mine in the corpus striatum was reported in the brains of patients with Parkinson's disease.[1] Next a correlation was shown between the degree of cell loss in the substantia nigra and the level of dopamine deficiency in the striatum.[2] Axons from the substantia nigra terminate in the striatum and are now known to be the source of dopamine; in other words, dopamine appears to be the neurotransmitter linking the substantia nigra and the striatum. When the deficient dopamine was replaced by using its immediate metabolic precursor levodopa and produced dramatic effects on the symptoms of Parkinson's disease the picture appeared complete.[3 4]

Yet this is not the whole story. Clinically, not all patients with Parkinson's disease respond to levodopa; even among those who show an initial response some become late treatment failures. One possible explanation might be that such patients develop irremediable damage to the striatum as a result of a continuing pathological process; but further biochemical studies have suggested alternative mechanisms. Deficiencies of neurotransmitters other than dopamine may be found in the brains of patients dying with Parkinson's disease.[5] Deficiencies have been found of noradrenaline, 5-hydroxytryptamine, and the enzymes concerned with the metabolism of gamma-amino-butyric acid and acetylcholine and further work is needed to establish the role of these abnormalities. These newly discovered chemical deficiencies in the striatum are much less dramatic than the deficiency of dopamine, and in post-mortem studies there are real technical problems in estimating the minute quantities of the transmitters concerned.

With these reservations, however, the findings appear consistent and suggest that defects in neurotransmitters other than dopamine may play a part in the symptoms of Parkinson's disease. Clearly the next stage of the investigation will be to try to correlate the biochemical findings at necropsy with clinical symptoms and their response to treatment. Should such correlations emerge, then specific drugs may be found for tremor, akinesia, and even dopa-induced dyskinesia. For the moment, however, striatal dopamine deficiency remains the central abnormality in Parkinson's disease and levodopa and dopamine agonists remain the drugs of choice in its treatment.

[1] Ehringer, H, and Hornykiewicz, O, *Klinische Wochenschrift*, 1960, **38**, 1236.
[2] Bernheimer, H, *et al*, in *Proceedings of the Eighth International Congress of Neurology*, p 145. Vienna Medical Academy, 1965.
[3] Birkmayer, W, and Hornykiewicz, O, *Wiener klinische Wochenschrift*, 1961, **73**, 787.
[4] Bareua, A, Sourkes, T L, and Murphy, G F, in *Monoamines et Système Nerveux Centrale*, ed J de Ajuriaguerra, p 247. Paris, Masson, 1962.
[5] Curzon, G, *Postgraduate Medical Journal*, 1977, **53**, 719.

Management of severe acute asthma

About 1500 patients, many of them children and adolescents, still die from bronchial asthma every year in Britain. These deaths are often described as "sudden and unexpected," implying in a sense that they are unavoidable. A substantial number still occur in hospital.[1] Yet, as experience in Edinburgh[2] and Cardiff[3] has shown, few patients with severe acute asthma need die if they reach hospital alive.[4] The reasons for this continuing high mortality rate are not easy to discover. In some fatal cases delay in starting systemic corticosteroid treatment at home or in hospital—or in raising the dose sufficiently—must be relevant. In others, the patient may fail to seek medical advice promptly when his asthmatic attack has clearly failed to respond to the inhalation of a bronchodilator aerosol. These patients are in a precarious state and can seldom be effectively or safely treated at home. Their admission to hospital should therefore receive at least as high a priority as that given to patients with myocardial infarction.

On their arrival in hospital it is now standard practice for patients with severe acute asthma to have their dose of systemic corticosteroids raised very high indeed. There seems to be little or no danger in giving doses of up to 2 g daily of hydrocortisone intravenously or 100 mg a day of prednisolone by mouth—or both—for short periods in gravely ill patients. Unfortunately, there is usually a delay of some hours before the airways obstruction begins to subside, and during this period the patient's condition may continue to deteriorate in terms both of respiratory distress and of hypoxaemia. This critical period places considerable demands on the medical team's judgment and skill. Severe hypoxaemia is invariable, and the continuous administration of oxygen is essential. Treatment with oxygen must be started before bronchodilators are given either parenterally or by inhalation, since these drugs all tend to reduce the partial pressure of oxygen in arterial blood still further.

