REFRESHER COURSE FOR GENERAL PRACTITIONERS**THE MANAGEMENT OF ASTHMA**

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Asthma is rightly included among the psychosomatic disorders. It is now widely recognized that in most cases there is an allergic basis, with secondary infection of the bronchial tree as an added factor of considerable importance. The neurotic individual who is also asthmatic may give expression to his subconscious conflicts by an increase in the frequency and severity of asthmatic attacks. It is less certain that asthma can occur solely as the result of infection or psychoneurosis in the absence of an allergic foundation, though the allergic element is often submerged by these factors and may be therapeutically of minor importance.

The principles underlying the management of asthmatic patients have not altered in recent years, though new therapeutic agents have been introduced. A careful history designed to establish the relative importance of these allergic, infective, and psychological factors is essential. It is important to recognize that the longer the duration of the asthma the more likely it is that all factors are playing their part in maintaining the asthmatic state.

Pure allergic asthma is most commonly seen in children and young adults. A family history of allergy and a personal history of associated forms of allergy are frequent. Eosinophils and Curschmann's spirals are often found in the sputum. Such patients are predisposed under suitable conditions of exposure to develop sensitivity to molecules, chiefly of a protein or protein-carbohydrate nature, including many forms of inhalants and foods, and to certain drugs which probably acquire antigenic properties as the result of conjugation with body proteins. It is therefore not surprising that most asthmatics are sensitive to a variety of agents, and that asthma due to solitary atopens (allergens) is relatively uncommon: sensitivity to grass pollens accounts for the majority of cases in which one atopen is responsible for the symptoms.

Hyde (1949) has published a chart showing the seasons during which the pollens of various anemophilous trees and plants are found in the atmosphere of Great Britain, and this should help in the diagnosis of the more unusual cases of pollen allergy. Hyde and Williams (1946) have also pointed out that *Alternaria* spores are present in great numbers during the latter part of the summer, and these, too, may account for some cases of seasonal allergy. Increasing attention has been paid to fungus sensitivity in recent years, and its importance in this country may be greater than was previously supposed. Sensitivity to house dust, animal hair, and to materials of animal or vegetable origin encountered at work or in the home may also be suspected from the history.

Skin Tests

Confirmation should be obtained by skin tests and by experimental exposure when this can conveniently be done, if possible without the patient's knowledge. In this country skin tests have never achieved the importance ascribed to them in the U.S.A., possibly because, owing to our climate, infection plays a relatively more important part, but also because positive skin reactions so often lack clinical con-

firmation. The potency of extracts put up by pharmaceutical firms varies considerably, and, except with pollen, no commercial attempt at standardization by biochemical methods has been made in this country. Most pollen extracts give reliable results when tested by the prick or scratch method. Extracts of most other atopens, including foods and inhalants, tend to give too few reactions by this method. On the other hand, intradermal tests, particularly to inhalants, give too many positive reactions and may be dangerous in inexperienced hands. Now that preparation of dust and mould extracts has been carried out in a scientific manner (Rimington *et al.*, 1947; Maunsell *et al.*, 1947) there is some hope that purified and standardized preparations of various allergens may become available for testing, and that scratch tests with all extracts will be as reliable as are those with grass pollen at present.

Infection should be suspected if the attack of asthma lasts for weeks or months rather than for hours or days, if there is yellow sputum, or if the patient is pyrexial; adrenaline will be relatively ineffective in these cases. The history of an infection of the upper respiratory tract before the development of asthma is also suggestive, but it must be remembered that allergic rhinorrhoea is often mistaken for a head cold. Examination of the sputum will show pus and organisms; typical Curschmann's spirals will be absent. Sometimes sputum cultures repeated at intervals of several weeks will show that an organism of one type persistently predominates, but more commonly organisms of low pathogenicity, which vary from time to time, are grown.

Psychological Factor

The importance of the psychological factor in asthma is now well recognized, in large part because of the work of British observers. Its relative importance is not always easy to assess, but the family doctor is in a particularly favourable position to do this. He knows the family background, the parents who are over-solicitous, the mother whose child is unwanted, and the unhappy home where the atmosphere is described as "stifling" or where anxiety lies like a "weight on the chest." In a series of severe cases of chronic asthma personally investigated an unhappy home atmosphere was surprisingly common. These patients may use their asthma as a means of obtaining sympathy, as a weapon or an excuse, as the expression of a mental conflict, or, more rarely, as a symbol which represents some childhood incident long repressed into the subconscious.

