Remarks

ON

THE PATHOGENESIS AND TREATMENT OF ASTHMA.*

BY

ARTHUR F. HURST, M.D., F.R.C.P.,
SENIOR PHYSICIAN TO GUY'S HOSPITAL.

THIS is the sixth occasion on which asthma has been discussed at the Annual Meetings of the British Medical Association since 1900. At the meeting in 1911 nothing was said which was not known to Hyde Salter when he wrote his admirable book on asthma fifty years before. At the meeting in 1921 the recent introduction of skin tests was regarded as holding out prospects of curing asthma with a frequency hitherto unapproached, a prospect which was already seen to be doomed to disappointment at the discussion in 1925. Though no new discovery of importance has been made in the four years which have elapsed since then, the large amount of work which has been done in the investigation of asthma in all parts of the world has, I think, led to a better understanding of the problem with which we are faced, and treatment founded on a thorough study of each asthmatic individual from every point of view is now likely to be followed by improvement, though unfortunately not often by cure.

The chemical constitution of the body fluids is not exactly the same in all healthy individuals, but shows slight variations from the average normal. I believe that these slight variations, though compatible with perfect health, form the basis of the congenital and often inherited constitutional tendency to develop certain diseases.

The balance between the vagal and the sympathetic constituents of that part of the respiratory centre in the medulla which, together with the associated peripheral ganglia, controls the activity of the muscular coat and mucous glands of the bronchi, is perfectly adjusted in normal individuals. I believe that the asthma diathesis—the congenital and often inherited constitutional abnormality which is the one essential factor in the pathogenesis of asthma—is caused by a slight deviation from the average blood chemistry, which results in the vagal constituent of the bronchial nervous system being the predominant partner. In such individuals certain chemical, reflex, and psychological stimuli, which have no effect on normal individuals, give rise to spasm of the bronchial muscles and hypersecretion of the bronchial mucous glands, together with congestion of the bronchi, which is the natural accompaniment of their excessive functional activity.

Some indication of the nature of the primary biochemical factors which predispose to asthma has recently been discovered by Dr. Oriel (*Guy's Hospital Reports*, lxxix, October, 1929), whose investigations at Guy's Hospital have demonstrated that even in the intervals between attacks the blood of asthmatics generally shows certain divergences from the average normal.

A further biochemical factor depends upon the varying activities of the internally secreting organs. The effect of fatigue, as shown by the increased tendency to asthma towards the end of each day, each week, and each period of work without holiday, is best explained as the result of exhaustion of the suprarenal glands, whose deficient secretion helps the vagal constituent of the bronchial nervous system to gain the upper hand over the sympathetic constituent, the activity of which requires an adequate supply of adrenaline. In accordance with this theory the blood pressure of asthmatics is generally low, and Oriel has found that many of them have well-marked hypoglycaemia. The increased tendency to attacks just before or during menstruation in many female asthmatics must also depend upon some alteration in the normal balance of the internal secretions.

In recent years so much attention has been directed to the question of hypersensitiveness to proteins and other chemical substances in asthma that there has been a tendency to regard this as the one essential factor. The

truth is, however, that an individual who is hypersensitive to one or more proteins only suffers from asthma if he has the constitutional tendency, the nature of which I have just described, and there is no doubt that many asthmatics are not hypersensitive at all, their attacks being caused by reflex and occasionally psychological stimuli. It is none the less of the greatest importance to give every asthmatic an exhaustive cross-examination with the object of discovering whether some or all of his attacks are due to his being hypersensitive to the proteins of one or more articles of food, an animal emanation, a pollen, house-dust, orris-root face powder, or the toxins of some organism, which is present in his body owing to infection of the bronchi themselves, the tonsils, nasal sinuses, teeth, or even the appendix or gall-bladder. I have used the skin tests in a very large number of cases since my attention was first drawn to them during a visit to America in 1919, but in spite of trying a great variety of American and English preparations I have regretfully come to the conclusion that they are of no practical value, except in the case of food proteins in children and of pollens at all ages. Harding has come to the same conclusion from his investigations at the Guy's Hospital Asthma Clinic.

