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LONG-TERM STEROID THERAPY IN CHRONIC INTRACTABLE ASTHMA

A STUDY OF 317 ADULT ASTHMATICS ON CONTINUOUS STEROID THERAPY FOR AN AVERAGE PERIOD OF 2½ YEARS

BY

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The purpose of this paper is to assess the value and risks of long-term steroid therapy in severe chronic asthma. The observations are based on 317 asthmatic out-patients treated with steroids for periods of from four months to seven years, with an average duration of two and a half years: 205 have been on steroids for over two years, 118 for over three years, 46 for over four years, and 12 for over five years.

Steroids were first described as beneficial in asthma by Bordley *et al.* (1949). The Medical Research Council (1956a) confirmed their efficacy in status asthmaticus but doubted their value in the long-term treatment of chronic asthma (M.R.C., 1956b).

There are now many favourable reports on the value of long-term steroid therapy in chronic intractable asthma (Gay *et al.*, 1954 ; Arnoldsson, 1958 ; Williams, 1959 ; Phear *et al.*, 1960 ; Serafini, 1960 ; Andersson and Bruun, 1960 ; Herxheimer, 1961 ; Pearson *et al.*, 1961 ; Livingstone and Davies, 1961 ; Baldwin *et al.*, 1961). That there is still confusion of thought on this subject is shown by the recent communications of Grant (1961), Asher (1961), Maxwell (1961), and Hart and Emerson (1961).

Materials and Methods

Care has been taken to include only patients with asthma, which we have defined as recurrent spontaneous attacks of dyspnoea and wheeziness, commonly occurring at night, due to a functional bronchiolar obstruction with a characteristic pathology (Gough, 1960). The numbers of patients with associated conditions are shown in Table I. Care was taken to include only those with "chronic intractable asthma" *in whom all other measures had failed* ; 133 patients (42%) had had repeated status asthmaticus. The pretreatment assessment is shown in Table IV. Of these 317 patients, 84% were to a greater or less degree chronically incapacitated, 32% permanently so. All of the 16% not incapacitated had considerably disturbed sleep at night and were dyspnoeic on exertion in spite of treatment. During the last two years all patients had simple lung-function tests before and during steroid therapy. No patients were started on steroid therapy unless they had a very low forced expiratory volume in 1 second ($F.E.V._1$) and forced vital capacity (F.V.C.), and none were maintained on steroid therapy unless there had been a marked increase in the $F.E.V._1$ and F.V.C. over an initial period of two weeks. This improvement was generally maintained except when other factors such as a chest infection supervened.

We would regard as a typical response an $F.E.V._1$ of 750 ml., an F.V.C. of 1,533 ml., and an F.E.V.% 48 ; 14 days later $F.E.V._1$ 2,233 ml., F.V.C. 3,400 ml., and F.E.V.% 60.

Patients were skin-tested as indicated by the clinical history and hyposensitization was carried out in appropriate cases. An E.N.T. surgeon (Mr. Alun Thomas) and a psychiatrist (Dr. Cyril Jenkins) examined and treated appropriate patients.

The age-and-sex distribution is shown in Table II. The male:female ratio was 1:2.6. Of the patients, 90% were over 30 years, 73% over 40, and 85% 30 to 69. No children were included, as only adults are seen at this clinic.

Prednisone was given to 279 patients (88%), cortisone or hydrocortisone to 13 (4%) because they preferred

TABLE I.—*Number of Patients with Associated Conditions*

Healed pulmonary tuberculosis on anti-tuberculous therapy	5
Controlled hypertensive heart disease	5
Coronary artery disease	3
Duodenal ulceration	3
Diabetes mellitus on insulin	1
Reactive depression	2

TABLE II.—*Age-and-Sex Distribution of 317 Patients on Long-term Steroids and Corticotrophin*

Age in Years	Steroids and Corticotrophin			Percentage
	Male	Female	Total	
–19	2	6	8	3
20–29	9	14	23	7
30–39	19	36	55	17
40–49	16	44	60	19
50–59	28	63	91	29
60–69	11	54	65	20
70–79	4	11	15	5
Total	89	228	317	100

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it, and triamcinolone to 23 (7%) in preference to prednisone. Triamcinolone was given to 12 because of excessive gain in weight and to four because of poor response ; in seven it was the initial steroid used because of associated obesity and/or hypertension. Two patients who had been given dexamethasone by their practitioners continued to take this drug. Patients were advised to take steroids with meals or milk.