The mechanism of the conditioned reflex must also be remembered: an incident which calls to mind the circumstances in which an asthmatic attack has taken place may itself lead to the recurrence of symptoms. The adult patient should be encouraged to discuss his environment at home and at work and the stresses which lie beneath the surface, and to relate emotional incidents to attacks of asthma. In children the attitude of the mother towards the child is often obvious, and impressions can be confirmed or modified in the course of conversation; the relations between the parents and between siblings should also be sought.

Treatment of the Allergic Factor

The allergic aspect is most easily dealt with and responds better to treatment. Suspected atopens should be avoided so far as is possible. The sorbo pillow can once more be obtained for those who are sensitive to feathers or kapok. Change of occupation or residence may sometimes be necessary, but should never be recommended without good evidence that the patient is likely to be better in a new occupation or locality; a preliminary trial period is advisable. The patient's occupation or the ubiquity of the atopen to which he is sensitive—for example, house dust—may make it impossible to avoid contact with agents to which he is sensitized: in such cases hyposensitization should be attempted by injection of increasing quantities of one or several extracts.

It is important to remember that the effect of this treatment is as a rule only temporary, and in successfully treated cases boosting doses at monthly intervals will sometimes keep the patient in good health. Even then fresh sensitizations may develop in the course of the disease. Most firms provide a suggested scale of dosage for desensitization with the extracts supplied. There is always a risk, however, that a severe general reaction may follow in very sensitive patients, especially after the first or second injection or on changing from a weak to a strong solution. This may take the form of severe urticaria, angioneurotic oedema, rhinorrhoea, asthma, and collapse. In order to avoid such an event the first dose should be gauged by the size of the skin test, and great care should be taken to ensure that the material is not accidentally injected into a vein. The addition of 3–5 min. (0.18–0.3 ml.) of adrenaline hydrochloride (1 in 1,000) to each dose of extract serves further to diminish the chances of severe reactions, but also delays their onset.

Every patient should be kept under observation for half an hour after each desensitizing injection. The symptoms of a reaction can normally be controlled by the injection of 5–10 min. (0.3–0.6 ml.) of adrenaline hydrochloride (1 in 1,000), but it may be necessary to repeat this several times before complete recovery occurs. Antihistamine drugs (50–150 mg.) may also diminish the effects of such reactions, but in severe cases they do not act quickly enough, nor are they ever as effective as adrenaline.

Treatment of Infection

Cases in which infection plays a predominant part are more resistant. This is partly because symptomatic treatment, which is discussed below, is far less effective and partly because eradication of infection from the bronchial tract is often exceedingly difficult. The remedies employed in bronchitis may be effective in the milder cases—that is, rest in bed in a constant temperature, the use of expectorants such as potassium iodide and simple alkaline mixtures, inhalation of tinct. benzoin. co., and breathing exercises designed to encourage expiration and expectoration.

In severer cases penicillin may be invaluable, and used in combination with sulphonamides can save life and will often reduce the period of invalidism by many weeks. These drugs should be given boldly, and, provided improvement takes place, they should be maintained for an adequate period of time—up to 30 g. of sulphonamide over five to seven days and full doses of penicillin for one to two weeks. The latter may conveniently be given as procaine penicillin or in the form of a stearate, 300,000 units twice daily. It may also be administered as an aerosol by means of an atomizer fitted with a mouthpiece and

attached to an oxygen cylinder; in this way 20,000 units may be absorbed intrabronchially every hour during inhalation for five to ten minutes. The too frequent use of penicillin will encourage the growth of resistant organisms, and it should therefore be restricted to cases of severe asthma which have not responded to simpler measures or in which life may be in danger. Sensitivity to penicillin or sulphonamides, which may themselves cause asthma, has been recorded, and for this reason, too, they should be employed with caution. Vaccines are still used, but in my experience are seldom of value: they may be helpful when one type of organism is grown in pure culture or constantly predominates in the sputum and seems to be responsible for maintaining the infection.

Psychological Treatment

The best results of psychological treatment are often seen in children; the approach should be indirect through the parents, who must be reassured so that they avoid the appearance of anxiety in the child's presence. They should be encouraged to allow him to lead as normal a life as possible, and helped to understand and so to relieve the underlying tensions.

Encouragement and a reasonably optimistic outlook are essential in the treatment of all asthmatics, and wise advice on how to live with and control the disease should be given. When there is an obvious source of anxiety this must be faced and the patient led to appreciate the connexion between it and his attacks. Adjustment of environmental factors is sometimes possible, usually by removal of the patient to more congenial surroundings. In difficult cases expert psychiatric assistance may be valuable.