One of the controversies in the treatment of severe acute asthma in hospital is over the choice of bronchodilator drug and its route of administration during the "crisis" when the doctor is anxiously waiting for the patient to respond to corticosteroids. There seems to be no place for subcutaneous adrenaline, but intravenous aminophylline remains a useful drug. Intravenous salbutamol, in bolus doses of up to 300 μg[5 6] or in a dose of 500 μg infused over 60 minutes,[7] appears to be as effective as aminophylline, more rapid in its action, and less prone to cause nausea and vomiting. Salbutamol may eventually replace aminophylline as the standard intravenous preparation for acute asthma, but until it has been more widely used some doctors may retain a preference for the older drug.

A more contentious issue is whether in patients with severe acute asthma salbutamol is better given intravenously or as an aqueous aerosol, either inhaled spontaneously or delivered from some form of positive-pressure ventilator (Bird or Bennett) with a tightly fitting oronasal mask. Despite several comparative studies of the efficacy of these three different ways of administering salbutamol the issue has not yet been resolved. In four such studies[8–11] intravenous salbutamol did not produce more bronchodilatation than the aerosol, its action was shorter, and it was apt to cause tremor, cardiovascular changes, and metabolic disturbances. Another report[12] last year, however, found that aerosol salbutamol in a dose of 5 mg delivered by positive pressure was much less effective in severe acute asthma than intravenous salbutamol when given in the initial phase of treatment. Unfortunately, in this study all the 10 patients were given aerosol salbutamol before intravenous salbutamol, instead of being allocated at random to the two forms of treatment, and the validity of the conclusions is therefore open to question. A large dose of nebulised salbutamol delivered by intermittent positive-pressure ventilation is more effective than a pressurised aerosol inhaled in the usual (200 μg) dosage, particularly if the degree of airway obstruction is severe.[13 14] But does giving the aerosol by intermittent positive-pressure ventilation have any advantage over inhalation from a simple nebuliser?[15] Only a carefully controlled comparison of the two techniques of administration (using the same inhaled dose) will provide conclusive evidence on this point—and such a trial is not easy to carry out on patients who are seriously ill.

If once in hospital a patient continues to deteriorate despite

corticosteroids in massive dosage, the repeated administration of bronchodilator drugs (by whatever route is favoured), and correction of hypoxaemia, dehydration, and metabolic acidosis, then the next step—urgently indicated—is tracheal intubation and mechanical ventilation, with heavy sedation to suppress the patient's respiratory drive. Rapid improvement usually follows, and ventilation is seldom required for over 24 hours.

So, while we still know very little about the fundamental causes of asthma, we now have at our disposal a wide range of effective, though empirical, treatments. Few deaths from asthma today are directly attributable to failure of treatment, but clearly we should give patients with severe asthma more adequate supervision and ensure that they are admitted to hospital with a minimum of delay when the need arises.

[1] Cochrane, G M, and Clark, T J H, *Thorax*, 1975, **30**, 300.
[2] Crompton, G K, and Grant, I W B, *British Medical Journal*, 1975, **4**, 680.
[3] Macdonald, J B, *et al*, *British Medical Journal*, 1976, **2**, 721.
[4] Cooke, N J, *et al*, *British Journal of Diseases of the Chest*, 1978, in press.
[5] Fitchett, D H, McNicol, M W, and Riordan, J F, *British Medical Journal*, 1975, **1**, 53.
[6] Femi-Pearse, D, *et al*, *British Medical Journal*, 1977, **1**, 491.
[7] Williams, S J, Parrish, R W, and Seaton, A, *British Medical Journal*, 1975, **4**, 685.
[8] Spiro, S G, *et al*, *British Journal of Clinical Pharmacology*, 1975, **2**, 495.
[9] Hetzel, M R, and Clark, T J H, *British Medical Journal*, 1976, **2**, 919.
[10] Lawford, P, Jones, B J M, and Milledge, J S, *British Medical Journal*, 1978, **1**, 84.
[11] Nogrady, S O, Hartley, J P R, and Seaton, A, *Thorax*, 1977, **32**, 559.
[12] Williams, S, and Seaton, A, *Thorax*, 1977, **32**, 555.
[13] Shenfield, G M, *et al*, *American Review of Respiratory Disease*, 1973, **108**, 501.
[14] Choo-Kang, Y F J, and Grant, I W B, *British Medical Journal*, 1975, **2**, 119.
[15] Shenfield, G M, Evans, M E, and Paterson, J W, *British Journal of Clinical Pharmacology*, 1974, **1**, 295.