For convenience corticosteroid dosage is described in number of tablets, and the equivalent of dosage of each tablet is 25 mg. of cortisone=20 mg. of hydrocortisone =5 mg. of prednisone=4 mg. of triamcinolone=0.5 mg. of dexamethasone.

Of the 317 patients 170 (54%) were given two tablets of steroids daily, 12 (4%) one and a half tablets daily, 117 (37%) one tablet daily, and 16 patients (5%) half a tablet daily ; two patients were given three tablets daily, none received four tablets daily.

Ninety-six patients, with a male:female ratio of 1 to 2.3, were given corticotrophin (gel or zinc hydroxide) in doses of 40 to 60 units, intramuscularly, at intervals of one to six weeks—average 40 units weekly. The duration of steroid and corticotrophin therapy is shown in Table III. Corticotrophin was used in the early years

TABLE III.—*Duration of Steroid and Corticotrophin Therapy*

Duration	Steroids Only	Cortico-trophin and Steroids	Total	
			No.	%
4–12 months	35	3	38	12·0
13–18 ,,	23	7	74	23·3
19–24 ,,	36	8		
25–30 ,,	21	8	87	27·4
31–36 ,,	46	12		
37–42 ,,	19	12	72	22·7
43–48 ,,	21	20		
49–55 ,,	10	7	34	10·7
56–60 ,,	6	11		
Over 60 ,,	5	7	12	3·8

of steroid treatment with the idea of preventing suprarenal suppression (Ingle and Kendall, 1937 ; Sydnor and Sayers, 1954).

Patients were encouraged to use simpler and safer measures such as ephedrine, aminophylline, and/or inhalers, with the smallest dose of steroids which gave reasonable and not total freedom from asthma.

During exacerbations of asthma, patients were advised to take four prednisone tablets daily for four days, three daily for 3 to 10 days then two daily, and to reduce this dose further where possible. Patients were advised to stay indoors in the event of a cold and to take the reserve supply of oxytetracycline or penicillin issued from the clinic immediately a chest infection started.

Patients were seen at the clinic at regular intervals from twice a week to once every two months, depending on their clinical condition and proper understanding of the use of steroids and symptomatic therapy. All had a " steroid " card. Patients were seen by a health visitor, who noted the degree of control of attacks, use of steroid, weight, height, blood-pressure, carried out urinalysis, and arranged an *x*-ray examination of the chest and dorso-lumbar spine. For the first four years the review by the health visitors and *x*-ray examinations of the chest and spine were carried out every three months. This period was extended to six months over the next three years. During the last year of the study the interval between *x*-ray examinations was extended to one year. A barium-meal examination was done if indigestion persisted for 14 days or longer.

Results

There were two deaths from asthma.

Case 1.—A man aged 42 who had had asthma for nine years and had been on prednisone 5 mg. b.d. for nine months died within a few hours of admission to hospital from status asthmaticus. He had had two previous attacks. Necropsy showed typical mucus plugging of the bronchioles ; the adrenal glands were normal.

Case 2.—A man of 59 who had had flexural eczema and asthma since infancy died at home from status asthmaticus. Necropsy was not performed. During his last three years he had had three attacks of status asthmaticus. He had been on prednisone 5 mg. b.d. for four years.

Status Asthmaticus.—Fifteen patients (4.4%) had repeated attacks of status asthmaticus and 22 (7%) had isolated atacks. Thus status asthmaticus occurred in 37 patients (12%).

Discontinuation of Therapy.—Fourteen patients (4.4%) were able to stop steroid therapy for periods of over six months and another six (2%) up to six months, but all still had mild asthma.