Control of Attacks

When the main aetiological factors have been dealt with the direct control of attacks must be considered. It cannot be too strongly emphasized, however, that to prescribe symptomatic remedies alone is to invite failure; asthma remedies must be intelligently used, and whenever possible should be complementary to treatment of the causal factors. In mild recurrent asthma, especially of fairly recent onset, breathing exercises are often beneficial. These must be given by a qualified instructor along the lines laid down in the booklet published originally by the Asthma Research Council.* Stress is laid on expiration and the movements of the diaphragm and lower thorax. The reason for the improvement which follows is unexplained; it may be partly psychological and partly brought about by helping the patient to expectorate mucus squeezed from the bronchioles during expiration. The best results seem to be obtained in those with mild bronchial infection.

In the same type of case with mild recurrent symptoms broncho-dilator drugs are helpful. There are now a good variety of these—ephedrine, $\frac{1}{2}$ gr. (32 mg.), still retains its value and is often more efficient if combined with theophylline, 2 gr. (130 mg.), phenobarbitone, $\frac{1}{2}$ gr., or "sodium amytal," 1 gr. (65 mg.). Certain synthetic adrenaline analogues (isopropyl-noradrenaline) are sold under various trade names, including "neo-epinine," aleudrine, "neo-drenal," and "isupren." These are prescribed in 20-mg. doses and have the advantage of being absorbed perlingually, but, like adrenaline, they often cause palpitations. I have not found them to offer any striking advantage over ephedrine, though some patients prefer them.

Antihistamine drugs are also disappointing in the treatment of asthma. Mild cases of allergic asthma may be

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controlled by regular administration three times daily : most of these drugs are prescribed in 50–100 mg. doses, but “antistin” is well tolerated in double this amount. The best results are obtained in those who are troubled by nocturnal wheezing. “Anthisan,” 50–200 mg., and “phenergan,” 25–75 mg., both exert their effects for at least twenty-four hours and may be given in one dose at bedtime, when the sedative side-effects which may be present are beneficial. As side-effects are relatively common, small doses must be given at first : if drowsiness develops amphetamine sulphate (5 mg.) may be used to counteract it, but in many patients the narcotic effect disappears spontaneously after a few days. It is also important to remember that after a course of treatment with maximum dosage the drug must be gradually reduced or so-called “rebound” effects occur with intensification of symptoms. Sensitization to antihistamines has been recorded, and they are of no value in severe attacks or when infection is present. It is worth remembering that the response to these drugs as regards both their anti-allergic properties and their side-effects is surprisingly individual and one may succeed where another causes only vomiting or drowsiness.

Nebulizers are widely used by asthmatic subjects in the form of small hand-sprays and of more elaborate apparatus attached to an oxygen cylinder : so long as they are employed only occasionally there is no objection to them. In severe cases, however, when they are used frequently they are certainly harmful whether they contain adrenaline hydrochloride (often employed in a concentration of 1 in 200 in 10% glycerin), adrenaline analogues, or proprietary preparations containing combinations of various antispasmodic drugs. It is not always recognized what a large quantity of these substances can be absorbed in this way.

Adrenaline still remains the chief symptomatic remedy in the severer case, and it is sometimes justifiable to teach the patient to give his own injection (2–5 min. (0.12–0.3 ml.) of 1 in 1,000 adrenaline hydrochloride) early in the attack. He must be warned against the danger of accidental intravenous injection, an error which may be followed by hemiplegia or, possibly, death. In severer attacks bigger doses can be safely given by Hurst's minim-a-minute method. Preparations of adrenaline in oil, or in the form of a mucate (hyperduric adrenaline), are sometimes useful, especially at night because of their slow absorption. In recent years aminophylline (theophylline with ethylenediamine *B.P.*) has achieved an importance second only to adrenaline and is a genuinely useful preparation. The intravenous injection of 0.24–0.5 g. may cut short severe and long-standing attacks when adrenaline in large doses has proved ineffective. A disadvantage is that it is most effective when given intravenously, and this is not always convenient. By mouth (1–3 gr.—65–200 mg.) it is of little value except as an adjuvant with other drugs ; it also is a gastric irritant.

Status Asthmaticus

Status asthmaticus still remains the bane of the physician and the patient's nightmare. In the early stages the bold use of adrenaline or aminophylline, and, if necessary, removal to hospital may arrest the condition, but the tragic patient who relapses after a short period of improvement, who is prevented from sleeping by his dyspnoea, and who becomes dehydrated and ketosed from inability to take food is always a source of anxiety. A low-grade infection is often present in these cases, and it is in them that penicillin can produce dramatic improvement. It may be given by the usual intramuscular route or as an aerosol delivered continuously into an oxygen tent or inhaled intermittently

with the aid of a nebulizer. In my experience the inhalation methods have little if any advantage over injection.