The nose is the most important reflex source of asthma. Brodie and Dixon showed that stimulation of an area on the septum in animals produces bronchial spasm. In individuals with the asthma constitution irritation of the corresponding area gives rise to a similar reflex. When a man with a narrow airway lies down at night, the passive congestion of the cavernous tissue of his turbinates may be sufficient to bring them into contact with the asthmogenic area on the nasal septum. The narrow airway may be congenital or result from a deflected septum or from chronic infection which leads to permanent congestion of the mucous membrane and the development of polypi. A distended stomach and a distended rectum may both produce reflex attacks of asthma quite independently of any form of alimentary toxæmia, an evacuation of the stomach or rectum producing immediate relief long before a change could take place in the blood from diminished absorption of poisons.

The most common psychological factor in asthma is expectation. An individual who has been accustomed to get attacks of asthma in certain places or under certain conditions is exceedingly likely to continue to do so when the original chemical or reflex cause has ceased to be operative. This is a result of auto-suggestion, but it must be remembered that no amount of suggestion can produce anything more than tachypnoea without any trace of over-activity of the bronchi in anybody who has not the asthma diathesis.

TREATMENT.

In discussing the treatment of asthma we have to consider the underlying constitutional abnormality, the chemical, reflex, and psychological factors which can initiate an attack, the attack itself, and the secondary changes in the lungs which result from repeated attacks. It is clear that the only true cure of asthma would be to abolish the diathesis by bringing the biochemical constitution of the body fluids to the normal level. Removal of exciting factors leads to diminution of the frequency of attacks, and complete success in this direction may lead to an apparent cure. But the condition is not really cured, as the diathesis remains, and at any time the individual may become sensitized to another protein—as, for example, after an attack of influenza or other infection involving the nose, throat, or bronchi—or a new peripheral source of irritation which leads reflexly to attacks may arise, or some psychological disturbance may develop which results in a relapse. Moreover, the effects of desensitization are only temporary, and avoidance of exciting causes, such as feathers, cats, or pollens, even for long periods, does not diminish the tendency to asthma on re-exposure. I used to say that the only cure of asthma was not to have it, by which I meant that one might hope that the bronchial nervous system might cease to be abnormally irritable as a result of disuse if it were never called into activity. But this is unfortunately not always true, at any rate in adults, as I have now seen numerous patients who have relapsed after thinking themselves cured for periods varying between one and twenty-five years. Lastly, treatment of the paroxysm

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is of the greatest importance, as, if successful, it may make it possible for a man to continue in full activity instead of becoming a hopeless invalid.

Among the innumerable forms of treatment which have been advocated two appear to attack the diathesis; these alone, if successful, might be regarded as genuine "cures." The first is by means of diet, a treatment which has been very successfully applied, especially in children, by Dr. Adam and Dr. Cameron. The second is by residence at a height between about 4,000 and 6,000 ft. Asthma is almost unknown among the natives of the Engadine, Davos, Villars, and similar centres in Switzerland, and at least 90 per cent. of asthmatics lose all, or nearly all, their symptoms within a very short period of their arrival in these places. Unfortunately, the effect is only temporary if the stay is a short one, the asthma returning, often within a few hours, on reaching the plains. But residence for one year, or preferably several years, in the Alps almost invariably leads to a permanent cure in children, in spite of complete failure of every known form of treatment at home. Storm van Leeuwen attributed the effect of the Alps to freedom from dust. I am convinced that this is erroneous, as there is no obvious difference between the hotels at a height of 4,000 ft. and those 2,000 ft. lower, and yet a man who is severely asthmatic in the latter is often quite well and can take vigorous exercise within twenty-four hours of moving to the former. Moreover, no house could be fuller of "allergens" of every kind than the hermetically sealed chalets of the Alpine peasants during the winter, although asthma is unknown among them. It is also a common experience among asthmatics that conditions which invariably lead to asthma when they are at home are innocuous in the mountains; it seems, in fact, that nothing could produce an attack when the 4,000-ft. level has been reached. It is clear that the effect is due to altitude, a conclusion which has been confirmed by the experience of asthmatic members of the Air Force, who find that they can always find relief by flying sufficiently high. It is unknown why altitude should have this remarkable effect, but I expect it will be found that the lowered oxygen tension leads to biochemical changes in the blood, which result in diminution in the irritability of the bronchial nervous system. The further lowering of oxygen tension when a still greater height is reached has the reverse effect, though each individual appears to have an optimum level. This accounts for the reappearance of attacks on reaching greater heights in the Alps and the frequency of asthma in such places as Johannesburg.