Relief of Symptoms.—Table IV shows the assessment of the severity of asthma before steroids were given and at the most recent interview. It will be seen that 56% of the 317 patients are now in grade 1 or 2—that is, only mild asthma and easily controlled—whereas originally there were none in these grades. There are 23% in grade 3 compared with 16% before treatment. Before steroid therapy was started 84% were in grades 4–6, whereas now there are 21% in these grades. In the M.R.C. (1956b) trial 36% were unable to work and 26% worked part-time only, so that our series contains more severe cases. Our figures show that on steroids

TABLE IV.—*Results with Long-term Steroids. Average Duration of Treatment, 2½ Years*

Grade*	Before Treatment		On Treatment	
	No.	%	No.	%
1	0	0	2	1
2	0	0	174	55 } 56 } 79
3	50	16	73	23
4	166	52	51	16
5	81	26 } 32 } 84	14	4 } 5 } 21
6	20	6	3	1
Total	317	100	317	100

* Grades.—1=No asthma. 2=Mild asthma easily controlled by simple measures. 3=Occasional severe exacerbations, considerably disturbed sleep, otherwise controlled by simple measures. 4=Losing considerable time from work. 5=Unable to work but able to get about. 6=Totally disabled; severely ill.

1% (instead of 6%) were still totally disabled and severely ill ; another 4% (instead of 26%) were unable to work ; and another 16% (instead of 52%) still lost considerable time from work. Thus there is a failure rate of 5 to 21% (depending on the standards set). Even patients assessed as failures claimed some benefit, so we did not feel justified in stopping steroid therapy.

Complications and Side-effects

There were no deaths in this series directly or indirectly attributable to steroid or corticotrophin therapy.

Operations.—Seven major and 24 minor operations were successfully performed under increased steroid dosage and four minor operations were successful without increased dosage.

Pregnancies.—There were nine full-term pregnancies with no maternal or foetal deaths. There were eight normal babies and one hydrocephalic baby with a spina

bifida: the mother of the hydrocephalic child later had a normal baby while on prednisone. There were four miscarriages. Two mothers had toxaemia of pregnancy and had caesarean sections; three women had episodes of status asthmaticus during pregnancy. It was possible to stop therapy in only one case.

Peptic Ulceration.—No cases of perforation occurred. A women of 62 had a small haematemesis and another of 54 had melaena, both from ulceration in a hiatus hernia. Forty-three barium-meal examinations were carried out on 38 patients and six ulcers were demonstrated—four duodenal and two gastric. Five of these ulcers occurred in those on steroids only and one in a patient who had steroids and corticotrophin.

Osteoporosis.—Radiological reports of osteoporosis were made in 32 patients (10.1%) and compression fracture of the spine was found by routine *x*-ray examination in four of these (1% of the series) (see Table V). These four patients did not have back pain and the central nervous system was normal on examination. Four women had fractured ribs, and another woman had an accidental fracture of tibia.

TABLE V.—*Details of Four Patients with Wedge Fractures of Mid-dorsal Vertebrae*

Sex	Age	Steroid and Corticotrophin Therapy	Duration of Therapy in Months
M	69	Cortisone, 25 mg. b.d.	41
		Prednisone, 5 mg. b.d.	5
		Hydrocortisone snuff, 15 mg./day ..	34
F	69	Prednisone, 5 mg. b.d.	31
F	72	Triamcinolone, 4 mg. b.d.	18
M	37	Prednisone, 5 mg. b.d., increased frequently during exacerbations. Corticotrophin 40–80 units weekly	38

Weight Gain.—A gain in weight of over 28 lb. (12.7 kg.) occurred in three patients, 14–28 lb. (6.35–12.7 kg.) in eight patients, and 4–14 lb. (1.8–6.35 kg.) in eight patients. In some the gain was reasonable because they had previously been under weight.

Hypertension.—Three women (aged 61, 54, and 59) developed a moderate degree of hypertension.

Cataract.—A woman of 55 had operations for bilateral cataracts and a man of 39 had a single cataract treated. Routine slit-lamp examination of the eyes was not carried out in patients on steroids.

Triamcinolone Myopathy.—Of the 23 patients on triamcinolone four developed muscular weakness with no objective signs; this soon disappeared on changing to prednisone.

Corticotrophin Allergy.—Of the 96 patients given regular corticotrophin injections, 19 (20%) developed localized oedema.

Other complications were deep venous thrombosis in three patients, oedema in 15, troublesome sepsis in six, mild hirsutism in five, inverted sleep rhythm in 14, sweats in six, Cushingoid state in one, apparent delayed growth in one, and acute pancreatitis with recovery in one. "Steroid purpura" was a common side-effect. No patient developed tuberculosis or adrenal failure, and one of the patients with wedge fractures developed withdrawal syndrome on stopping steroids.

