.

I have given these reinjections of blood many times, chiefly for urticaria, but consider them quite unreliable in comparison with the mixed coliform vaccine, or the use of histamine or of autogenous vaccines, as the different types of urticaria may require. I usually give ½ c.c. of blood, increasing rapidly to 10 c.c., giving the injections twice weekly.

Autoserum Therapy.—Reinjection of the patient's own serum has been used, but the technique and the necessity for prolonged asepsis throughout is so complicated that it need not be considered as a routine method.

Other Non-specific Desensitizing Agents.—As stated at the commencement of this section, all injections made parenterally will have an effect upon the asthmatic. A great

number of different substances such as sulphur, turpentine to produce an abscess, and other methods, have been used, all with some effect. This book is not concerned so much in providing a catalogue of all the methods as in giving the authors' opinions on those methods that have been used constantly and with good effect.

Shock Therapy.—By this is meant the reaction of the patient to an injection such as will cause him to have symptoms which in general are akin to those of malaria, loosely called 'protein shock'.

In Petersen's[12] words :—

> After the injection, following the more powerful and active ones, there is usually a severe chill, sweating, a febrile rise of 4 or 5 degrees Fahrenheit, a leucopenia followed by a leucocytosis, occasionally gastro-intestinal hypermotility, lowering of the blood-pressure, and a number of changes in the serum, such as an increase in fibrinogen, enzymes, thrombokinase, blood-sugar, and antibodies. A general increase in malaise usually goes over into a pronounced euphoria.

During the cold stage the patient will require hot bottles and blankets until the hot stage commences, being suitably changed when the sweating necessitates dry clothes and sheets.

The treatment of general paralysis of the insane by infecting the patient with malaria-carrying mosquitoes makes use of the protein shock consequent upon the malarial seizures. These patients may also be treated by using Sulfosin, a 1 per cent sterilized suspension of sulphur in olive oil, to produce the protein shock.

An asthmatic suffering from malaria as well as asthma will usually have periods of remission following each attack of malaria.

A great variety of substances may be used to produce the so-called protein shock, intravenously by injection of typhoid bacilli or mixed coliform vaccine, peptone, proteose, or colloidal metals, and intramuscularly by injections of milk.

The only method of producing protein shock that I use is the intravenous injection of bacteria—*the T.A.B. vaccine or the mixed coliform vaccine.* The method is worth trying in obstinate cases that are refractory to the usual therapeutic measures, especially if there is any history of improvement following upon chance temperatures in the past.

Unless the patient can easily reach home within half an hour of the injection, it must be given at his house, in a

nursing home, or hospital. The patient must go to bed at the first sign of a shiver, be wrapped up warmly, and have help at hand to nurse him until the shock has passed off.

An essential phenomenon in these attacks of protein shock would appear to be the temperature that accompanies them; so much so that we may note excellent results following other contingencies that produce the temperature, but without the rigor, the shivering, and other marked symptoms of protein shock. During an attack of measles or whooping-cough there is usually a complete abeyance of the asthmatic symptoms, which will return again in a few weeks after the temperature has subsided.

In diseases accompanied by more marked pyrexia, as in pneumonia and typhoid fever, a much longer period of immunity from asthma may occur; in fact, the violence and frequency of the attacks may be greatly subdued for ever afterwards. These complaints are gross microbic infections, and as such may cause a non-specific desensitization apart from the effect of the temperature produced.

The late Sir Malcolm Morris told me that he had suffered from asthma very severely as a young man. He was thrown out of a dogcart and suffered a comminuted fracture of the elbow (autohæmotherapy) which halved the incidence and severity of his asthma when he had absorbed the extravasated blood. Later he had an attack of pneumonia (protein shock) and the asthma left him for good.

An injection of 20 millions of T.A.B. or the mixed coliform vaccine can be injected intravenously. If no shock is produced another larger dose is given in a day or two. Having found the correct dose and obtained a ' good ' rise of temperature and the shock effect, the same-sized dose can be repeated in a month's time for two or three doses.

Case 37.—A lady, aged 38. First seen ten years ago. Asthma disappeared after a course of Dansyz's vaccine but returned a year or two later. Repetition of vaccine with no benefit, but asthma subsided after injections of Aolan. Later again returned rather badly. During a course of autogenous vaccine contracted influenza with a temperature of 103° and asthma disappeared for many months. On its return, injections of T.A.B. given with the production of much protein shock, since when, for nearly a year, there has been no return of asthma.

Boiled milk may be used intramuscularly to produce protein shock; 5 to 10 c.c. is injected twice a week. Care must be taken

that the patient is not sensitive to milk and has not become so by previous milk injections. A death has been recorded from a subsequent injection of milk.

The milk can either be boiled up before use, or more conveniently already prepared in ampoules as Aolan, and possibly more impressive to the patient. I have used milk injections but not to any great extent, because there was no need to do so.

In all fairness to many unusual methods that I have tried in treating asthma, I must confess that I have used them chiefly in the hope of curing the aspirin-sensitive type and other cases of profound asthma. Until quite recently all methods have failed without exception to cure this particular type, but that fact is no bar to their sphere of usefulness in other cases.

Colloidal Metals.—Fine dispersions of metals which are stable in suspension may be prepared by chemical or electrical means. The continuous phase, in which the metal particles are suspended, is a complex solution containing gelatin, peptone, or other protective substances, salts incidental to the reduction process and others added to render the solution isotonic, and finally phenol or other preservative.

By the dark-field illumination—a method of producing a microscopic sunbeam—the particles of metal can be seen to be undergoing active Brownian movement, being buffeted about by the molecules of the solution. The whole is therefore a complex collection of material.

The various metals carry negative or positive electrical charges. The effects of an intravenous or other injection of a colloidal metal into the body will be those common to all such injections—a greater or lesser degree of shock, together with those effects that are specific to the metals contained and their individual electrical charges. The effects are particularly directed to the vast colloidal system of the blood, the cells, and, in fact, all living material.

The colloid which I use frequently is Collosol Manganese. If given by the intravenous route it must be used already mixed, and not made immediately before use. It is apt to give some local pain after intramuscular injection, and I always give it intravenously. From 15 to 20 minims causes the patient to flush all over within a minute after the injection. I have never noticed any other injection causing this universal blush. It seems to enhance the value of other vaccines, and

has a peculiarly satisfactory result on those patients whom the French would call the colloidoclasic type.

They are subject to rhinitis, asthma, and urticaria, and usually have painful and scanty menstruation. The symptoms are increased just before the periods. Collosol manganese given intravenously will cure their symptoms, and often make the next period abundant and painless.

Premenstrual pain and swelling of the breasts will subside within an hour of an injection. I have used Collosol Calcium with no marked success in hay fever or asthma. Colloidal sulphur has been used, and, of course, preparations of colloidal gold. Sobhy[13] reports very favourably on the results obtained by the intravenous injection of small doses of sanocrysin in asthma.

4. OTHER METHODS OF TREATMENT

Histamine.—Histamine plays such an important part throughout the whole of anaphylaxis that it has naturally been tried as a therapeutic agent. A sufficient dose of histamine will produce all the symptoms of anaphylaxis, specific to the animal injected.

If we are to inject patients with this extremely poisonous substance, the rationale must be to commence with minute doses, and to increase very gradually. Finally a dose can be tolerated which will parallel the amount of histamine now causing the patient's symptoms.

Acting on the experimental fact that adrenaline neutralizes the effect of histamine to the extent of preventing the shock it would otherwise produce, and also on the same basis as adrenaline is mixed with desensitizing doses of proteins to contract the blood-vessels round the injection and isolate the dose, so adrenaline is mixed with the histamine injections.

The strength used is 2 mg. of histamine and 1 mg. of adrenaline to the c.c., or histamine 1–500 and adrenaline 1–1000. The initial dose of this mixture of histamine and adrenaline is 0·1 c.c. Many writers use a much smaller dose, but the important thing to remember is that patients react very differently to histamine. Some hardly notice anything after the injections, others within about two minutes will complain of headache, throbbing of the heart and temples, pallor from the adrenaline, and sometimes violent shaking. For this reason the patient should always be lying down when the

first injection is given. If there should be any uncomfortable symptoms subsequent doses can be given with the patient in the recumbent position.

The size of the dose is increased by 0·1 c.c. each time unless the immediate after-symptoms forbid it. Injections can be given two or three times a week.

I have used histamine in many cases of asthma and urticaria. Most dramatic effects may follow in urticaria. In the two following cases the urticaria stopped after the first injection and did not return :—

Case 38.—Male, aged 70. Had eczema, hay fever, and asthma as a boy. Has now had urticaria for fifteen years, all the year round. Has some dermatographia. Has had urticaria on the lips occasionally but never on the tongue or throat. No dermal reactions obtained. After the first injection of histamine and adrenaline 0·1 c.c. the urticaria disappeared and did not return. Ten injections given in all.

Case 39.—Male, aged 69. Appears very young for his age ; plays three rounds of golf each week, has had urticaria very severely for three weeks after eating tainted fish. The whole of the symptoms disappeared after the first injection of histamine. A course of injections was given and there was no return of the symptoms.

In other cases it has not appeared to be of the slightest value. Good results obtained have been in cases of asthma, urticaria, migraine, and eczema, and it is often worth a trial in cases which do not respond easily to other methods of treatment.

Other workers give very minute doses of histamine. Dszinich[14] uses doses ranging from 0·00001 mg. to 0·1 mg. in treating asthma and urticaria. Possibly this is necessary when it is given without adrenaline.

The usual dose at which I commence treatment is 0·2 mg.

Lennox and von Storch[15] treated 120 cases of migraine with histamine, and 107 were relieved. Apparently it was given to relieve each individual headache.

Histaminase.—Histamine undergoes rapid destruction in the body. Appreciable quantities disappear five minutes after injections, so that apart from the fact that histamine is undoubtedly freed or formed during anaphylaxis, its action and power to cause symptoms may depend not only on its being formed but upon the failure of the body to destroy it quickly.

Histaminase, as its name signifies, is an enzyme which has the power of breaking down histamine or at any rate of removing its physiological properties.

Best and Henry[16] have found this substance in various parts of the body, notably in the kidneys from which they have extracted it. Roth and Horton[17] have used it to treat a case of urticaria from cold, one of the physical sensitizations, and with success.

In four days 67 units of histaminase were given, each unit being capable of detoxicating 1 mg. of histamine *in vitro* during twenty-four hours at 37°. The difficulty of procuring histaminase confines its use to such experimental purposes.

Formaldehyde has a similar power of inactivating histamine.

Sachs and Ivie[18] find that the addition of acetic acid or lactic acid to a bath in which is suspended a loop of the ileum of a guinea-pig relaxes the loop when contracted with histamine or acetylcholine. The amount required is, within limits, dependent upon the amount of histamine, but independent of the amount of acetylcholine.

Histamine acts directly on the smooth-muscle cells, acetylcholine on the nerve-endings in the muscle.

Acetylcholine.—'The Clinical Aspects of the Transmission of the Effects of Nervous Impulses by Acetylcholine' was the subject of last year's Croonian Lecture (Fraser[19]). Impulses passing down the parasympathetic or cranio-sacral autonomic nerves in some way cause the formation of acetylcholine, by which the impulse is carried to the effector organs, amongst which is the bronchial muscle. Acetylcholine is rapidly destroyed by an esterase. Physostigmin causes the bronchial muscle to contract by inhibiting the action of the esterase, thereby allowing impulses passing down the vagus to cause increased and prolonged effects, by the unimpeded action of acetylcholine. The effect of atropine in annulling this action is to block the effect of the acetylcholine, not to lessen its formation or to increase the production of esterase. Injections of acetylcholine may provoke attacks of asthma, but the drug is very rapidly destroyed by esterase.