It is, I think, possible to look forward to the time when sufficient is known about the biochemical changes which constitute the asthmatic diathesis to make it possible to imitate the effect of high altitudes by well-defined changes in the diet, aided, perhaps, by drugs which can correct deviations from the normal reaction of the body fluids and make good any deficiencies in their mineral or other constituents. I should mention here the success obtained by Dr. Oriel, especially in children, by adding glucose to the diet, together in most cases with the regular administration of alkalis.

Some of the many chemical stimulants of the irritable bronchial centre can be avoided by a change in habits, diet, or environment. Others can sometimes be rendered innocuous by desensitization.

With regard to reflex exciting causes, it is necessary to emphasize the importance of avoiding distension of the stomach and the rectum. In the case of the nose there are three distinct factors which require attention. The first and most common is chronic infection of the sinuses, especially the ethmoids, with secondary development of polypi; this must be dealt with by the cure of the infection, which can generally be effected by vaccination and packing with silver preparations without more radical operations than the removal of polypi. The second factor is obstruction of the nasal passages; it is essential to overcome this, as few asthmatics can be permanently relieved if they remain mouth-breathers. Lastly, the asthmogenic area on the nasal septum should be either destroyed by cauterization or rendered inoperative by so correcting the other factors present that the turbinates no longer come into contact with it, even when distension of their cavernous tissue

occurs as a result of gravity on going to bed. Chronic bronchitis, which also acts both as a reflex cause and as a focus of infection with organisms to the toxins of which the individual is sensitized, should be treated by autogenous vaccination, small doses of iodide, and climate.

The psychological factor requires consideration in the treatment of every case of asthma. At least 75 per cent. of patients become either completely free or almost free from symptoms directly they enter a hospital or clinic. This is doubtless often in part due to the fact that they have got away from the allergens present in their homes, which were responsible for some of their attacks; it is often partly and sometimes entirely due to the expectation that they are going to derive benefit from the treatment they are about to receive. It is essential to bear this in mind in estimating the effect of any treatment. If, for example, they are at once put into a dust-free chamber or are given some new drug, it is natural that they will ascribe the inevitable improvement to the specific treatment, whereas in all probability an equal degree of improvement would have occurred without any active treatment at all. It is always wise to instil a spirit of optimism into asthmatics, and to make them realize that improvement may at any time occur and that conditions which formerly gave rise to asthma may cease to do so. In this way alone can the influence of expectation in the production of attacks be overcome. A wise physician will also rarely fail to find some way in which unobtrusive psychotherapy benefits his patient.