Happy to starve

When a baby is bottle-fed his mother can easily see how much he is taking; but when he is breast-fed it is not so simple for her to know whether he is taking enough. In the newborn period a baby may be difficult about taking the breast, crying and fussing so that his mother thinks that her milk is not suiting him. Between about the fifth and the tenth day he may demand feeds about every two hours, so that she thinks that she has not enough milk. Some awkward babies in the early days fall asleep after suckling from one breast only to awaken an hour later and demand another feed. Mothers may misinterpret the baby's crying: the cause of his discontent may be difficult to pinpoint, and often it seems to represent a call to be picked up and cuddled, for it stops immediately when she obliges. Sometimes the crying is due to wind from air swallowing—which in turn may be due to the baby's being kept on the breast too long after he has obtained all the milk. (In the evenings rhythmical screaming attacks are usually due to evening colic, which is readily prevented by the anticholinergic drug dicyclomine hydrochloride.)

The baby may be a rapid feeder, taking all the milk in the first three or four minutes and then refusing more or falling asleep, so that again his mother thinks that he is not getting enough. She may ascribe his normal posseting to the milk not suiting him. Many a mother, seeing the first part of her milk, thinks that it is too watery—not knowing that the latter part of her milk is the richest in fat. For all these and other reasons the mother can be reassured by seeing that the baby is gaining weight normally. Regular weighing, beginning, say, at a week of age, and then weekly for the first three months and fortnightly up to six months of age, does much to reassure her that all is well: it shows the mother that her milk is suiting the baby (as it virtually always does) and that she has a good supply of it; and it provides a baseline if anything goes wrong or the baby falls ill.

There is another reason for weighing breast-fed babies regularly. Some of them give no outward sign, in the way of crying or irritability, to indicate that they are half-starving. Back in 1953 Illingworth[1] wrote that many breast-fed babies are perfectly willing to starve without complaining that they are not getting enough. Now Evans and Davies[2] have drawn fresh attention to this possibility, describing four contented babies who gave no sign other than defective weight gain and poor growth in length and head circumference that they were being starved. All four had been demanding infrequent feeds, and this itself may reduce the milk supply: some babies demand only three feeds a day, which is too little stimulation to the breast. Nevertheless, by no means all babies who are content to starve demand such infrequent feeds. A mother may have a false feeling of security for another reason—galactorrhoea. The leaking of milk between feeds by no means necessarily denotes an adequate supply of milk.

So doctors should encourage regular weighing, but over-frequent weighing may itself cause anxiety. A trivial infection, such as a cold, will temporarily retard the weight gain, and for unknown reasons babies may take less on some days than others. Most babies gain around 6 ounces (19 g) each week in the first three months. A little less or a lot more is no cause for anxiety.

[1] Illingworth, R S, *The Normal Child*, 1st edn. London, Churchill, 1953.
[2] Evans, T J, and Davies, D P, *Archives of Disease in Childhood*, 1977, **52**, 974.

If I Had . . .

For many illnesses there is little debate about the investigations needed and the treatment to be given once the diagnosis has been established. In a few cases, however, the procedures are not so clear cut and in trying to do his best for the individual patient the doctor relies on a middle of the road approach based on a consensus of medical opinion. But if he or one of his family has the same condition these principles may not be applied: on anecdotal grounds he may refuse an investigation which is fundamental to the diagnosis but which he has seen disable or even kill a patient, or he may go straight for an unproved and hazardous treatment on the strength of a single unvalidated report. Starting this week (p 896) we have invited a number of contributors to discuss what investigations and treatments they or their family would prefer to have for a particular condition: the subjects include breast cancer, a transient ischaemic attack, and melaena. A distinguished doctor we invited to contribute to this series refused on the grounds that it might seem to imply the existence of dual standards of medical care. We disagree: for various reasons doctors sometimes investigate and treat themselves or their relatives inadequately by conventional standards, and these reasons are of interest and should be debated.