This gives some further explanation of the physiology of asthma, but little therapeutic help, except the indication that increased production of esterase would be of value, and might be achieved possibly by the stimulation of small but repeated and increasing doses of acetylcholine.

Oriel's Proteose.—By the following method Oriel[20] extracted from urine what is known as Oriel's proteose :—

400 c.c. urine was treated with 25 per cent sulphuric acid until acid to Congo-red paper, and shaken with a one-fifth volume of ether until the ether was in a fine state of suspension. When the suspension had separated, the lower layer, consisting of urine, was run off, and the upper layer, which consisted of fine globules of ether, was shaken with an equal quantity of alcohol. A precipitate was formed which was centrifuged off. The precipitate thus obtained was suspended in distilled water and again centrifuged. The resulting precipitate was found to be of a protein nature, with a large carbohydrate content, and for want of a better term was called a 'proteose'. It was soluble in very dilute alkalis. The interesting fact was observed that this substance, obtained from an allergic case, gave positive skin tests when these were carried out on the patient from whom it was obtained, and with other patients sensitive to similar antigens.

The following claims were made for this proteose :—

i. That the autogenous proteose extracted from urine passed during an attack of asthma, urticaria, and so forth was specific to whatever antigen had caused that attack.

ii. That the patient would respond with wheal formation when the proteose was applied to his skin by the intradermal method.

iii. That the same proteose would also cause wheal formation when applied to the skin of other persons sensitive to the same foreign proteins.

iv. That proteose from normal patients did not cause wheals on themselves or on others.

If these findings had been confirmed, Oriel's work would have made a very considerable addition to the therapeutic agencies available to cure asthma, especially as the proteose gathered during an attack would contain the causal agents of that attack, no matter what their nature might be.

Unfortunately, confirmation has been entirely lacking. Freeman,[21] testing out the specific proteose for hay fever, was unable to find any specificity in the proteose with other hay-fever patients. A carefully conducted experiment on five persons, three grossly allergic and two normal, resulted in dermal reactions which could not be distinguished from each other. Each of the five patients, the three gross allergics and the two controls, were injected at five sites with each of the proteoses. No material difference was noticed in the response of any one patient to the various proteoses injected.

The general finding of other observers has been the same—a total absence of specificity in the reactions.

For treatment minute doses of the proteose are given. I had full opportunity to see the whole process of the extraction of the proteose, the results of the dermal reactions, and listened to full discussions of the pros and cons of the whole subject. In the end I was certain that the claims to specificity of the proteose were not proven.

I can state, however, that I saw two cases who had been through my hands some five years previously, without much benefit, apparently cured by injections of the proteose. Whether this was due to some non-specific action of the proteose or whether its curative value far outruns its claim to specificity I do not know, but these cases seemed to be cured by its use.

Black and Shelmire[22] find that with the proteose there is also some unchanged protein (antigen) excreted in the urine. A non-sensitive person was given pollen by the mouth and this was later recovered in weak solution with the proteose from the urine.

Sodium and Magnesium Thiosulphate.—Lumière found that the intravenous injection of sodium thiosulphate had the power of inhibiting anaphylactic shock if given to an animal with the exciting dose of protein.

On this basis sodium thiosulphate and the magnesium salt have been used therapeutically. I have always used that made up by Martindale in sterules containing 10 c.c. of a 10 per cent solution of magnesium thiosulphate and injected it into the gluteal muscle. In spite of the large 10-c.c. syringe, it is only necessary to use a fine needle for these solutions; the injection is without pain, and has no after-effects locally or in general. I have used it with success in urticaria. The drug can also be given by the mouth, and is particularly useful with children.

The following is a valuable prescription for a child 10 years old;—

℞	Ferri et ammon. cit.	gr. ij
	Liq. calc. sacch.	℥ss
	Magnes. thiosulph.	gr. vij
	Sod. bicarb.	gr. x
	Aq. chloroformi	ad ℥ss

Three times a day.

Wide-field Radiation Therapy.—The technique of this method of treatment was devised by Gilbert Scott as early as

1920. Its perfection in the last three or four years has led to a measure of success in the treatment of asthma. The initial experiment, as so often has happened in the advancement of medical knowledge, was the result of happy chance. While treating a patient for malignant metastases at the London Hospital in 1920 by the wide-field technique Scott found that the immediate result was to relieve her asthma, from which, unknown to him, she had suffered for many years.

Since that time much research has been carried out on this method in all types of asthma, and a large number of cases have been treated. It is now extensively employed in many parts of the British Isles, and also with marked success in New Zealand. The method, which may be summed up in the phrase 'an X-ray bath', consists in exposing the whole trunk to the action of X rays of medium low voltage (100 to 130 kv.) filtered through 1 or 3 mm. of aluminium according to the type of case, the single total body-dose being usually about 60 to 100 r units. Exposures are given once or twice weekly, the interval being gauged by the activity and progress of the condition, care being necessary to avoid oversaturation or overdosage. In cases with bronchial infection Scott recommends that the initial doses be given with the thorax protected by lead-rubber covering.

At the moment it is difficult to determine beforehand which type of case will respond the most satisfactorily. It would seem, however, to have particular application to those where there is ill-development and endocrine imbalance. Scott's theory of the action of this particular method of X-ray application is that it leads to a stimulation or restoration of balance of general metabolism, through some influence on the ductless-gland system as a unit. He suggests that results in asthma are probably obtained through some effect on the suprarenal glands in particular.

Mucklow[24] has found the treatment remarkably efficacious.

Maytum and Leddy[25] used X-ray treatment on several cases of hitherto incurable asthma, and 20 per cent received lasting benefit. Some general symptoms were noted after radiations. The dosage used was 135 kv., filters 6 mm. aluminium, distance 40 cm., ma. 5, time 22 to 26 minutes. All types were treated, but they were a very severe series of cases.

Marked relief has been obtained in many cases from each of the three groups of asthma; nevertheless, although its value

is undoubted, the full assessment of the usefulness of the radiation method is still a matter of trial and research.

Entirely independent biochemical work in association with the differential sedimentation test led to the hypothesis being formed in 1932 that as a result of the determination of the colloidal changes in the serum of patients with asthma, such a method of radiation would theoretically have the desired effect clinically as well as serologically. The hypothesis was later confirmed as a fact.

This section may be concluded therefore with a short table of ten cases treated with the wide-field technique on which the differential sedimentation test was performed before and after treatment by this method, the clinical histories of these cases being typical of the group to which they belonged serologically.

TABLE SHOWING EFFECT OF WIDE-FIELD RADIATION THERAPY ON DIFFERENTIAL SEDIMENTATION TEST

CASE NO.	D.S.T. BEFORE				TYPE	D.S.T. AFTER			
	Per cent	Red	Green	Ratio		Per cent	Red	Green	Ratio
(*Normal*)	..	..	..	..	..	*5*	*15*	*18*	*0·8*
2442	19	9	19	0·47	II	8	23	20	1·1
857	−1	13	7	1·9	I	18	18	21	0·86
2258	8	43	17	2·5	III	8	17	20	0·85
2203	−2	29	1	29·0	I	6	16	12	1·3
769	19	21	21	1·0	III	4	21	21	1·0
2335	15	15	13	1·1	III	6	21	10	2·1
2384	17	11	17	0·65	II	9	17	19	1·1
2539	−15	19	10	1·9	I	1	22	12	1·8
2339	26	19	17	1·1	III	12	30	17	1·7
1055	9	22	1	22·0	I	7	22	17	1·3

Lipiodol.—There is considerable mention of the use of intratracheal instillation of lipiodol in the literature. I have seen it being given but have not used the method myself. Fink[26] speaks favourably of its value.

Sympathectomy.—In some cases there appears to be great value in ablation of certain sections of the dorsal sympathetic ganglia.

Levin[27] describes his technique for treating asthma by dorsal perisympathetic injections of absolute alcohol, with many successes.

A full symposium of the anatomy, physiology, diseases, and surgery of the sympathetic ganglia is given by Lawrence Abel.[28]

He writes :—

Work is progressing at the present time in many centres on this difficult subject [asthma]. Variable success has been attained by attacking the sympathetic ganglia in the mid-dorsal region which supply the pulmonary plexuses, either by excision or by injection of alcohol. Some workers combine this with resection of the vagi, but the matter is still *sub judice*.

This statement is more guarded than that of others, who claim considerable success in the use of alcohol.

Insulin Shock.—Wegierko[29] finds that a series of insulin shocks may help asthma, but places the treatment in the same category as other forms of protein shock.

Hydrochloric Acid.—Acting upon the fact that he found the secretion of hydrochloric acid in the stomach to be deficient in many cases of asthma, Bray[30] advised the giving of hydrochloric acid in such cases. Loveless,[31] however, found no correlation between allergy and a hypochlorhydria ; in fact, the HCl content appeared to be higher in the asthmatics tested, nor did intensive hydrochloric acid therapy appear to be of value. The number of cases tested was 138.

A case of very severe and persistent asthma was treated by Giles et al.[32] with a solution of hydrochloric acid intravenously. On December 7th, 10 c.c. of a 1–1500 solution of HCl was injected and repeated on the two following days. The attacks were greatly modified. Another injection was given on December 29th, as the asthma showed signs of returning. This was an aspirin-sensitive case. Two others with severe sinusitis were similarly treated, with marked improvement.

ASTHMA CHARTS

Each chart has sufficient space to record every attack of asthma that occurs during a month, the time at which it occurs, the violence of the attack, and its relationship to the therapeutic means in use, the details of which are recorded at the side.

Charts are lined horizontally with thirty-one days and subdivided vertically into eight three-hourly intervals. A single line is marked from the time at which the attack starts, across the chart as far as the hour at which it ceases. If the severity of the attack is sufficient to necessitate the taking of ephedrine or an injection of adrenaline, a double line is scored. If the attack is of exceptional violence it can be denoted by three lines. In this way a complete record can be kept of all

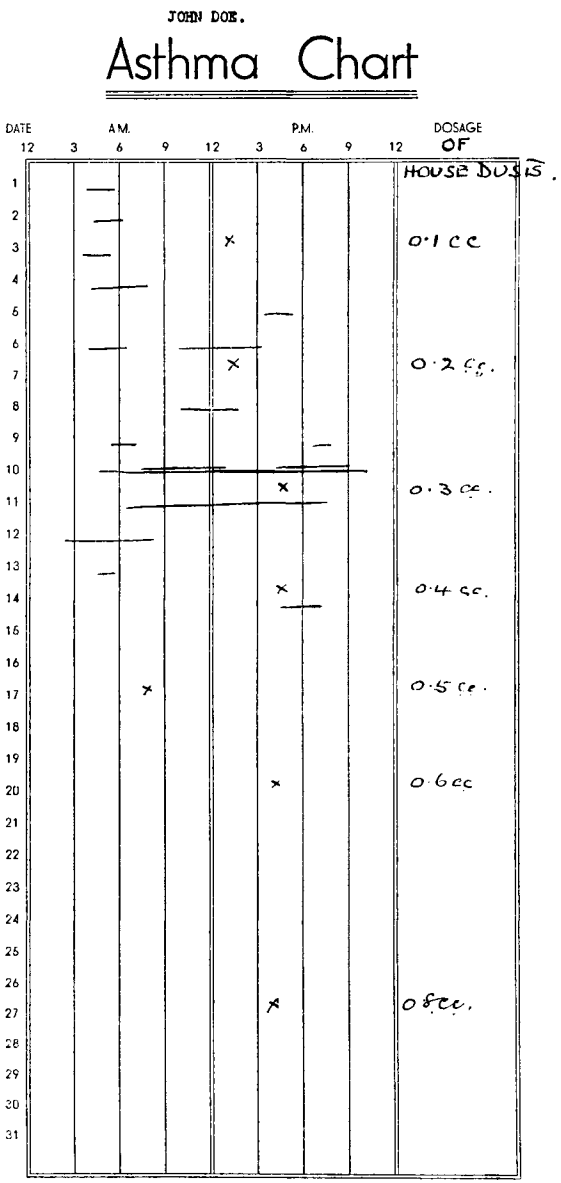

Fig. 19.—Specimen asthma chart.

attacks of asthma, to which reference can be made in order to see at what hour of the day or night attacks are most prevalent. A small cross can be used to note the time of the giving of each injection. Nothing else should be marked on the chart, and a sample chart should be shown to the patient to describe exactly what is required. Charts are returned at the end of a month, when advice as to the future conduct of the case can be given. They are of great value, and save an immense amount of time and correspondence. A specimen chart with typical record filled in is shown in *Fig.* 19.