Treatment with intravenous infusions of aminophylline in a glucose-saline drip may be useful : 0.5 g. of aminophylline may be added to a litre of glucose-saline (0.4% glucose, 0.18% NaCl) and run in at the rate of 60 drops a minute. If the drip is to be maintained for twelve hours or longer the rate should be reduced by half ; a total of 3 g. of aminophylline may be given safely in twenty-four hours. Ethyl alcohol 5% in glucose-saline, with the addition of 0.3–1 ml. of adrenaline hydrochloride 1 in 1,000, has also been used and helps the exhausted patient to sleep. These remedies should be given cautiously and should not be continued if improvement is not early apparent ; adrenaline may be harmful to those who are “fast” to this drug, aminophylline can cause circulatory collapse, and with intravenous therapy there is always a risk of pulmonary oedema if bronchopneumonia is present. The rectal administration of ether in olive oil (3 oz. (85 ml.) in 5 oz. (142 ml.) of olive oil for an adult) may give much needed sleep. Paraldehyde is also useful in this respect ; it is most effective given intramuscularly in an adult dose of 2 ml., repeated if necessary after an hour.

Bronchoscopy carried out under local analgesia, with removal by suction of thick mucus obstructing the bronchi and bronchioles, may bring about dramatic improvement in resistant or apparently hopeless cases.

Morphine unfortunately is still given in asthma ; this is inexcusable because of the high death rate due to respiratory failure and because of the possibility of addiction, which is always present when this drug is used in chronic illness. Aspirin is also dangerous in asthma ; Salén and Arner (1948) estimate that 9% of asthmatics are aspirin-sensitive, and death following its use is not rare. The administration of a single tablet of tab. codein. co. or of aspirin, phenacetin, and caffeine can cause status asthmaticus and death.

The severe intractable case of chronic asthma, often beginning in middle age and failing to respond to any form of treatment, remains to be discussed. The prognosis in regard to expectation of life is bad. Desperate measures are justifiable, and in such patients surgery may have a place. Bilateral resection of the pulmonary plexus by interrupting the vagal supply to the lungs is reported to have been successful in some cases (Rienhoff and Gay, 1938).

Conclusion

In conclusion, it is perhaps not out of place to point out that asthma is not only a trying disease for both patient and doctor, but that it not infrequently causes death. The rarity of death from asthma is overstressed in textbooks : whilst it would be unwise for the patient to be undecieved, doctors should realize the true position. Flensburg (1945) states that, of 378 children admitted to hospital with asthma between 1926 and 1939, 15 (5%) out of 298 patients traced had died before 1945. A follow-up of some of my own cases has shown a surprisingly high death rate : in one family two children died in status asthmaticus at the ages of 11 and 18 years. A predominant psychological factor is no bar to a fatal outcome. The immediate cause of death is varied and includes secondary infection with bronchopneumonia, status asthmaticus, and the effect of aspirin in sensitive patients or of morphine. Rarely, death follows the administration of adrenaline, probably delivered accidentally into a vein, or an overdose of a desensitizing solution. The death rate from associated

conditions not apparently related to the asthma may also be higher than for the normal individual. These hazards must be recognized and their risk reduced by careful and thorough treatment at an early stage, and at all times the serious nature of the disease must be appreciated.

(All doses mentioned in this paper apply to adults: appropriate reduction should be made for children.)

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LIFE OF THE RED CELL

The second Frederick Price Lecture was delivered by Professor L. J. WITTS at Trinity College, Dublin, on May 18, his theme being "The Life of the Red Blood Cell." He began by emphasizing the value of co-operation between the basic scientist and the clinician. Over ten years ago the late Professor D'Arcy Thompson had asked him why he thought the red cell was the shape it is. It was interesting to hear a great biologist asking why and not merely how, because Professor Wits was one of those who believed that one of the characteristics of vital processes was their purposive nature.

The red cell was a biconcave disk, he said, first, because that shape was the ideal compromise between a haemoglobin container, which would be a sphere, and a tonometer, which would be a thin disk. Secondly, it was the best shape for low viscosity of the blood and easy flow through the capillaries. It was difficult to explain how the erythrocyte resisted the surface forces which might have been expected to shape it into a spheroidal droplet. There must be an ultramicroscopic architecture of the outer wall and the stroma. Evidence suggested that an important part was played by the nature and orientation of the haemoglobin molecules with which the cell was so closely packed. In certain hereditary diseases in which the red cell was abnormal in shape its viability was reduced, and the patients suffered from a haemolytic anaemia.