In the treatment of the asthmatic paroxysm the preponderating activity of the vagal nerve supply to the bronchi can be overcome by means of drugs, such as atropine, which paralyse the vagus, or by adrenaline, which stimulates the broncho-dilator fibres of the sympathetic. The inhalation of fumes from powders containing stramonium or belladonna, which was formerly the universal method of treatment, had the grave disadvantage of causing chronic bronchitis by irritating the bronchial mucous membrane. This treatment should now never be used, as the opposite method of restoring the balance by means of adrenaline has no such disadvantage and is also more promptly and more constantly effective. The patient should be taught to inject the adrenaline himself, as if he does this at the first sign that an attack is developing it will be aborted, and a single minim will often be sufficient, though five or more would have been required if he had had to wait for a doctor or a nurse to give the injection at the height of the attack. This small dose gives rise to none of the unpleasant symptoms often caused by larger doses, and as it does not even raise the blood pressure there is no danger of damaging the arteries. Its use has in many cases the further justification of making good a deficiency in the secretion of adrenaline, just as thyroid preparations do good in myxoedema. The treatment also reproduces the way in which relief may on rare occasions occur under natural conditions. If an individual during a severe attack of asthma comes under the influence of sudden fear or anger, the two emotions which Cannon showed stimulate the secretion of adrenaline, the attack immediately ceases, the patient having had an "autogenous dose" of adrenaline. We may hope that the time will come when asthma will be curable, but until that consummation has been attained the proper use of adrenaline deprives asthma of most of its terrors and makes it possible for every asthmatic to live a life of moderate activity. Before its introduction many asthmatics rarely slept for more than three or four hours a night, and the morning found them exhausted by the long-continued fight for breath. Now it is unnecessary for any asthmatic to resort to hypnotics, as even if he has three or four attacks in the night the prompt injection of the right dose of adrenaline will each time send him to sleep within a few minutes.

The rare condition of status asthmaticus, in which severe asthma continues uninterruptedly for days or weeks and may end in fatal exhaustion, can always be arrested by the method of continuous adrenaline injection, which I introduced a few years ago, and which we have since found is equally effective in the treatment of anaphylactic shock. The needle is kept constantly in position, and after an initial injection of a dose which is known to cause no

unpleasant symptoms, such as two or three minims, one or more minims are injected every fifteen, thirty, or sixty seconds, according to the patient's reaction, the rate being varied until it is found how frequently the injection can be made without any unpleasant symptoms arising. The injections are continued, if necessary, for even half an hour or more; relief always follows and generally manifests itself by the patient falling into a deep sleep, which is often the first he has had for several days.

During the last few years a vegetable product, ephedrine, has been much employed as a substitute for adrenaline. Its chemical constitution is very similar, and it has the advantages of acting when taken by the mouth, whereas adrenaline is destroyed in the stomach, and of producing a much more prolonged effect. But it acts less rapidly and only controls minor degrees of bronchial spasm, being quite useless in the treatment of severe paroxysms. It is specially useful in overcoming the slight dyspnoea and wheeziness from which many asthmatics suffer in the intervals between attacks, and it is a very useful prophylactic when taken before going for a walk or doing anything else which is known by past experience to be likely to bring on a mild attack. Sometimes, when taken in the evening, it prevents an attack in the night, but occasionally it has the disadvantage of causing insomnia.

As the increased positive intrathoracic pressure during forced expiration increases the bronchial obstruction in an attack of asthma, whereas the negative pressure during inspiration diminishes it, the dyspnoea of asthma is characterized by being mainly expiratory. The result is that from the onset of the attack the lungs are in a state of full expansion, which after a time tends to persist in

the intervals between attacks, especially if, as is often the case, the spasm does not completely disappear. The distended condition of the lungs is not true emphysema, as the latter depends upon permanent structural changes in the tissues of the lungs, which make it impossible for them to be restored to their normal size. On the other hand, the distended lungs of the asthmatic remain capable of contracting unless secondary emphysema has occurred as a result of associated chronic bronchitis. The distended lungs are in a condition of great disadvantage, as there is no means of increasing their capacity when exertion calls for more oxygen. It is therefore of the greatest importance to teach every asthmatic to perform regular expiratory exercises, by means of which his barrel-shaped chest and shrugged shoulders become much less obvious, and in the case of children often disappear completely. Corresponding with this his capacity for taking exercise is enormously increased, as deep inspiration now becomes as easy as deep expiration. Ordinary breathing exercises are quite useless, if not actually harmful. Each exercise should begin with expiration, and an effort is made by active and passive movements to restore the thorax to a normal position of rest, after which diaphragmatic breathing with the mouth closed and the body fully relaxed should be taught.