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CHAPTER XVII

TREATMENT OF THE INFECTIVE TYPE (TYPE II)

THE methods and technique employed in carrying out the bacteriological investigation of a case of asthma are fully described in Chapter XI.

In this chapter will be set out specific measures, such as the use of vaccines, that are applicable to those asthmatic conditions associated with bacterial micro-organisms, acting either directly as a cause of the paroxysms or indirectly by the physiological results they produce.

With bacterial complications, the treatment of the acute paroxysm and the general measures to be adopted are in no way different from those already described.

Primary infective types of asthma often produce such a long-continued and severe state of bronchial spasm as to call for a trial of the whole armamentarium of antispasmodics and the full therapeutic ingenuity of whoever is in charge of the case.

In the general measures advised elsewhere in the present book, aimed at getting the patient into hard training, there must be some moderation in the procedure with these infective types, and some greater care in avoiding sudden changes of temperature and the rigours of the English climate. The degree and extent of the bacterial infection will have been ascertained on the lines laid down in Chapter XI. Treatment of infective asthma consists of (1) general treatment as by vaccines, and (2) measures applicable to the focus of infection.

1. THE USE OF VACCINES

We consider that for the use of vaccines in the treatment of asthma to be effective, it must be carried out on a definite plan and with strict regulations as to dosage, whether by autogenous or stock vaccines.

It has been our fortunate experience to determine that where an infective element plays a significant part in a case of asthma,

then treatment by vaccines is the most satisfactory and effective method available, and one which in our opinion not only supersedes all other methods of treatment by a wide margin, but in certain particular cases—in pure Type II (the infective group) and in the aspirin-sensitive cases of Type III—gives results which have proved so satisfactory as to demand this method of treatment from physicians in the future.

The successful use of vaccines depends upon certain important considerations.

In the first place the vaccine, whether stock or autogenous, must be of a comprehensive nature and made of potent material. Secondly, whatever may be the method of action of large doses of vaccines and of those given to produce protein shock, we have found that with specific autogenous vaccines a rigid adherence to the small-dose subreactional technique is imperative to ultimate success. This may require some experience, and perhaps courage to revolt against the academical background of vaccine therapy as taught to one, but will amply repay any additional burden imposed in carrying out to the letter the basic laws to be enumerated.

Specific Autogenous Vaccine Therapy

Certain general questions crop up so frequently in correspondence that they must be answered in some detail before proceeding.

Site and Method of Administration.—Vaccines should be injected subcutaneously, and at a site remote from any injection likely to cause local tissue reaction. Convenient places are the forearm, the upper arm on the outer side near the insertion of the deltoid, the chest (especially in women) just below the middle third of the clavicle, or the outer aspect of the thigh. Care should be taken to wash the syringe through with sterile saline to avoid pain and inflammation either from minute traces of spirit, or from the hypotonicity of distilled water. The bottle or ampoule containing the vaccine should be very thoroughly shaken and the rubber cap wiped with spirit which is allowed to evaporate. If many doses have already been removed, it will be necessary to inject into the bottle some air to level the pressure and facilitate further withdrawals.

The Dilution of Vaccines.—If small quantities of vaccine have to be measured, either a narrow-bored tuberculin syringe can be used, or a dilution made in the ordinary 1-c.c. syringe

with sterile carbol saline. For instance if a dose of 0·05 c.c. of the vaccine is required, 0·3 c.c. of sterile carbol saline is drawn up into the syringe and 0·1 c.c. of vaccine added to it. The syringe will now contain 0·4 c.c. As there is only 0·1 c.c. of vaccine in this, it is simple to give a dose of 0·05 of the vaccine by giving half of the fluid now in the syringe, that is, 0·2 c.c.

A far simpler method is to have bottles containing 9 c.c. of sterile normal carbol saline to hand (diluting fluid).

By taking 'John Brown's vaccine', which contains 1·0 million organisms per c.c., and removing 1·0 c.c. in a syringe and injecting it into a bottle of 9·0 c.c. of diluting fluid, a one-tenth reduction or dilution is effected. One c.c. of this will contain 0·1 million organisms, and 0·5 c.c. will contain 0·05 million. This strength may be labelled 'John Brown/10'. Of this dilution 1·0 c.c. may then be added to a further 9·0 c.c. of diluting fluid, making John Brown/100, and a dose of 0·5 c.c. will contain 0·005 million organisms. Dilutions down to John Brown/10,000 may have to be prepared before a sub-reactional dose is determined, never forgetting to shake the bottles well before making each fresh dilution.

The Interval between the Doses.—As a general rule the vaccine should be given once a week. In the initial stages, and provided there are no reactions (*see* p. 225), doses may be given once every five days. This is, however, usually unnecessary. In the later stages of treatment the intervals may be lengthened out, so that perhaps a dose may be given only once every six weeks.

Simultaneous Allergic Treatment.—One of the most difficult problems comes forward in discussion as to which of other specific treatments should or may be given at the same time as a course of vaccine therapy. Special local treatments have been discussed above, but as so often occurs in the common mixed or Type III case, the infective element necessitates the use of vaccines, whereas the allergic element requires specific desensitization.

As will be seen immediately, the success of vaccine treatment depends on the assessment of that dose which brings forth a particular quantitative degree of response on the part of the patient. Since the assessment of this depends essentially on the condition of the patient for the three or four days following the administration of the vaccine dose, it becomes essential

that nothing else should be injected or other special treatment performed during that time which might change the conditions primarily causative of a paroxysm. If this response is modified in a non-specific way by protein injections, the adjudication of the correct dose of vaccine becomes exceedingly difficult. Three recent cases demonstrate this point. All three had previously been desensitized by peptone and proteose injections, and it was patently obvious that they were totally unresponsive to vaccine in any form, or in any particular dose from 100 organisms to 1000 million. We have on the other hand in these cases of mixed type the fact that the asthmatic paroxysm will persist as a result of protein hypersensitivity alone, the physiological consequence of which exacerbates the infective element.

Where therefore there is a pure microbic type with no patent foreign protein hypersensitivity, vaccine treatment alone is sufficient and effective. This type includes the aspirin-sensitive group and a number of urticarias. However, where there is additional protein hypersensitivity, two courses of treatment are necessary. If the offending protein antigen is a 'rare' one, and can be eliminated even temporarily, the vaccine should be given for at least six or eight doses, and when the dosage has been assessed and the infective element is well in hand, a further course of specific protein desensitization given correctly will complete the treatment.

Finally, where causes of the hypersensitivity are ever present in the air, as dust or pollen, then an attempt to run the work of desensitization together with the vaccine should be made. This involves considerable experience in interpretation of the immediate results due to either, and some unavoidable complications, but has given some very satisfactory results. The only course that seems, on theoretical grounds at least, to be barred, is to give a long and complete course of protein desensitization and then to follow with the vaccine, because the non-specific element of this desensitization militates against the necessary response to small doses of vaccine being obtained from the patient.

Dosage.—The general basis of the dosage of these bacterial suspensions for use in asthma is a modification of the sub-reactional dose therapy as given to patients with rheumatic conditions (Crowe,[1] Warner,[2] Nutter and Watson,[3] Voss,[4] etc.). The main principles or laws of this procedure are as follows :—

1. A realization that each patient responds to a given dose of vaccine and to various types of organisms to an entirely different degree. Each case must therefore be considered individually and the correct dosage assessed anew for each patient. No dogmatic regulations of actual quantities can be given as general rules, but rather the rules should refer to the indications for altering the dose.

2. The main fact is to determine the optimum dose for each individual patient, and then to continue to give that amount until indications arise for altering it.

3. The optimum dose is that dose which gives the longest period of improvement before relapse, and without initial, general, or focal reactions.

4. A *general reaction* is evidenced by varying degrees of headache, tiredness or lassitude, nausea—a general feeling of depression and being ' off colour '. It may be evident sometimes in a slight rise of temperature. It occurs most frequently on the first to the fourth day immediately following an injection. At times it may be delayed one or two days. The worst type of general reaction follows a feeling of great improvement in the first twenty-four hours, followed immediately by severe symptoms of the nature just described above.

5. A *focal reaction* is of great importance in cases of asthma or allied conditions. This is essentially an exacerbation of the symptoms during the first two, three, or four days following a dose of vaccine : increased asthma and bronchitis, rhinitis, eczema or urticaria ; increased production of sputum or other pathological secretion ; an increase in the severity of the spasms or their number ; or more simply it may be noted as a general but slight increase in the wheezing or difficulty in breathing.

6. The *response* or *optimum effect* is an improvement in signs and symptoms commencing immediately or on the day following an injection of vaccine, and lasting for a period of days which may vary from one day to several weeks, which interval tends to increase as treatment progresses.

7. A *relapse* is the recurrence of signs and symptoms of the condition, following a response or a period of improvement.

8. A *local reaction* as an inflammation, irritation, or induration at the site of injection should never occur, being caused by spirit or water in the syringe, or the injection being intradermal or too deep in a fibrous area. Occasionally a small bruise may

occur by the inadvertent puncture of a small vein. Extremely rarely patients are found who are either sensitive to the preservative phenol (1 in 10,000 or more) or to other special constituents of oil-emulsion vaccines (olive proteins, gum arabic, or gum acacia). In carbolic-sensitive persons the vaccine is made throughout with 1–10,000 merthiolate.

9. When a *general reaction* occurs the next dose *must* be reduced to one-tenth.

When a *focal reaction* occurs the next dose *must* be reduced to one-fifth.

When a *response* or an improvement in symptoms occurs, the dose *must* be kept at the same amount and not increased.

When a *relapse* occurs the next dose *must* be increased slightly, by one-tenth or one-fifth.

10. The initial dose should be 100,000 organisms (0·1 million), except in severe cases, where 0·01 million should be the starting-point.

These ten considerations constitute the main principles on which to proceed, the course being best understood by reference to the three cases outlined at the end of this section.

Commencing with a dose of 0·1 million there is nearly always a reaction, and the following week a dose of 0·01 million is given. There may be no reaction and the dose is repeated, this time with a definite reaction, demonstrating the increasing sensitivity of the patient. It is far more satisfactory to show one or two definite reactions in the initial stages of the course. The dose is then lowered *pari passu* with the increasing sensitivity until it becomes small enough to be subreactional, at which time definite improvement occurs. It is therefore as well to warn the patient beforehand of the probable occurrence of degrees of reaction in the earlier stages of the vaccine therapy. Counterbalancing this there is a better prognostic outlook if reactions occur. Unless the warning is given it may be that after two doses giving even mild reactions the patients or their relatives become persuaded that the treatment is going to make them much worse, with the result that these highly favourable cases decide to discontinue treatment, to their great disadvantage.

When there is a favourable response, followed for instance in three days by a relapse, a slight increase of dose may give a response for five days before relapse, and with a slightly larger dose still, a response is obtained which lasts

seven days, and another injection is then given before relapse occurs.

When the condition is well in hand and improvement progressing satisfactorily, the time interval between the doses may be lengthened out, so that another dose is given only when evidence of relapse occurs, until finally only a very occasional dose is required.