Discussion

Osteoporosis.—Radiologically 32 patients (10.1%) had frank osteoporosis, and four of these had wedging of vertebrae. We have no control group for comparison, so interpretation of these figures is difficult. However, Lindholm (1960) found that 19.7% of 144 patients treated with steroids (one to two tablets daily) for up to six and a half years developed osteoporosis and three (2.1%) had spontaneous vertebral compression fractures. The incidence of osteoporosis was 11% in a control group of asthmatics not given steroids. Livingstone and Davies (1961) found 2.8% of 71 patients developed wedge fractures, but routine *x*-ray films of the dorso-lumbar spine were not taken. *X*-ray films of the dorso-lumbar spine should be taken initially and at intervals of six months in anyone in whom it is intended to use long-term steroids. We now ensure that all our asthmatics consume a reasonable amount of milk and cheese. Some had been avoiding milk as they thought it upset them, and we have the impression that this may have contributed to the osteoporosis in some cases. We give extra calcium, vitamin D, and hormonal therapy in selected cases. Our results suggest that special care is necessary in elderly patients, for three out of four with wedge fractures were 69 to 72 years of age (Table V).

Peptic Ulcers.—The low incidence of new peptic ulcers—1.9% of this series—over the whole period of the survey was surprising. Arnoldsson (1960), in Sweden, carried out routine barium-meal examinations (at intervals of about four months, irrespective of indigestion) and found an annual incidence of 5.3% of new peptic ulcers in patients on steroids, and 5% of asthmatics not on steroids had peptic ulcers at a single examination (Arnoldsson, 1958). That there were no perforations, and the fact that there were only two haemorrhages from peptic ulcers suggests that, with care, the complication of peptic ulceration in steroid therapy need not be a serious risk.

Allergic Reaction to Corticotrophin.—Studies of pituitary adrenal function were not carried out, but there were no obvious differences in the clinical results in the group treated with corticotrophin as well as steroids. The high incidence of allergy (19.5%) to corticotrophin and its attendant risk of death (Arnoldsson, 1958; Pearson, 1958) has influenced us in not now using it routinely, especially as corticotrophin is such an effective treatment for status asthmaticus.

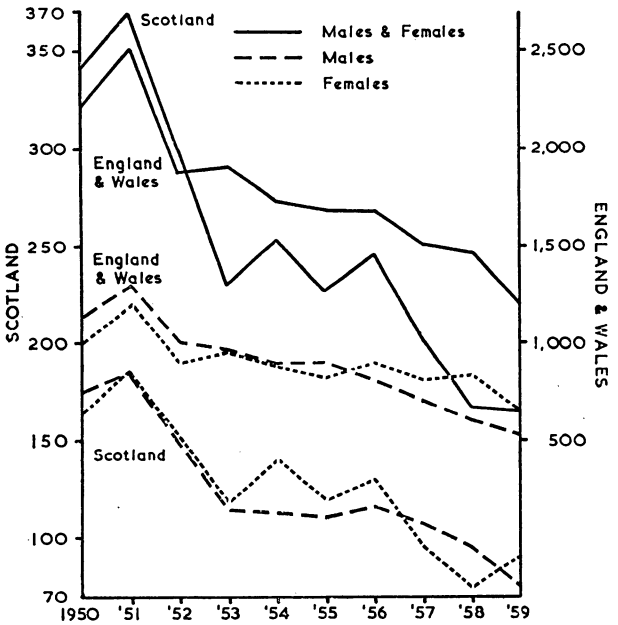
Adrenal Suppression.—Paris (1961), of the Mayo Clinic, after a review of the literature, considered further evaluation necessary to see if intermittent corticotrophin administration during long-term steroid therapy would decrease the severity of complications of post-operative collapse and death. No case of post-operative collapse occurred in this series.

Failure Rate.—The failure rate of 5 to 20% is in agreement with the literature, which records rates from about 10% (Andersson and Bruun, 1960; Phear *et al.*, 1960; Baldwin *et al.*, 1961) to about 30% (Arnoldsson, 1958; Pearson *et al.*, 1961). Our low failure rate may be explained by our care to exclude patients with bronchitis from this series. The causes of failure were repeated chest infections or psychological reasons, but in many there was no obvious cause.

