1960; Halprin, 1960; Hollander *et al.*, 1960; Russek, 1960; Winsor and Zarco, 1960; Wolffe, 1960) claim excellent results, and it is noted that these are all clinical impressions and lack any adequate control. The results of published double-blind trials with other M.A.O. inhibitors summarized in Table II make sober reading.

TABLE II.—Summary of Double-blind Trials with M.A.O. Inhibitors

Authors	Drug	Result	No. of Cases
Dewar <i>et al.</i> (1959)	Iproniazid	Failure	20
Snow and Anderson (1959)	"	"	41
Fife <i>et al.</i> (1960)	"	"	51
Shoskes <i>et al.</i> (1959)	"	Success	23
Mackinnon <i>et al.</i> (1960)	Pheniprazine	27	
Sandler (1961)	"	Failure	12
Phear and Walker (1960)	Pivazide	"	19
Murphy <i>et al.</i> (1961)	"	"	30
Allanby <i>et al.</i> (1961)	Nialamide	Partial success	28

In the present report more patients were assessed than previously, and a significant number of them found symptomatic benefit from isocarboxazid. The proportion of patients favouring the drug was higher in the severer grades of angina, and if the trial had contained more of the milder cases it is possible that a negative result might have been obtained. It is suggested that further trials should consider only severe grades of cardiac pain. The cardiograph appeared important only in the group with gross ischaemic change short of infarct. The danger of producing infarcts in such persons has precluded any attempt to find out whether aemeliomeration of anginal pain can be of benefit to them. This danger has, of course, been a source of anxiety to many people and requires further investigation.

Summary and Conclusions

In a double-blind trial of isocarboxazid, using the cross-over technique, patients were randomly treated with both the drug and placebo. The trial was conducted sequentially, and was stopped when a decision was reached. In the 55 patients whose responses were recorded isocarboxazid was more effective in a dosage of 10 mg. three times daily than the placebo, 18 cases of moderate to severe angina claiming a marked preference to the drug alone and five with the control. Over half the patients (25 out of 55) did not appear, however, to obtain significant relief with either treatment. Factors suggestive of help from isocarboxazid were: male sex; major ischaemia rather than actual post-infarction changes in the electrocardiogram; and severer grades of anginal pain.

Side-effects were insignificant, and isocarboxazid may be of symptomatic help in some cases of angina pectoris.

I am indebted to Dr. Evan Fletcher for assessing the results on some of his patients and to Dr. P. Gorman and Dr. W. D. Linehan for their valuable assistance. My thanks are also due to Dr. M. Corbett, of Messrs. Roche Products Limited, for supplies of "marplan" and placebo, and to Dr. P. C. Elmes for helpful criticism.

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COMA AS PRESENTING SIGN OF ADRENAL FAILURE AFTER STEROID WITHDRAWAL

A REPORT OF THREE CASES

BY

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Patients with latent adrenal insufficiency may suffer an unexpected adrenal crisis when subjected to stress (Williams, 1955). As a consequence of the therapeutic use of the corticosteroids and the resultant depression of the patients' adrenocortical function, this has become a fairly common occurrence. A surgical procedure has classically been cited as the stress factor, and there have been numerous reports of post-operative collapse, sometimes fatal, in patients who have been on corticosteroid therapy (Fraser *et al.*, 1952; Salassa *et al.*, 1953; *Lancet*, 1957; *Brit. med. J.*, 1959; Smyth *et al.*, 1960).

The purpose of this paper is to record the case histories of three patients who, while on long-term corticosteroid therapy, were admitted to hospital in a semi-comatose state with an acute infection, having concomitantly stopped their therapy. Only one of these presented with features more typical of an adrenal crisis.

Case 1

A 68-year-old white woman first developed bronchial asthma in 1940 and continued to have attacks each year, but these were never severe and were easily controlled. In 1952 corticosteroid therapy was first begun in the form of cortisone in a dosage which varied from 50 to 100 mg. daily. In 1955 cortisone was replaced by hydrocortisone for a few months and then by prednisone in equivalent doses. On this treatment the asthma was well controlled until August, 1958, when she was admitted to hospital in severe status asthmaticus. With the use of steroids, bronchodilators, antibiotics, and sedatives, the attack gradually subsided after six days. After her discharge in September she was maintained on triamcinolone, 12 mg. daily, and remained well until March 16, 1959, when she was again admitted to hospital. She had on that morning developed an acute pharyngitis with a temperature of 103° F (39.4° C.), had vomited, and, as a consequence, had failed to take her usual dose of triamcinolone. Later she had become drowsy,

and when seen at home by the family doctor was found to be in a semi-comatose state with increased tone and exaggerated tendon reflexes in the right upper and lower limbs and a right extensor plantar reflex. A provisional diagnosis of "cerebral vascular accident" was made and she was admitted to hospital.