It is useless on such a scheme to attempt to ' push the dose up ' by gradual weekly increments. There is a range of dose above that of 1·0 million organisms in which no reactions occur until bigger doses—5, 10, or even 20 millions—are reached. Experience of both methods makes it evident, however, that in asthma the small subreactional dose is much the better of the two methods.

The correct interpretation of the effect of any given dose of vaccine comes with experience, but with a rigid adherence to the principles laid down, the treatment should progress satisfactorily and with ease. But there are several minor complications that may occur, and to which short reference may be made with advantage.

The Subsensitive Patient.—Increasing sensitivity in the early stages is the usual course : but, in the more insensitive cases that occasionally occur, before it is decided to increase the dose following a negative or indefinite effect it is always best to repeat the previous dose. There is a danger of getting it too low. As occasionally occurs, one may ' lose oneself ' ; and whenever the position of the optimum point in the dosage scale becomes indefinite, doses should be given of widely varying strength, multiplying or dividing the previous dose by five or ten until a definite reaction or response puts the patient again within the limits of the regulating principles. A coincident attack of an acute infective condition may temporarily improve the condition, only to make it worse later. No vaccine should be given while such an acute condition as influenza or coryza is in being.

The Supersensitive Patient.—The only other difficulty likely to be met with in practice is the supersensitive person. The vaccine may be diluted many times until the equivalent of a dose of 0·00001 million or 10 micro-organisms is given. If a patient still shows reactions to these amounts he may be said to be supersensitive. Various measures may then be taken. In the first place it frequently occurs that the patient is only

sensitive to one type of organism which is causing the reactions. Most frequently this is a pneumococcus, a staphylococcus, or the *Micrococcus catarrhalis*. These various portions may be tested separately on the patient, thus reassessing the optimum effect to each group, and finally reconstituting the vaccine on the results obtained.

This, however, is not a common occurrence. It is therefore not necessary as a routine to introduce such a procedure, but rather to reserve it as a possible line of action in those supersensitive cases with which satisfactory progress cannot be attained.

Measures may be adopted in the preparation of the vaccine to reduce the reactive effect of a dose. These are mainly two. The dose of vaccine may be mixed in the syringe with an equal quantity of 4 per cent eucaine (benzamine lactate), which has the effect of enabling a dose of approximately five times the amount to be given without reaction. Secondly, the vaccine may be made up in an isotonic olive-oil emulsion, the theory being that the bacterial material becomes adsorbed to the colloidal oil particles, and thus is taken up into the tissues at a very much slower rate than an ordinary saline solution of bacterial materials. Ten times the strength of an oil-emulsion vaccine is equivalent in effect to a saline one, i.e., where a dose of 10,000 organisms in saline is just subreactional and 20,000 gives a reaction, a dose of 100,000 in oil emulsion will still be sub-reactional.

Examples.—Consideration of the three following cases illustrates all the essential points outlined in regard to the administration of specific autogenous vaccines :—

Case 40.—Male, aged 62. Asthma started at the age of 50, following two severe colds. No previous history of allergic complaints. Now wakes each night with attack. Much worse after colds. Short of breath and wheezing with exercise. Old sinus trouble and occasional polypi removed from nose. Not aspirin-sensitive. Dermal tests entirely negative to a large number of substances.

Bacteriological: Strongly positive pathogen-selective blood-culture to a fæcal streptococcus and *B. asiaticus* in the fæces, and to two varieties of *Str. viridans* in the sputum. Post-nasal swab negative. Differential sedimentation test indicated pure Type II or microbic case ; i.e., there was no evidence of protein-hypersensitiveness, but the typical picture of a patient ' responding to an infective condition '. Treated by vaccines only.

1*st Dose*—0·01 million aa. streptococci and *B. asiaticus* with stock vaccine.

Same day—Headache. No asthma or tightness.

Next day—Increased phlegm, more so in evening. Headache afternoon.

2*nd day*—Woke with headache, asthma and wheezing all day.

3*rd day*—Felt somewhat better.

4*th day*—Felt very fit. Roast pork for lunch, asthma that evening.

5*th day*—Slight asthma, more phlegm.

6*th day*—Better.

Remarks: Definite general reaction and focal effect as well. To reduce the dose to one-tenth. Dietetic indiscretion caused asthma, but this had no connexion with the vaccine dose.

2*nd Dose*—0·001 million aa. vaccine mixture as above.

Same day—Felt slack, increased wheezing, headache in morning.

Next day—More tightness in chest, headache, "feel something has taken effect".

2*nd day*—Woke early with asthma attack. Felt poorly. Some asthma all day.

3*rd day*—No asthma; feeling better.

Remarks: A further general and focal reaction. Reduce again to one-tenth.

3*rd Dose*—0·0001 million aa. of vaccine mixture as above.

Same day—As usual.

Next day—Felt very well.

2*nd day*—A little below par and slight headache.

3*rd day*—Very fit and had 'lovely day'.

Etc.

Remarks: Probably a slight reaction, but now feeling very well. Repeat to make sure.

4*th Dose*—0·0001 million aa. as above.

Very good week with absolutely no asthma at all. Very slight tightness on third and fourth days.

Remarks: Apparently correct dose, though possibly one slightly smaller would have been better.

5*th*, 6*th*, 7*th*, 8*th*, 9*th*, 10*th*, *etc. Doses*—0·0001 million aa. as above.

After the 7th dose there was no further asthma and the asthma chart kept by the patient was completely clear. On one occasion after the 9th injection there was slight tightness during a November fog. Dose interval was lengthened out, and despite catarrhal colds in December there was no asthma.

Case 41.—Lady, aged 32. Bronchitis as a girl while living near factory with noxious fumes. Series of coughs and colds gradually led to severe asthma. Now always wheezing during the day and bad attacks every night. Overweight at 14 st. 8 lb. Dermal tests all negative.

Bacteriological: The pathogen-selective blood culture was positive

to a catarrhal *Str. viridans* in the posterior nares and throat, and also a *Staph. albus* in the posterior nares. The fæces were negative. Had wide-field radiation therapy, and became very much worse; could hardly move about. Vaccine treatment instituted.

Reaction given by 0·1 million, which made asthma worse, with similar results but less in severity during the consecutive weekly doses—0·01, 0·001, 0·0001, and then 0·00001 million. Apparently supersensitive and no improvement at all.

Commenced oil-emulsion vaccine, anti-retentional diet of Földes, and ephedrine hydrochloride gr. ¼ nocte. Diet reduced weight from 14 st. 8 lb. to 12 st. 13 lb. in the first month and to 11 st. 13 lb. in the third month.

1st Week—0·00002 oil vaccine; wheezing in the morning. No asthma. Took tablets.

2nd Week—No vaccine; 4 attacks every 24 hrs. Tablet every night. Weight down.

3rd Week—No vaccine; 3 attacks every 24 hrs., milder. Only 1 on 3rd day.

4th Week—0·00005 oil vaccine; very tired. Asthma same.

5th Week—0·00003 oil vaccine; lost 4½ lb. in one week. No asthma.

6th Week—0·00003 oil vaccine; no asthma. Some slight bronchitis.

7th and 8th Weeks—0·00003 oil vaccine; no asthma. No tablets taken at all.

9th Week onwards—0·00004 oil vaccine; no asthma. No tablets. Slight wheeziness on exercise.

Case 42.—Lady, aged 32. Severe aspirin-sensitive asthmatic, having had two previous and severe attacks after aspirin. Continuous asthma for last two years with rhinorrhœa and polypi. Attacks of spasm stimulated by coughing. Dermal tests completely negative, except for slight reaction to aspirin in guinea-pig serum against controls.

Bacteriological: Strong pathogen-selective blood culture to *Staph. citreus E* in posterior nares and fæces. Ordinary culture of the post-nasal swab showed the staphylococcus together with three varieties of *Str. viridans*, *Str. mucosus*, and a few Pfeiffer's bacilli. Vaccine given.

1st Dose—0·2 million *Staph.* + 0·2 million stock asthma vaccine.
Much better, but a feeling all week of an imminent cold in the head which never matured.

2nd Dose—0·02 million. *Staph. E* only.
Much more wheezing for few days after the dose.

3rd Dose—0·02 million. *Staph.* only.
Worse all week. (Note patient's increasing sensitiveness.)

4th Dose—0·002 million *Staph.* + 0·002 million stock asthma vaccine. No evidence of reaction, better week.

5th Dose—0·002 million aa. repeated.
Better until sudden attack of bronchitis developed with much phlegm. Vaccine stopped for six weeks.

6*th Dose*—0·002 million aa.

Much better next day and maintained for a week.

7*th Dose*—0·003 million aa.

Chest practically clear of all rhonchi now.

Later the dose was raised to 0·004 million aa. and then to 0·005 million aa. until the patient became very fit indeed and without any sign of this severe and relentless form of asthma. Twelve months later a sharp attack of bronchitis was followed by some asthma. One dose of 0·005 million aa. cleared the whole condition up, and a few further doses were given to substantiate the position.

Three years later: An occasional dose is given once in six weeks or two months, which would seem to keep her quite fit. This interval is reduced to ten days should there be any tendency to bronchitis. Later doses have been incorporated as follows: 0·003 million *Staph.*, 0·003 million stock vaccine, 0·015 mg. histamine, and 0·008 mg. adrenaline.

Stock Vaccines

Particularly in asthma are autogenous vaccines indicated, or at least bacteriological investigations in order to determine the type of micro-organism that is of importance. Stock vaccine may however be applied in many cases on the lines indicated and with considerable success. The range of its effectiveness depends largely upon a very comprehensive constitution. The actual stock vaccine we have used contains a large number of different types of organisms as well as several strains of the one type—streptococci of the hæmolytic and *viridans* groups in a large number of different types; five varieties of staphylococci, various types; and strains of *M. catarrhalis*, pneumococci, *Anaeromyces bronchitica* (Thompson), *B. Friedländer*, *M. flavus*, and Pfeiffer's bacillus.

From such a heterogeneous mixture one may well wonder whether the action is not entirely of a non-specific character. Experience of bacteriology in asthma, however, necessitates the construction of a comprehensive stock vaccine if it is to meet and counteract the multiplicity of organisms which have been found during the preparation of autogenous vaccines for a series of this group of bacterial asthmas.

2. LOCAL SPECIFIC MEASURES

Where bacterial infections play a part in a case of asthma there are local measures that may be applied with advantage in addition to the general vaccine therapy. These resolve themselves into treatment of the 'focus', and are therefore

best discussed under their anatomical situations. In general, little is to be gained, and in many cases much harm may accrue, from a premature interference with an active infective focus—excepting the one particular case of a closed focus; in this case surgical attention is called for forthwith. Infective foci in the posterior nares and adjacent regions, if receiving surgical interference, frequently cause an acute exacerbation of the asthmatic condition. One can well understand that in the first place surgery will cause an activation and increased absorption of toxins of the toxin-histamine type; and in the second place in such a region surgery will leave a still more favourable pabulum for reinfection, either from the air or from the bacteria already present, since a surgical knife cannot by itself be expected to eradicate every bacterial micro-organism present. In the later stages, when the asthmatic paroxysms are under control and the resistance of the patient to the infection is raised by a course of vaccine therapy, much benefit from surgical corrections of deformities, removal of foci, and other abnormalities may be obtained. Polypi and the maintenance of an adequate airway are dealt with later, but it must be remarked here in connexion with microbic factors that after an initial number of doses of vaccine, then surgical assistance will aid in some cases by correcting deformities or abnormalities which would otherwise lead to the continued presence of a suitable pabulum for bacterial growth. Surgery cannot remove the infection, but it will assist the patient, stimulated by the vaccine therapy, to eradicate the focus.