Deaths from Asthma

Before steroids were freely available mortality rates from asthma were reported as being 5% in asthmatics of all ages (Unger, 1945; McCracken, 1950), 7% in those with intrinsic asthma (Rackemann, 1951), and 19% of 32 patients who developed asthma over the age of 35 years and who had recurrent status asthmaticus (Leigh and Rawnsley, 1956).

The Chart shows the death rate from asthma to have halved from 1950 to 1959 (Reports of Registrars-General for England and Wales and for Scotland). In the Cardiff district, the population of which has remained of the same order throughout the period, the number of confirmed deaths from asthma has fallen from 14



Number of deaths from asthma (from reports of Registrars-General).

in 1953 to 2 in 1960 (Table VI), a fall which we believe to be due to the use of steroids. The fall in the national death rate from asthma is also probably due to the increasing use of steroids. Steroids became freely available in 1955 and were in limited supply from 1951 till that year.

TABLE VI.—*Deaths from Asthma in Cardiff District,* 1951 *to* 1960

Year	Male	Female	Total
1951	5	8	13
1952	2	10	12
1953	6	8	14
1954	4	8	12
1955	3	9	12
1956	3	3	6
1957	2	4	6
1958	3	5	8
1959	1	1	2
1960	1	1	2

In this series there were only two deaths (0.6%) from asthma in 317 patients treated for an average period of two and a half years and 42% of whom had had recurrent status asthmaticus. Our previous experience of 3 deaths (9.4%) in 32 patients treated with intermittent short courses of steroids (Williams, 1959) suggests that long-term therapy is better in the severely chronically ill asthmatic. The reduction in the death rate from asthma is a major point favouring the use of steroids in chronic asthma. The two deaths that occurred might possibly have been avoided had the dose of steroids been promptly increased early in the terminal illness. It is important that in severe exacerbations not responding to simple measures the patient should seek medical attention early on, the dose of steroids should be increased, and when necessary antibiotics should be used.

The frequency of status asthmaticus has also been reduced: 42% had repeated status asthmaticus prior to treatment and now only 4.4% have recurrent severe attacks. This reduction in its frequency, particularly in view of its high mortality (Leigh and Rawnsley, 1956, and see above) is another factor favouring long-term use of steroids.

Symptomatic Improvement

The sustained symptomatic improvement on long-term steroids shown in Table IV reflects the considerable symptomatic relief and reduction of incapacity given to a group of patients for whom little could be done without steroids. It is perhaps worthy of mention that we have not found that steroids became ineffective with long-continued use. We have found, as the occurrence of status asthmaticus in some of our cases shows, that from time to time there is a variation in the degree of asthma and sometimes obviously a complete temporary failure, but this is related to factors affecting the asthma, such as stress, naso-respiratory infection, and exposure to allergens such as pollens and mould spores, and not to the duration of steroid therapy.

Dose of Steroids and Weaning

It has been shown that the incidence of side-effects of steroids increases steeply when the dose of prednisolone or its equivalent is above 15 mg. daily (Black *et al.*, 1957), and we have constantly tried to find the minimum effective dose of steroid which, with the free use of an inhaler and/or ephedrine or aminophylline, would allow the patient to lead an active and reasonable life. Only three of our patients were having 15 mg. of prednisone a day, all the rest were having 10 mg. or less. In our series 42% of patients were controlled on half to one tablet daily, which is in accordance with the findings of Shuster and Williams (1961). They found that the therapeutic efficiency of small doses of steroids is due to summation of endogenous and exogenous steroids and that these small doses do not suppress secretion by the adrenal glands.

Whenever the steroids could be discontinued this was done. The difficulties of weaning have been well brought out by Knowles (1961). He found that the most easily weaned patients were those whose asthma was seasonal, and that there was a marked tendency for treatment to be continuous with asthma of late onset —that is, after 30 years of age. It is of course generally accepted that the type of asthma developing or becoming worse in middle age or later is the type particularly apt to become chronic and intractable. Over a half of our patients (54%) were over 50 years and 25% over 60. In the M.R.C. (1956b) trial only 22% were over 50 and none were over 60. We have not included any seasonal asthmatics requiring steroids for three months or less. In only a very small proportion (4.4%) of our series were we able to discontinue therapy and then only temporarily. In a different series one of us (Williams, 1959) found that of 202 patients started on steroids 40% were able to discontinue them.