New Methods of Measuring

One of the big advances in haematology in the last 20 years was that they could now measure the process of blood formation and destruction in man with reasonable accuracy and simplicity. The reticulocyte count and the output of pigment in the stools could not be used for exact analysis, though they remained useful in clinical work. One of the oldest methods of determining the life of the red cell was to watch the return of the blood to a normal level after haemorrhage or artificial plethora. This method was not theoretically satisfactory, because the normal course of blood formation and destruction was disturbed by those procedures.

All modern methods depended on the formation or introduction of marked red cells in the organism. The marking of red cells depended on the fact that certain characteristics, such as the blood-group substance and the haemoglobin molecule, including the relevant fractions which were analysed, were stable throughout the life of the cell and were not exchanged with other red cells or with the rest of the body. The improved Ashby technique was used in the second world war for determining the best method of storing blood for transfusion. It was found that *in vitro* changes in the fragility, volume, and chemical properties of stored blood cells bore no direct relationship to survival in the recipient, since the cells could re-condition themselves *in vivo* after certain types of exposure and not after others. At that time it was discovered that red

cells survived up to about 120 days *in vivo* and that with appropriate care and the use of solutions containing dextrose they could be stored up to about three weeks. The survival of red cells in different forms of anaemia was then studied, particularly in those forms where there was other evidence that blood destruction was accelerated.

Dacie and Mollison had found that normal erythrocytes injected into patients with acholuric jaundice survived as long as in recipients without haemolytic disease, the survival periods being from 100 to 130 days. When spherocytic cells were injected into normal people they disappeared completely within 14 to 19 days. Similar results had been obtained in paroxysmal nocturnal haemoglobinuria, pernicious anaemia, and sickle-cell anaemia. In all these conditions the evidence was that the red cell was abnormal from its birth, but that its environment was normal.

Very different results were obtained when similar experiments were carried out in cases of acquired haemolytic anaemia in which haemolysins were present in the plasma or the environment was otherwise at fault. Loutit had found that normal red cells were rapidly destroyed by patients with acquired haemolytic anaemia, whereas cells of acquired haemolytic anaemia transfused into normal recipients survived normally. That finding indicated that red cells which had lived dangerously might be capable of recovery and normal survival when transfused to a healthy environment. That was not always true. Foy and his colleagues had found that transfused cells were extremely rapidly destroyed in the active phases of blackwater fever. The patient's own cells which escaped destruction during the acute crisis were nevertheless irreversibly damaged by the haemolytic mechanism, and their survival was brief, whether in the patient's circulation or transfused to a normal environment. In haemolytic disease of the newborn, Rh-positive erythrocytes were rapidly destroyed, but Rh-negative erythrocytes survived for about the normal 100 days.

Survival Curve

By treating the data of red-cell survival mathematically Professor Wits and his colleagues had found that in normal men the survival curve was rectilinear, reaching the base line at about 120 days from transfusion, and it corresponded with Schiødt's theory of longevity. The straight line indicated that the mixed population of cells of all ages which had been transfused was dying up to expectation. In haemolytic anaemia the survival curve not only reached the axis earlier but was curvilinear—that is, there was an exponential component, corresponding with Schiødt's theory of destruction. In healthy men there was no exponential component, and the average life and theoretical longevity were the same. In women the survival curve seemed normally to be slightly curvilinear because of an exponential component, which was larger than could be explained by the losses at menstruation.

Recent work on the biosynthesis of haemoglobin indicated that the iron of the haemoglobin molecule was derived either from dietary iron or, apparently preferentially, from the destroyed red cell itself. The porphyrin appeared to be freshly synthesized from simple precursors such as glycine and acetic acid, while amino-acids from the dietary protein were used in the synthesis of globin. Each of those three fractions had been used in determining the haemopoietic equilibrium by means of isotopes. Methods based on the synthesis of haemoglobin from isotopes had the advantage that it might be possible to determine the rate of formation of red cells as well as that of destruction.

In America red cells tagged with radioactive iron had been stored under test conditions and then transfused and followed in a recipient. It was possible to measure the mechanical and osmotic fragility of the tagged cells and to show that their mechanical fragility increased in their old age. The re-utilization of radioactive iron for haemoglobin synthesis might be prevented either because the marrow of the recipient was producing little or no blood, as in aplastic anaemia, or when the iron stores of the organism were greatly enlarged, as by treatment with intravenous injections of iron.