Urinary Infections.—Coli cystitis and even pyelonephritis have from time to time been determined as the cause of a case of asthma. Chemiotherapeutic measures such as mandelic acid, ketogenic diets, and the sulphonamide group of drugs have all been used, and have no contra-indication in asthma or urticaria. Vaccine injections play relatively little part in treating coli infections of the urinary tract. One case may be mentioned, however, of a man who has a number of a particular type of fæcal streptococci in the urine (confirmed on separate occasions), who responded actively to vaccine injections, showing typical asthma attacks as focal reactions.

Pelvic Infections.—Pelvic infections as a cause of asthma in women occasionally occur. Treatment on standard lines

with vaccine is indicated, together with the usual surgical or physiotherapeutic measures.

Abdominal Infections.—Appendicitis of a subacute or chronic nature, if the primary cause of the asthma, requires surgical removal of the appendix, which may be followed by a remarkable alleviation of the symptoms. The same remarks apply to cholecystitis. In the intestine and the colon lies a very common and potent source of bacterial toxæmia in the asthma patient, and more particularly so when there is an associated achlorhydria. Adequate regulation of the bowel, lavage, and acid medication are discussed elsewhere, but local specific measures aimed against bacterial growth are often of much use. Reduction of the carbohydrate intake reduces fermentation by coliform organisms, and lessens the production of gas and toxins and eventually the whole degree of bacterial multiplication. This may be further controlled by giving such emulsions as the *B. acidophilus* emulsion and Yoghourt milk containing *B. bulgaricus* and similar harmless non-pathogenic organisms, which produce on their own account an acidity of such a degree as to restrain the multiplication of the toxin-producing bacteria. Various bacteriophage mixtures may be given by the mouth after testing them in the laboratory against the patient's own bacteriological flora. Allied allergic complaints such as urticaria and eczema are more frequently associated with intestinal bacterial toxæmia than any other single focus. All cases, however, should be treated generally with vaccine therapy in addition to the local measures outlined above.

Dental Infections.—In our experience dental infections, either of the chronic apical, pyorrhœic, or abscess type, are rarely determined as a primary cause of these types of asthma ; but that they do occur rarely has been evident, and they require adequate treatment without reserve. More commonly, however, chronic dental infection plays the part of adding an additional but not controlling burden on a detoxicating mechanism already overloaded from one or more other sources. Consequently its radical treatment, if necessary, should be attended to in due course, but again, on general principles, not until the paroxysmal condition is well in hand, and the immunity and resistance raised by a period of vaccine therapy.

The Tonsils.—The general tendency in recent years has been to be more conservative over tonsillectomy. As in many other pathological conditions, this knotty problem arises in asthma and follows the same lines. Grossly enlarged tonsils in younger children are undoubtedly better removed by enucleation when in a quiescent state, perhaps not so much because they are an infective focus as because of the anatomical abnormalities they may induce, together with the pathological pabulum in the adenoid tissue of the posterior pharynx. In adolescents and older patients they should not be removed while the asthmatic condition is in a severe or active state. Tonsillar abscesses or quinsies come, of course, into the sphere of surgical emergencies. As a general rule one may say that they should be left until it is apparent that as a result of local and general measures the infection is either persistently recurrent or uncontrollable. Attacks due to infected tonsils are particularly those in children, recurring at fortnightly intervals and accompanied by a temperature.

Adenoids.—The adenoid tissue is an excellent culture medium for bacterial micro-organisms, especially when inflamed or œdematous as a result of allergic response to airborne allergens. In children and the pre-asthmatic states adenoids are best removed if of pathological dimensions. When infection already exists and is causing asthma, much harm may develop as a result of immediate surgical removal. Subsequent treatment is best considered together with nose and accessory sinuses in the following subsection.

Local specific treatment by means of sprays or direct applications is, however, frequently useful in this region. Specific antitoxins or antisera are particularly valuable, especially where the patient, by being previously non-specifically desensitized, is not as responsive to vaccine therapy as the normal person. Care must be taken to determine that the patient is not sensitive to the animal whose serum is used. Antiseptic solutions such as collosol silver preparations may be employed, provided that their application causes no increased hyperæmia or irritation of the tissues.

The Nose and the Nasal Sinuses.—Of all situations in which micro-organisms responsible for asthma are to be found, the nose and nasal cavities are the most important and the cultures from the post-nasal swab the most illuminating. Where an

antrum or frontal sinus is thought to be full of pus, as evidenced by radiographs, by dullness to transillumination, or by the other symptoms of these infections, adequate drainage at the hands of a rhinologist should be undertaken, particularly if it appears that the natural orifice to the cells is obstructed, making the infected cell a closed focus of infection. Massive operations as the Caldwell-Luc are not advised until the microbic element is well under control by vaccines, in which case they will usually cease to be necessary.

Many of these infections arise during the process of an ordinary cold, and if it appears from there being pain over the antra or frontal region that the congestion of the mucous membrane is causing the orifices of the sinuses to become occluded, a spray or swabbing with cocaine and adrenaline may lessen this inflammation, and allow the contents to be discharged. 'Squeaks' heard by the patient in the nose may denote that this freedom and equalization of pressure is taking place. The pain will subside at once and the tenderness within the next four hours. Similarly 'popping' of the ears denotes that the pressure in the middle ear is being regulated.

The presence of deflected septa and other bony deformities can usually be seen on inspection. Clinically, for perfection, the air should enter freely up both nostrils and the sense of smell on both sides should be equally well observed. When there is trouble in the ethmoid cells and polypi are present, the olfactory sense is often entirely absent, returning as treatment meets with success.

Chronic Infections.—Rarely, a case may be seen with a chronic infection such as an old sinus from an osteomyelitis, in which infection is persisting. Surgical procedures, X-radiation, or physiotherapeutic measures, combined with autogenous vaccines, usually clear up the condition, with relief of the asthmatic symptoms.

Chemiotherapy and Antisera.—Where a hæmolytic streptococcus is the causative organism in a focus, or any organism known to be susceptible to the chemical action of the sulphonamide group, such drugs may be given with benefit. However, they should all be given to these hypersensitive patients with caution until it is certainly determined that no particular idiosyncrasy is evident.

Very recent research work has provided another member of an allied nature, said to be especially antagonistic to the pneumococcus. This may prove of inestimable benefit in the asthma problem, in which the organism plays so frequently a predominant part.

Antisera are not applied in asthma to any extent.

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CHAPTER XVIII

TREATMENT OF THE MIXED AND ASPIRIN-SENSITIVE TYPES (TYPE III)

ALTHOUGH the treatment of this type is essentially that of a bacterial asthma, the aspirin-sensitive cases have so many peculiarities in common with each other that they merit some special mention apart from their treatment.

By the differential sedimentation test they rank as Type III, with features of the allergic Type I and the bacterial Type II combined. Clinically some of them are frankly allergic, but all are microbic.

Certain asthmatics, then, are unable to take acetylsalicylic acid in any form without provoking an immediate attack of asthma and one of extreme severity. Several features appear so constantly as to classify them even clinically into an easily recognizable group and one of unusual interest.

I have been unable to discover from their personal histories or from the use of skin tests to which part of this chemical, the salicylic acid or the acetic acid, they are sensitive. Some few seem to object to vinegar, others have had experiences with the salicylates; but in no case have there been any symptoms of the dramatic nature that always follow at once upon the taking of the combined acetylsalicylic acid.

I have tested these patients dermally with acetic acid, salicylic acid and the salicylates, with acetylsalicylic acid and various soluble salts of it, without obtaining any response beyond the fact that such intradermal tests are uncommonly painful.

I have used guinea-pig serum taken after the animal had had a large dose of aspirin, using normal guinea-pig serum as a control. That from the pig which has had aspirin gives a larger reaction than that from normal guinea-pig serum, but there is no enormous wheal formation as one would expect in these very sensitive people. As a scratch test I have used my own blood after I had taken ten grains of aspirin, again with a reaction but not a markedly severe one.

In spite of their complete avoidance of this drug by reason of its extremely poisonous nature to them, these patients suffer from continuous asthma in its gravest form. Unless therefore we adopt the hypothesis that some microbe or mould present in their bodies is continually forming acetylsalicylic acid, it is obvious that the gross symptoms of asthma which they have, day and night, are not contingent upon the taking of aspirin.

Statistical.—In the last 1000 cases of asthma that I have seen, there have been 23 cases of the aspirin-sensitive type; 65 per cent were women, against an equal division of the sexes in the 3000 cases of asthma reviewed in this book.

They gave a family history of allergic complaints in 35 per cent compared with the usual 52 per cent; only 1 case had a history of early eczema as against the usual history of 25 per cent.

The average age of the patients when first seen was 47 years; the age of onset was 40. This is noticeably older than the corresponding figures of 34 years and 20 years in the whole series of 1000 cases.

The aspirin-sensitive type, therefore, is more common in women, more rarely has a family history of asthma, and very rarely has a personal history of eczema. Symptoms commence on the average in the fourth and fifth decades of life.

History of the Complaint.—Some infection of the respiratory tract usually antedates the commencement of the complaint. The attacks, always extremely severe, are at first of short duration—an hour or so. They may increase to six or more attacks in twenty-four hours and become practically continuous, with no respite whatever over a period of several years, except when the patient is under control with adrenaline. Work and play are alike entirely out of the question. The patient is a confirmed invalid. The worst attacks are always at night, and in no case does the state of the weather, the changing season, or the locality in which the patient lives or visits, make the slightest difference to the course of the disease. Practically all are adrenaline addicts, taking 10 minims or more for each attack. Sooner or later the complaint proves fatal.

Physical Signs and Symptoms.—In no other form of asthma do we see such a pure spasm of the bronchial muscle. During the day when free from attacks the chest may be entirely clear of all adventitious sounds. A very important feature is the

cough which initiates each fresh attack. A sudden cough or hearty laugh will be followed at once by an uncontrollable paroxysm of coughing, and a bronchial spasm that develops directly into an attack of asthma. A chest which a moment before was clear becomes at once full of rhonchi. With these incessant attacks the patient rapidly loses weight and after a year or two becomes extremely thin, and habitually tired from want of sleep.

Polypi.—Nasal polypi were present in 13 of the 23 cases. They produce the symptoms common to all nasal polypi. The sense of smell is often entirely lost. Removal of the polypi should be undertaken as often as is necessary to clear the airway, but I have never seen the slightest benefit to the asthma from extensive major removals of the polypi and the area from which they grow.

Treatment.—Until two years ago I had tried every known method of treating asthma upon these patients, without benefiting them in any way. Besides this the majority had had special treatments under many other medical men, at home and abroad, before seeing me. Attempts at desensitization by the injection of minute doses of aspirin have always broken down sooner or later, sometimes at absurdly small doses.

Effective treatment, however, is now available. The patient must be tested against the bacteria found in the respiratory tract, the vagina, the urine, and the fæces by means of a pathogen-selective blood-culture.

A vaccine made as a result of these findings is given by subreactional doses. This method is fully described in the last chapter. Of the cases there given, *Case* 42 was an aspirin-sensitive patient, and another is given here.

Case 43.—A thin, spare lady of 65. Severe asthma continuously for four years. Wintered abroad two years with no benefit. Could take aspirin at one time. Four months previously polypi were removed and an aspirin given afterwards by mistake. The consequent asthma was so severe that oxygen was given for 12 hours, and her life was despaired of. She used to take 4 or 5 injections of adrenaline, ℥ vij each night. Very thin indeed. Chest practically clear during daytime. Had no sense of smell, nose full of polypi. Pathogen-selective blood-culture strongly positive to *Str. viridans* in sputum and post-nasal swab. With the differential sedimentation test the serum showed her to be a Type III asthmatic. Treatment commenced November 12, 1935, with an autogenous vaccine. Dosage varied from 500,000 to 10,000 organisms. Asthma disappeared in two months, adrenaline given up, and sense of smell came back. Asthma returned in mild form, but on a slight readjustment

of the size of the dose, the attacks again disappeared. Now (February 20, 1937) sleeps well, no adrenaline for many months; recently the polypi were removed with no ill-effects, and she is about a stone heavier in spite of her age.