It depends on the degree of severity and chronicity of the asthma whether or not steroids can be discontinued. Although every effort should be made to discontinue their use, patients should be kept under observation for at least 12 months after this is done, for there is the real risk of death from status asthmaticus (Pearson *et al.*, 1961). Due regard must be paid to their previous state and their liability to status asthmaticus. There is, of course, a constant need to try to find and treat underlying precipitating causes of asthmatic attacks in patients on steroids.

Conclusion

We would agree with Grant (1961) that every attempt should be made to avoid giving steroid therapy continuously, but that in many cases it is the only effective treatment available: some patients can be kept well by occasional short courses, but these are the exceptions in cases of true chronic asthma. The benefits of well-managed corticosteroid therapy far outweigh the risks involved.

Summary

Results and side-effects of prolonged treatment of 317 patients with steroids and corticotrophin are described: in 205 of them for over two years, in 118 for over three years, and in 46 for over four years. All were patients *in whom all other measures of treatment had been tried but had failed.* Patients were given the smallest dose of steroid to keep them reasonably but not totally free from asthma; 58% had one and a half to two tablets of prednisone or its equivalent daily and 42% half to one tablet daily.

It would appear that the long-term use of steroids has reduced the frequency of status asthmaticus and the numbers of deaths from asthma.

Striking clinical improvement occurred in 56%. There was a complete failure of 5%.

There were no deaths attributable to steroids or corticotrophin. Four patients had compression fractures of the spine and two bled from peptic ulceration.

Our experiences suggest that long-term therapy is beneficial in cases of chronically intractable asthma in which all other measures have failed. The serious side-effects are difficult to assess, since we have no control group of asthmatics for comparison, but the benefits obtained seem to outweigh any possible risks.

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ADRENAL FUNCTION AFTER PROLONGED CORTICOSTEROID THERAPY

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Corticosteroid therapy is now being used with increasing frequency for the treatment of a wide variety of disorders. Some of these are diseases which are likely to necessitate the steroid therapy being continued indefinitely, but some of the disorders treated will have a self-limiting course so that the corticosteroid therapy may be eventually stopped.

The adrenal inhibition which results from such steroid therapy becomes important only when the therapy is stopped. That the patient's own adrenal activity should be inhibited during corticosteroid therapy is inevitable unless corticotrophin is given as well. But after the period of steroid therapy has ceased there may persist for a greater or less period of time a sluggishness of reaction of the whole or some part of the pituitary–adrenal axis. The resultant impairment of adrenal function is not easy to assess objectively, but clinical experience suggests that there is a wide individual variation in the rate of recovery (Bayliss, 1958). Indeed, the suggestion was early made (Salassa *et al.*, 1953; Lewis *et al.*, 1953; Hayes and Kushlan, 1956) that impaired adrenal function may persist in some patients for months or even years after treatment has been stopped.

A variety of methods for testing pituitary and adrenal function in such circumstances have been proposed at various times (Forsham *et al.*, 1950; Engleman *et al.*, 1953; Christy *et al.*, 1956; Holub *et al.*, 1959; Amatruda *et al.*, 1960), but these are generally either too difficult to apply to many routine clinical situations or do not sufficiently test out the whole pituitary–adrenal axis. It would be of great clinical value to have some simple way in which to pick out those patients in whom the recovery of adrenal function was delayed, but to be useful it must be one which tests out the whole pituitary–adrenal axis.

A strong natural stimulus to corticotrophin release is provided by an abnormally low plasma cortisol level. This indeed is the basis of the tests using the 11-beta-hydroxylase inhibitor, metopiron (SU 4885). But the same stimulus is automatically provided when the steroid therapy is suddenly stopped, for then the adrenal is atrophic and inert and the plasma cortisol level falls to near zero. Recovery of adrenocortical function and rise of plasma cortisol to normal levels can then occur only if the corticotrophin-releasing centres are sensitive to the stimulus of low plasma cortisol and can act on the adrenal cortex. A spontaneous rise of plasma cortisol to normal levels will thus indicate recovery of pituitary–adrenal function. The only important