Sir John Floyer, the author of the first monograph on asthma in any language, "panted on to ninety," in the expressive words of his fellow townsman, Dr. Johnson. There is, I think, reason to hope that before long our knowledge of the fundamental cause of asthma and of its treatment will have advanced so far that restoration to good health, and not merely the attainment of a miserable old age, will be the usual outlook for the asthmatic.

THE CEREBRO-SPINAL FLUID IN INTRACRANIAL INFLAMMATION.*

BY

J. G. GREENFIELD, M.D., F.R.C.P.,

PATHOLOGIST, NATIONAL HOSPITAL, QUEEN SQUARE, FOR DISEASES OF THE NERVOUS SYSTEM.

THE subject chosen for this discussion offers considerable difficulties. In no part of the body is it more necessary to understand all the stages and processes of inflammation, and in no place is this more difficult than in relation to the meninges overlying the cranial air sinuses. The subject has been made still more difficult by an old-fashioned nomenclature, which reflects theories of pathogenesis bearing little relation to modern physiology and pathology. The terms "meningitis sympathica" and "meningitis serosa," for example, are not only meaningless in themselves, but are interpreted by every author in a different way. Attempts have therefore been made to discard these terms, and new terms, such as "protective meningitis," have been introduced. This term seems to be little less meaningless than the older ones, as all forms of inflammation are regarded as "protective" by some pathologists, and in the case of meningitis the success of the protective mechanism is usually very uncertain. I prefer, therefore, to think of these forms of meningitis as either generalized or more or less localized.

We are now considering an infective process which resembles inflammation elsewhere in the body so long as it remains localized, but which is likely to prove fatal if it spreads a short distance from its starting point. Thus, if it penetrates the dura mater and reaches the brain, or spreads along the subarachnoid space to the larger cisterns, or causes inflammation of the walls of the dural venous sinuses, it at once becomes dangerous to life.

The first question that arises, therefore, is, What are the chances that the infection will remain localized? In this connexion we have to remember the density of the dura mater and the remarkable power it has of preventing the spread of infection so long as there is free external drainage. Of the infections that reach the dura mater very few penetrate it. We must also remember that the subarachnoid space over a large part of the base of the

brain is very narrow. Keith considers that the beautiful convolutional pattern which is seen on the floor of the skull indicates that the brain rests firmly on the bone with no fluid cushion between. The bony ridges which run along the lines of the sulci must reduce the subarachnoid space there to an almost negligible size. There is therefore a good chance that an infective leptomeningitis over the outer parts of the anterior and middle cranial fossae may be limited by meningeal adhesions. With regard to the posterior cranial fossa it is probable that the subarachnoid space over the lateral lobes of the cerebellum is also very restricted, except in the immediate neighbourhood of the pons. On the whole, therefore, an infection from the middle ear is more likely to pass across the subarachnoid space to the brain and cause cerebral abscess than to cause widespread meningitis. On the other hand, an infection which runs inwards to the tip of the petrous bone, or which arises in one of the more centrally placed air sinuses, is much more likely to cause generalized meningitis, owing to the proximity of the large cisterns.

In my experience it is in the cases of more or less localized meningitis that the chief difficulties of diagnosis arise. When we are presented with the fluid from a typical case of septic meningitis containing numerous organisms in films and on culture it needs none of the refinements of the clinical laboratory to establish the diagnosis. When, on the other hand, no organisms are visible and cultures remain sterile the difficulties begin.

The examination of such sterile fluids requires special care and a well-devised routine, as the quantity of fluid is limited. We must first determine whether the fluid is normal or not in cell count and protein percentage. If it is normal in these respects, especially if the pressure is also normal, the prognosis is usually good. But even slight abnormalities, such as a small admixture of polymorphonuclear cells in a "high normal" lymphocyte count, or a rise in the protein with little or no cell increase, may be danger signals. In some cases the fluid is quite normal but the pressure is increased, a condition more often found in the "meningism" of general diseases in childhood than in local inflammatory conditions of the skull and dura mater. In general diseases the symptoms of meningitis usually disappear quickly after the first puncture; in inflammatory conditions the increase of pressure may remain for some little time and only disappear after several punctures. It is probable that in the first case we are

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