These chapters may be brought to a close conveniently by a few cases which demonstrate various types of asthma affected by microbic causes.

1. *Allergic Case Secondarily Infected.*—

Case 44.—Lady aged 47. Influenza twelve years ago left her with "catarrh". The nose becomes occluded at times: much sneezing and running at the nose. Shortly after commenced to have asthma. Has never been able to take fish. Found to be extremely sensitive to fish, horsehair, dust, and cat hair. Some hay fever in the summer. Controlled with mixed coliform vaccine and later with specific dust and hair proteins, though the dust could only be taken in a dilution of 1–10. As the asthma continued in spite of having had sufficient desensitization to control it, a full pathogen-selective bacterial examination was made. The pathogen-selective culture-test from the sputum was strongly positive in that one type of streptococcus grew out in all three dilutions. The asthma has now disappeared entirely for many months after doses of the vaccine, of 0·00005 million organisms.

2. *Primary Infection of the Respiratory Tract.*—

Case 45.—Male, aged 59. Influenza 1918. Much mucus and sputum each morning and nasal catarrh. For the past ten years has had asthma. Many fine sounds to be heard at the left base. A vaccine was made from the sputum, containing several varieties of *Str. viridans*, pneumococci, and *M. catarrhalis*. With a long course of vaccine the fine sounds at the bases and the sputum disappeared, and he gradually became entirely free from asthma.

Case 46.—Male, aged 55. Asthma for the last three months following upon "a cold on the chest". There is much sputum every morning and fine sounds can be heard at both bases. With a stock vaccine these symptoms soon disappeared, and he became entirely free from asthma.

3. *Infections from the Nose.*—

Case 47.—Male, aged 60. Asthma commenced ten years ago, following a cold and bronchitis. Indifferent to climate or any outside influence. Catarrhal mucus to be seen at the back of the pharynx, feels something dropping down the back of the throat. Strongly positive reaction to one variety of *Str. viridans* by the pathogen-selective blood-culture. A vaccine from this proved effective in freeing him from his asthma and 'drying up' his sputum.

4. *Infection from Outside the Respiratory Tract.*—

Two cases of very severe asthma which defied all forms of treatment became entirely cured after the removal in each case of a septic gall-bladder.

CHAPTER XIX

OTHER COMPLAINTS ALLIED TO ASTHMA

THERE are many other conditions which are closely allied to asthma, having a common aetiology of anaphylactic, allergic, metabolic, and microbic nature, recurring in paroxysms, and relieved by the same methods of specific and non-specific treatment as are applicable to the various types of asthma.

Asthma is certainly the master complaint of the series. It is commoner and more persistent, while it affects an individual's life and social commitments more than does nettle-rash or paroxysmal rhinitis. Secondary infections in the lungs pave the way for subsequent grave ill-health.

In asthma the dermal reactions play a very important part in enabling the cause of the asthma to be discovered with a certainty and reliability that is not found in these other complaints, with the exception of seasonal hay fever.

Colmes[1] records the results of dermal reactions in 250 patients with asthma, 93 with urticaria, 222 with perennial vasomotor rhinitis, and 314 cases of hay fever. A large total number of reactions were obtained, but he places the value of the reactions in each complaint as follows: hay fever, nearly 100 per cent; asthma, 40 per cent; rhinitis, 25 per cent; and urticaria, 2 per cent only. Of the proteins used he found the house-dust protein to give results which were 70 per cent reliable in asthma and paroxysmal rhinitis.

My impression is that our cases would show much the same results, though possibly higher in asthma.

A difficulty is that reactions in urticaria even when obtained are not constant. Many years ago Schloss[2] demonstrated that a child sensitive to egg and having urticaria as a result could often take egg without symptoms. Testing the child regularly over some weeks, he found that on those mornings when a skin reaction was obtained the urticaria would follow the taking of an egg, while on other mornings the child could take egg with impunity. Again, using the hæmoclasis crisis as a gauge of sensitization, a case is mentioned in the French literature in which only on those mornings when a hæmoclasic crisis

developed after taking chocolate did the patient suffer with a subsequent attack of migraine.

Sensitization seems to come and go in these cases, so that negative skin reactions do not guarantee that the protein tested is harmless. In asthma, possibly because the blood is more fully charged with reagins, skin reactions are very constant and reliable. Their failure in these allied complaints makes it even more important to use the grcatest care in eliciting the history of each case. Use may be made of eliminating diets.

Régime I.—If the attacks of urticaria or migraine occur rarely, a complete list of all foods taken and all other circumstances that take place, such as washing the dog, putting on different clothes, or visiting the hairdresser, must be put down on a list. After each subsequent attack this list can be called over and such happenings as did not recur in the twenty-four hours before the second attack can be scored out, until it is possible that a cause may be discovered that is common to all attacks as an immediate precedent, quite apart from the fact that the patient can at other times take the same food with impunity.

Régime II.—When the attacks are of such constant occurrence as to make this method impossible, the following régime can be adopted. A diet consisting of four single proteins, such as wheat, beef, oranges, and tea, can be tried for a week. This allows a very wide variety of dishes, and one of which no one need complain. Dripping can take the place of butter.

If successful in that the symptoms disappear, other articles of diet can be added one by one and their effect noted. If not successful a diet of four other proteins can be tried, as mutton, potatoes, apples, with milk ; or pork, rice, a fruit in season, and beer.

When on trial all other proteins must be avoided, and if taken duly recorded as possible causes of the complaint.

At the earliest opportunity the patient's blood should be examined by the differential sedimentation test, as the information gained may be sufficient to classify the patient primarily into either the allergic or the microbic type.

For some reason there is a difference in the way in which the same protein will affect two different people ; one will have urticaria and another a sick headache from the same protein. Hence there is talk of ' shock organs '. No better example is to be found of the varied sites at which the storm breaks than

the response of different patients to aspirin, already considered in Chapter XVIII. One patient cannot take aspirin without being sick; in another the sequel is urticaria; in another palpitations, or a vast asthmatic seizure; or again, the patient may pass temporarily into a comatose condition.

The peculiarity of each patient is constant to that patient. Possibly something occurs to make the cells of one part of the body more sensitive than those of another area from a local microbic cause, from injury, or other reason. With these few remarks the various allied complaints will be considered in brief, and cases given illustrating successful methods of cure.

PAROXYSMAL RHINITIS

The scheme for examining the patient is exactly the same as that advised for a case of asthma. The history may tell that the attacks are limited entirely to the hay-fever season, when a dermal test with grass pollen will at once clinch the diagnosis of hay fever. All patients must be thoroughly tested with each of the air-borne proteins, house dust, the animal hairs, feathers, and orris-root. A large proportion of all cases of paroxysmal sneezing is due to house dust, desensitization to which is a most satisfactory treatment.

But any protein, even those taken by the mouth, may cause the patient to sneeze immoderately, notably egg. Wines, which seem to play an unimportant part in asthma, are frequently the cause of sneezing. One well-known rhinologist cannot take Chablis without sneezing, though he may be considered an authority on port! Other people sensitive to egg cannot take port, because eggs are used to clear that wine. The time of election for all forms of paroxysmal sneezing is the early morning on waking.

In spite of much close cross-questioning it is difficult to identify any conscious action that precipitates these attacks. The nasal secretion seems to be in abeyance during the night. If one has a cold, one's pillow does not become saturated with moisture as does a handkerchief during the day, and it may be that the early morning sneezing is merely the return of the nose to its waking condition.

More theoretically, one may suppose that movement, especially stretching, would cause a flood of material accumulated during sleep to be expressed from the lymphatics into the

blood-stream through the thoracic duct, and thus cause sneezing, secondarily to changes in the blood-stream.

The patient may sneeze ten or twenty times and then be clear for the day. Turgescence of the mucous membrane may lead to the closing of the nasal airways, sometimes on one side, sometimes on both. If of any considerable duration and the orifices of the accessory sinuses become closed, uncomfortable headaches result.

The symptom of rhinorrhœa may accompany the attack, the nose literally pouring like a tap. The mucous membrane is often extremely sensitive, and when swollen sufficiently to just touch the septum, prolonged sneezing turns may be provoked.

Having exhausted the search for 'allergic' causes, the microbic factor must be investigated. Symptoms of a chronic catarrhal condition: something dropping down the back of the nose, the necessity for the constant use of handkerchiefs, the presence of pus to be seen inside the nose, symptoms of antral or other sinus infection, with loss of transparency on transillumination from the mouth, muco-pus to be seen on the back of the nasopharynx—all point to the probability of a microbic cause.

As in asthma, the examination of a post-nasal swab is of great importance. But in the total absence of all gross symptoms of infection the cause may yet be the presence of some organism, perhaps found to be growing in pure culture in the nose.

The treatment of these conditions, both 'allergic' and microbic, is exactly the same as that already described in detail for asthma.

A small residuum will be left over that cannot be fitted into either of the two main types and which will require non-specific treatment. Many cases can be completely relieved by ionization with zinc. Light cauterization is helpful to others. The assistance of a rhinologist may be necessary to deal with deformities, spurs, and greatly deflected septa, and by their treatment permanent benefit is often obtained. A fuller consideration of these matters by the author is to be found elsewhere[3, 4].

Case 48.—Lady, aged 23. Never sneezes, but nose becomes entirely stopped up and then pours. Pain at times over antra and frontal sinuses. Said to have sinusitis, for which a large radical

operation was recently suggested. A post-nasal swab provided a *Str. viridans*, an anhæmolytic streptococcus of Berghaug, and other streptococci. A vaccine given in doses ranging around 100,000 organisms completely cured her.

Case 49.—Lady, aged 35. Paroxysmal rhinitis. Sneezes with maddening frequency. One of those plump ladies with beautiful skins who bruise easily; used to have urticaria. Four applications of zinc ionization and the whole thing cleared up.

Case 50.—Lady, aged 20. May sneeze fifty times running, nose pours, and she may get asthma; has suffered on and off for twelve years; very sensitive to house dust and the animal hairs. Symptoms gradually disappeared with desensitization and has now been three months entirely free from any sign of sneezing or asthma.

Case 51.—Lady, aged 22. Had asthma at one time; nose has always poured, and she sneezes in the early morning ever since she can remember. No positive skin reactions obtained. All her symptoms ceased after four applications of zinc ionization.

Case 52.—Lady, aged 41. A very interesting case of paroxysmal rhinitis. Nasal catarrh for ten years; early morning sneezing and nose pours. Has found during the last three months that she cannot take aspirin—will sneeze for $1\frac{1}{2}$ hours after taking it and have an attack of asthma on these rare occasions. Has no asthma except for this. No reactions. Treated with an autogenous vaccine with no good effect. Later had polypi removed; immediately after the second operation frequent attacks of asthma came on, the symptoms being those of the aspirin-sensitive type. A second post-nasal swab then revealed a *Str. mucosa* and the *Staph. citreus*, usually found in these aspirin-sensitive people. With a vaccine of these organisms the asthma has since cleared up, as has the paroxysmal sneezing.

HAY FEVER

This was the first of the protein sensitizations to receive full attention and to have cause and effect clearly defined (Blackley[5]).

To-day the diagnosis is extremely easy and the treatment extraordinarily effective. All patients suffering from seasonal hay fever give large wheals when pollen is applied to their skin by the scratch test.

For dermal testing (scratch method) I use a series of tenfold dilutions of a solution of 6 per cent of mixed grass pollens.

The initial dose for treatment is 0·1 c.c. of the weakest solution, which gives a dermal reaction appreciably larger than the control test. Two or three minims of adrenaline is added to each injection. The secret of desensitization consists in repeating the doses as frequently as every few days, making

at each successive dose an increase of 25 per cent in the amount of pollen, so that the point may be reached when the patient is able to take a dose of 50 to 100 mgm. of pollen without subjective symptoms, before the hay fever season commences.

In America, besides the grass pollen, an enormous number of people are sensitive to ragweed pollen, so that there is an autumn season due to pollen as well as the summer hay-fever.

A third season is provided by the tree pollens, but sensitization to these is very rarely met with in England. One patient of mine is sensitive to the yew pollen, which flowers extremely early in the season, another gave reactions to the hornbeam, which pollinates very plentifully in Epping Forest.

In America large tracts of land are covered with a single species of tree, as pine or oak, thus providing enough pollen in the air at one time to cause specific sensitization and its effects.

No such specificity occurs with the various grass pollens; a patient sensitive to one is sensitive to all and can be treated by a mixture of any of them.

The hay-fever season lasts from the end of May until the middle of July. The patient may be so slightly affected as to have symptoms only at the height of the season in the middle of June. The grosser types have asthma as well. The peak of the season, when there are most pollen granules in the air, passes gradually from the south to the north, so that it is possible, other things being equal, to avoid much of the season by spending the summer holiday in Scotland during June, coming south again in July.

Many people complain that highly scented flowers will provoke attacks of hay fever, and there is no doubt that they do so. It is simply an olfactory reflex which disappears when the patient is desensitized to grass pollen.

The pollens of the sweetly scented flowers and those that are highly coloured are sticky and adhere to the bees' legs, fertilization being carried out by this means. Grasses and trees having no features to attract insects have air-borne pollens: for this purpose they are very small discrete granules, very light and easily carried miles in the air.

Once upon a time people used to go to Heligoland to escape the pollen season. A more modern escape is offered by the various sea cruises now available. The effect of merely staying

at the seaside is entirely dependent upon which way the wind is blowing. To visit Thanet is useless if it is in the south-west; such a wind will have passed across Kent and will carry the pollen into Margate and far out to sea. I usually advise Littlestone or Dungeness as being more suitable, but with modern treatment there should be no symptoms unless the patient is subjected to an abnormal glut of pollen.

One of my patients last year, a games supervisor at a large London factory, had to attend the Aldershot Tattoo; the sleeping accommodation provided was a tiny bivouac in the long grass on the Aldershot racecourse. Except for that one night she had no hay fever last season.

Many people sneeze in the bright sunlight, and for this reason dark glasses are often worn by hay-fever patients.

Mechanical assistance to prevent the pollen granules from reaching the mucous membrane of the eyes and nose consists of the use of tightly fitting goggles, and covering the nasal mucosa with vaseline, paraffin, or olive oil. The best of these is liquid paraffin. With a coarse nasal spray the whole surface of the nasal mucosa can be covered in paraffin with the minimum amount of interference or touching of the nasal mucosa. In severe cases cocaine eye-drops should be used; the guttæ cocainæ cum adrenalina of the *Extra Pharmacopœia* contain 5 per cent of cocaine hydrochloride, or 21·9 gr. per fluid ounce, in adrenaline solution 1–1000. But half this strength, or even less—5 gr. of cocaine hydrochloride with adrenaline solution one ounce—may be used successfully.

Cauterization and ionization are of great use in those cases in which the nose is abnormally sensitive, even before the hay-fever season is in progress. If the patient's history shows that the symptoms commence too early or last into August and September the cause of this must be sought:—

1. The nasal mucosa may be unduly sensitive, so that very much less pollen will affect the patient.

2. The patient may be sensitive to other proteins, notably house dust, with which every patient should be tested.

3. There may be a microbic factor at work, allowing a more ready entrance to the pollen as a result of the inflamed state of the mucous membrane.

Case 53.—Male, aged 17. Hay fever and hay asthma since 2 years of age. Very sensitive to pollen, giving a + + + + reaction to a one-tenth dilution of the 6 per cent solution. Treatment

commenced in October, was carried on for a year, and recommenced after a short interval. By June the reactions were greatly reduced in size, and he had no symptoms of hay fever last season at all.

Case 54.—Male, aged 16. First seen May 5, 1936. Had very severe hay fever for six years. Three applications of ionization and pollen injections daily. He reached a dose of 50 mg. and had no hay fever at all that year.

Case 55.—Male, aged 28. Severe hay fever for four years.
1931 : + + + + reactions to pollen ; 1–200 for treatment.
1932 : Had no colds at all last winter ; pollen 1–75, later 1–10 with adrenaline.
1933 : The same ; cauterized thoroughly.
1934 : Much better last year ; no colds last winter ; 1–100, later 1–10 with adrenaline.
1935 : 1–50, later 1–5 pollen and adrenaline.
1936 : Very good season lately.
1937 : Now gives only a + reaction to the strong pollen. Treatment 1–10 to 1–2 solutions.

The last case would now be treated with larger doses, given more frequently than when he was first seen, but the fact emerges that at the commencement of each year he has been less and less sensitive to the pollen. In fact, he gives such a small reaction now that further treatment hardly seems necessary.

URTICARIA AND ANGIONEUROTIC ŒDEMA

Urticaria may be caused by any protein to which the patient is sensitive reaching the sensitized skin. The route taken by the protein may be from within or without.

Proteins from Within.—

1. *By Injection.*—A common result of an overdose of protein, particularly grass pollen, is a generalized urticaria.

2. *When Taken as a Food.*—Fish, crab, lobsters, and mussels are notoriously poisonous to certain persons, causing sickness, diarrhœa, and nettle-rash in those sensitive to them. But any protein can cause nettle-rash. I saw a child of 16 months recently in whom egg in any form produced an attack of urticaria.

3. *From Parasites.*—The invasion may be by the foreign proteins of intestinal worms, hydatids, and other parasites. Morenas[6] noted an eosinophilia and sneezing bouts in some cases infected with thread-worms.

Proteins from Without.—

1. *Through Abrasions in the Skin*, as in the application of the dermal tests. The applied foreign protein to which the patient is sensitive meets the specific reagin circulating in the blood at the site of the scratch test; histamine or H-substance is formed at the seat of the abrasion and a wheal results. The application of histamine directly to the skin produces the same resulting wheal.

2. *Through Unbroken Skin.*—In very sensitive people, urticaria results from contact with the protein through the unbroken skin. The lips will swell on eating fish, apples, eggs, oatmeal, and other foods to which the individual patient is sensitized; also handling these foods may cause the hands to swell.

3. *Contact Dermatitis.*—A large series of plants and other articles cause dermatitis on contact; some are universally poisonous, as the stinging-nettle; others, like *Primula obconica*, only affect certain people; others again such as hyacinths, chrysanthemums, and dahlias, though almost universally harmless, may cause symptoms in a few people sensitive to them or cause other allergic symptoms.

Case 56.—Market gardener, aged 45. For the last five or six years has been troubled with a chrysanthemum rash on face and hands each autumn. Prior to the next year he had a course of desensitizing injections, with subsequent relief of his symptoms.

4. *By Sensitization to Parasites Growing on the Skin.*—Waldbott-Ascher[7] traced the cause of an urticaria to the presence of a fungus, a *Trichophyton* infection of the feet, to which the patient gave a large dermal reaction.

Physical Allergy.—Urticaria is a prominent symptom of the 'allergies' due to physical causes—heat, cold, and exercise. Special study and description of these causes has been undertaken by Duke,[8] so that now these peculiar cases are easily recognized and correctly treated.

During the course of years one sees a considerable number of cases of physical allergy. The work of Lewis shows conclusively that any injury to the skin from heat or cold will lead to the formation of the H-substance locally, causing tingling, inflammation, wheals, or worse, depending upon the degree of heat or cold applied. In these peculiar people, the physical allergics, the stimulus needed to produce symptoms is often extremely slight.

Heat.—Urticaria may result from sunlight. A very uncomfortable swelling of the face and itching follows the slightest exposure to the sun. One patient I saw had to go about London inside a closed taxi if the sun was shining. In these cases it seems to be the ultra-violet rays that are so harmful. If a piece of cardboard with a small hole or mark cut out of it is placed on the arm of the patient and exposed to the mercury-vapour lamp for a minute, at the end of another ten minutes a large wheal will have arisen where the light passed through the hole. Others have a generalized urticaria when getting overheated from any cause, either bodily exercise or lying in a hot bath.

Case 57.—Male, aged 25. The taking of acid fruits makes his face and scalp irritate with the production of an urticarial rash. Aspirin will always cause it. After a hot bath he becomes covered in a fine urticaria; after exercise, even from swimming; but also when overheated from any other cause. Alcohol will always cause it unless he is in hard sweating exercise at the time, which appears to free him from all symptoms. He is a considerable tennis player, so that he will often be in full exercise and sweating and will be free throughout a long tournament. The differential sedimentation test showed a normal blood, neither allergic nor microbic element being suggested. Treatment by histamine seemed to be without effect. His symptoms finally subsided with injections of magnesium thiosulphate and a long series of daily baths, each being one degree hotter than that of the previous day, passing from tepid through warm to hot.

Exercise.—

Case 58.—Lady, aged 23. For the past three years had become increasingly affected by urticaria upon taking any exercise, either in a warm sunlight or when dancing, or after swimming in the sun.

In this case, the affection was not due to heat, because she could sit 'boiling' in the sun without getting urticaria, and also sit in a cold bath without being affected, but the exercise of dancing in a hot ballroom or swimming in a cold pool would be followed by urticaria.

In a similar case Joltrain[9] caused a wheal on the patient's skin after injecting serum from a limb that had been exercised. Serum from the same limb when it had not been exercised provoked no reaction.

Cold.—Urticaria following upon exposure to cold is far commoner. All that is necessary to produce the urticaria is to place the arms and hands in cold water for a few minutes; the rash will appear soon afterwards. A piece of ice laid on

the skin produces an urticarial wheal at the site some ten minutes later.

The ease and regularity with which the application of cold is followed by symptoms offer us a very easy opportunity for experimental procedures.

The hæmoclasic crisis can be studied by this means. The most alarming symptoms of this cold allergy occur when the patient is totally immersed in cold water, as in sea-bathing. Syncope may occur, necessitating the patient's immediate return to land and warmer conditions.

Case 59.—A nurse, aged 32. Hay fever for ten years, giving a + + + + + reaction to pollen. Treated for seasons 1921, 1922 with the Dansyz vaccine and has had no hay fever since. Had taken cold baths for years, but bathing in the sea began to upset her, always producing a pain in the neck, not apparently from swimming. At the next bathe she became blue and unconscious, and was so ill she has not bathed in cold water since.

Paroxysmal hæmoglobinuria is of the same nature.

There seems to be some connexion between these physical allergies and sepsis. Saylor and Wright[10] instance the case of a woman who had a poisoned finger, which was incised. Two months later she noticed that the hand swelled in cold water; later this peculiarity spread to the rest of the body. The throat almost closed on eating an ice.

A patient seen by Leriche[11] suffered from rhinitis and asthma. Later she developed urticaria whenever she ate beef. Two years later she had her appendix removed, after which the urticarial tendency disappeared. The same relief happened after appendicectomy to a patient who had urticaria from cold, reported by Chevalier and Colin.[12]

It is not at all uncommon to hear, during the history of a patient suffering from asthma, that attacks are brought on by eating ices, or even by a drink of very cold water.

A full dissertation on the physical allergies is to be found in Duke's[29] book on asthma.

Chemicals.—A great many drugs are capable of causing urticaria in patients who are specifically sensitive to them. Aspirin and quinine are perhaps the best-known examples. A long list of drugs to which patients may be sensitive is to be found scattered throughout the literature.

I have had patients in whom ipecacuanha, liquorice, and even morphia caused asthma.

Case 60.—Lady, aged 22. Suffering from asthma and found to be sensitive to wheat. A sudden increase in the severity of the attacks was found to be due to the taking of a medicine which contains extractum glycyrrhizæ liquidum—explaining to the mother why she had always persisted in being sick when given liquorice powder as a child.

Case 61.—A young man, son of a manufacturing chemist, was sent round the world as a cure for asthma which had recently developed. Asthma returned within a week of his recommencing his work. His office was situated next to a room in which large quantities of morphine were handled, powdered, or cut into various shapes to suit the requirements of foreign markets. He gave a larger reaction to morphine than normal. His office was moved to another part of the works, and he had no more asthma. A clerk who suffered in the same way was moved to the office in the city.

Metabolic Causes.—The bouts of urticaria in *Case* 57 did not occur as long as the patient was in hard training with plenty of sweating exercise. In other cases the sole cause of the urticaria appears to be metabolic, and dependent upon being out of condition.

Case 62.—Male, aged 51. Urticaria for 18 months especially on the face and the tongue, usually on waking and particularly on Monday mornings. Is putting on flesh rather quickly and takes no exercise. After suitable adjustments in this direction the urticaria entirely disappeared and has not returned during ten years.

Microbic Causes.—In treating cases of urticaria the patient is best pleased with a quick diagnosis of the cause, and will judge one's skill entirely by the rapidity with which the symptoms are controlled. One case responds to one form of treatment and another to something quite different. One may make a lucky hit with, for instance, histamine, whereas this drug will not be of the least use in other cases.

A very careful history must be taken, skin tests may be applied, but the most urgent investigation is the differential sedimentation test. This should be done at once. Direct evidence may be obtained that the case is allergic or microbic, and if the latter a full pathogen-selective routine should be carried out.

Just as in asthma, the appearance of urticaria in middle age, and its persistence, little or much each day, will suggest the microbic type, the toxæmia from heavy streptococcal growth in the fæces being the commonest factor.

The following are two such cases successfully treated with an autogenous vaccine :—

Case 63.—Male, aged 32. For five years has suffered almost daily from nettle-rash ; particularly severe in the morning on every part of his body, especially the face. Has had skin tests, many vaccines which made him worse, autohæmotherapy, fractional test-meals, and many other investigations. Finds calomel and thyroid perhaps is best. D.S.T. suggested " a long-standing toxic absorption ".

The pathogen-selective test was strongly positive to a streptococcus in the post-nasal swab. He had injections of this organism, with some general reactions. The size of the doses was reduced to 10,000 organisms per dose. In six weeks' time the whole of his symptoms had disappeared.

Case 64.—Lady, aged 50. Urticaria ten years ago and again now for three months, on all parts of the body. No dermal reactions obtainable. Type III by the D.S.T. Slightly positive reactions to an enterococcus and to a *Str. viridans* in the post-nasal swab. Like the last case, having tried a great variety of other treatments, she was soon well with minute doses of an autogenous vaccine.

General Diseases.—There are, lastly, general diseases in which urticaria is a symptom, but they are rarely seen by those dealing solely with allergy.

ECZEMA

A history of eczema in the first few years of life is a very usual antecedent to the development of asthma at the age of three onwards. Very commonly this infantile eczema disappears with the advent of asthma, but it may persist throughout the patient's life. A generalized weeping eczema may lessen, becoming drier until the only sign of it is an irritable reddened area of skin in the flexures of the arm and behind the knees. The irritation is very marked and leads to rubbing and scratching that continues unconsciously even during sleep. " The other boys say they don't hear me scratching in my sleep as much as usual ", shows improvement. The skin of these people is often ichthyotic, so that in the colder weather cracks on the skin of the wrists are common. Secondary infections add further troubles to these unfortunate children.

A history of infantile eczema is obtained in 23 per cent of all asthmatics, in 30 per cent of those sensitive to foreign proteins, and in 34 per cent of those sensitive to foods. Of those sensitive to wheat, no less than 60 per cent gave a history of eczema. Even with tiny infants, large wheals are obtainable with the scratch tests, especially to egg.

It is very difficult to say exactly what happens when the change-over from eczema to asthma takes place. One may

imagine that as sensitization becomes more pronounced and a greater amount of specific reagin is to be found in the blood-stream, so grosser forms of anaphylaxis occur, the earlier eczema being a true allergic phenomenon before full anaphylactic sensitization has developed.

By the percentage of cases associated with food sensitization, especially to wheat, we can see that in the majority of the cases the cause of the eczema reaches the skin via the intestinal tract. But given a child of this nature with eczema on those portions of the skin which are uncovered, who is also sensitive to house dust, then that antigen will be continuously reaching the skin, and will itself cause symptoms from direct contact through the eczematous skin.

Case 65.—Lady, aged 30. "Born with eczema". which disappeared: asthma until 14; sneezes often in the early morning, when nose may pour. Six years ago injured her hand, which became septic. Since then dry eczema on the hands, the skin being thickened and swollen with deep cracks over the joints. Gave a + + + reaction to house dust. After desensitization the whole cleared, with one return after washing some curtains.

Here was a patient with asthma, paroxysmal rhinitis, and eczema, all due to sensitization to house dust. Her right hand was always worse than the left because, as with all other right-handed people, it met more dust and became 'dirtier' more easily.

Certain cases of eczema in which the rash is limited to the face, head, and neck are found to be due to sensitization to feathers. Cosmetic rashes may be due to sensitization to orris-root, increased in intensity by an acne formation due to blocking of the glands with the powders and greases applied to the face. The treatment consists of the discovery of the cause and its removal. The mixed coliform vaccine treatment and histamine will cure many cases.

Unfortunately cases will be seen in which full and ample skin reactions seem to have very little to do with the eczema.

MIGRAINE

As we pass further from asthma and hay fever to these allied complaints, their allergic basis becomes less and less solidly founded; that is to say, the greater is the proportion of cases whose only label can be one of idiopathic nature.

In migraine, headaches, frequently hemicranial, of a violent and disabling kind occur at intervals, associated with sickness

and abnormal sensory disturbances, particularly of the vision. Probably the pathology is some vasomotor disturbance in the cerebrum or its membranes akin to urticaria.

Goltman[13] describes the case of a young woman who was trephined for severe headaches of a migrainous type. In subsequent attacks the depression at the trephine hole filled up, showing that there is an increased intracranial pressure at these times. At the operation performed during an attack there was much increased intracranial fluid and a wetness or œdema of the brain.

Points in favour of any case being ' allergic ' are—a strong family history, a personal history of previous allergic complaints, possibly an eosinophilia, positive skin reaction, and their clinical confirmation by a cessation of symptoms on cutting out the food or other protein from the patient's surroundings.

Degowin[14] tested 60 cases with a full list of foods ; he claims 78 per cent were benefited by the elimination of the foods concerned. I have not had a great number of migraine cases through my hands, but I should not expect to get so much information from the dermal reactions as does this writer.

The diet régimes mentioned for the discovery of the cause of urticaria should be used on these cases. More complicated, but highly spoken of in America, is the trial of foods and their identification as harmful by the appearance of the hæmoclasic crises.

Again, there should be great scope for the use of the differential sedimentation test in this class of case. Apart from discovering the cause of the attacks of migraine, the most useful line of defence is histamine, or ergotamine biphosphate, of which histamine is the active principle. Von Storch[15] finds that it is possible to abort attacks by this means. O'Sullivan[16] controlled 1042 headaches in 97 patients with only 8 failures. The earlier it is given the better.

The dose used is 0·25 mg. by injection and 1·5 mg. by the mouth. Apparently no adrenaline was given with the ergotamine biphosphate. Untoward results may be controlled with $\frac{1}{100}$ gr. of atropine.

Headaches which do not conform to true migraine are not cured by histamine (Lennox[17]).

Migraine can be successfully treated with histamine and adrenaline injected twice weekly between attacks.

Wolff[18] discusses the psychological aspects of migraine, but the very important work of Riley alluded to on page 56 must not be forgotten. The presence of prolan A, the pituitary hormone that regulates the supply of œstrin, is found in large quantities at the times of the attacks of migraine. One's natural leanings are to look for and expect to find an organic cause, such as endocrine imbalance, rather than to accept psychological explanations, though these may well be a controlling adjuvant cause.

Inexplicable happenings occur in migraine, as in others of these so-called allergic complaints. A case of migraine of sudden origin in which the eye symptoms were predominant is described by Vallery-Radot et al.[19] The attacks increased in violence until with one attack a retinal hæmorrhage occurred, after which the symptoms almost ceased.

CYCLICAL VOMITING

Like paroxysmal sneezing, cyclical vomiting often starts before breakfast. It may continue all day. The child soon becomes pinched-looking, wastes rapidly, becomes extremely thirsty, but is sick directly anything reaches the stomach.

This is popularly called acidosis, but probably acidosis is the result and not the cause of the disease. Glucose and salines help when the child can keep them down. Probably the method adopted by Smith[20] of giving ½ gr. of sodium bromide per pound weight by the rectum most rapidly deals with the situation. An interesting point is that many of these cases later develop into migraine.

EPILEPSY

Many cases of epilepsy have been proved to be due to the taking of certain foods, the proof being the production of attacks after eating the foods and their elimination by avoiding the foods concerned. The discovery of the responsible foods, dust, or animal hair has been made by the dermal reactions, and by the diet tests already detailed at the commencement of this chapter.

Clein[21] describes a case of epilepsy due to sensitization to house dust; one due to pollen is given by Rowe.[22] Many of these patients also suffered from asthma and paroxysmal rhinitis.

An exceptionally sound article was written by the late Mackenzie Wallis together with Nichol.[23] A number of cases

of epilepsy selected by Sir Maurice Craig were tested with proteins. In those giving reactions the food at fault was eliminated, and in most cases the fits ceased entirely. Amongst the proteins to which they were found to be sensitive were eggs, wheat, vegetables, fish, and meat.

ANGINA PECTORIS

There is considerable evidence that, given a patient with symptoms of cardiovascular disease and sensitive to a protein, anginal attacks will be precipitated when the protein is taken.

Shookhoff and Lieberman[24] give a full description of a man whose symptoms were greatly aggravated during the ragweed season, severe attacks occurring without any over-exertion or other cause that would be necessary to cause them, outside the ragweed. A few pages earlier they describe anginal attacks occurring in three other cases after taking acetylsalicylic acid, some generalized arteriosclerosis and hypertension being present.

Eiselberg[25] found that the removal of carrots and tomatoes from the diet of a patient sensitive to those vegetables relieved the patient of his attacks of angina pectoris.

'ALLERGIC' SYMPTOMS IN OTHER AFFECTIONS

Bray[26] has noticed that some cases of enuresis have an allergic cause. Three cases out of 15 of long-standing enuresis lost their symptoms after the offending protein had been removed.

It is suggested that some cases of duodenal ulcer are of similar nature (Balyeat and Rinkel[27]). Episcleritis was found to disappear after the removal of the foods to which the patient was sensitive. I had a similar experience in a patient sensitive to fish.

Zeidler[28] noticed that patients with psoriasis who were being desensitized with pollen against hay fever lost their psoriasis in proportion to the extent to which the reaction to pollen disappeared. This has unfortunately not been my experience, the psoriasis continuing as before.

Many other people have various idiosyncrasies, especially to drugs, the normal action of the drug being produced in exaggerated form, as witness the heavy acneform rash and rhinitis produced in some patients by the smallest doses of

iodine. This cannot be considered a form of hypersensitiveness, because the effects produced are not those of the 'allergic' complaints. In the same way the effect of tobacco in thromboangiitis deformans is not an 'allergic' phenomenon. Rheumatism may well be a true allergy in the von Pirquet sense, but is not of general anaphylactic nature.

In conclusion, we may hope that something has been said to assist the understanding of these allergic or anaphylactic complaints, and to stress the importance of alternatively searching for a microbic cause in these cases. The separation of the one type from the other, the allergic from the microbic, by means of the differential sedimentation test, appears to us to be a sure step in the right direction, and a sound contribution to the understanding of asthma and its allied complaints.

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