Examination revealed a semi-comatose patient, responding to painful stimuli but not to questions or commands. The temperature was 102° F. (38.9° C.), pulse rate 96 a minute, and blood-pressure 115/65 mm. Hg (her usual blood-pressure). An acute follicular tonsillitis was present, tendon reflexes were slightly depressed in the left upper and lower limbs, but both plantar reflexes were normal. Further systematic examination of the central nervous system, cardiovascular system, respiratory system, and abdomen revealed no abnormalities. Urine contained acetone but no sugar, the total leucocyte count was 17,500/c.mm., blood urea 28 mg./100 ml., blood sugar 81 mg./100 ml., and the serum electrolyte values were normal. Cerebrospinal fluid was normal in respect of pressure, chemistry, and microscopy. A radiograph of the chest was normal.

Within 30 minutes of admission 50 ml. of 50% dextrose in water and 100 mg. of hydrocortisone (free alcohol) were administered intravenously, followed by an infusion of 1,000 ml. of 10% invert sugar in 0.9% sodium chloride to which had been added 100 mg. of hydrocortisone. Intramuscular penicillin, 1 million units six-hourly, was started, being continued for five days. Within two hours the patient had regained consciousness, was able to converse normally, and was found to have no abnormal neurological signs. The following day oral prednisone was begun in a dose of 5 mg. thrice daily for seven days and was then reduced to 5 mg. twice daily as a maintenance dose. The tonsillitis subsided rapidly and the blood-pressure was maintained at its initial level. The patient was discharged from hospital on March 27, and when last seen, 12 months later, was well.

Case 2

A 54-year-old white woman had a long history of chronic illness. She had a haematemesis in 1945, and when this recurred in 1954 a gastrectomy was performed. Attacks of acute diverticulitis occurred in 1955 and in 1956, and a deep vein thrombosis in 1957. Early in 1957 she developed rheumatoid arthritis, which deteriorated rapidly. In July, 1957, prednisone was instituted in doses of 20 to 30 mg. daily for a few months, after which methylprednisolone, then dexamethasone, in equivalent doses, was substituted. She remained relatively well until April 4, 1959. On that day she gradually became drowsy and confused and later lapsed into a state of semi-coma. It transpired that for 48 hours she had not taken the prescribed corticosteroid, having failed to replenish her exhausted stock of tablets.

On admission to hospital she was in a semi-comatose state, responding to painful stimuli but not to commands or questions. Temperature was 98° F. (36.7° C.), pulse rate 80 a minute, and blood-pressure 125/60 mm. Hg (her usual blood-pressure). Marked wasting was present, and severe rheumatoid arthritis involved the joints of all limbs. The cardiovascular, respiratory, gastro-intestinal, genito-urinary, and central nervous systems revealed no further abnormalities. Urine contained no albumin, sugar, or acetone. The total leucocyte count was 5,200/c.mm., blood urea 36 mg./100 ml., and serum potassium 3.6 mEq/litre; serum sodium, chloride, and bicarbonate levels were normal, and the cerebrospinal fluid was normal in respect of pressure, microscopy, and chemistry.

Shortly after admission hydrocortisone (free alcohol) 100 mg. was administered intravenously. Her mental state improved, and within four hours full consciousness was restored. Oral prednisone was then begun in a dose of 10 mg. thrice daily, and during the next few days the dosage was adjusted to the minimum which afforded relief of symptoms—that is, 5 mg. thrice daily as a maintenance dose. On April 9 a non-productive cough developed, and four

days later fine crepitations were detected in the right lower zone of the chest posteriorly. A radiograph of the chest showed pneumonic consolidation of the right middle lobe and the posterior basal segment of the right lower lobe. Intramuscular penicillin, 1 million units six-hourly, was administered for six days, in response to which the infection subsided rapidly. On April 22 she was discharged from hospital on a maintenance dose of 15 mg. of prednisone daily, and when last seen, 12 months later, was relatively well.

Case 3

A 64-year-old white man developed rheumatoid arthritis in 1941. The condition gradually deteriorated until, in 1952, corticosteroid therapy in the form of hydrocortisone, 60 to 150 mg. daily, was instituted. In 1955 prednisone, 30 mg. daily, was substituted, and gradually over the period of a year the daily dose was reduced to 10 mg., which became the maintenance dose. He remained relatively well until early in July, 1959. On the morning of July 3 he was found unconscious in the lavatory and was admitted to hospital.

It transpired that he had experienced left-sided chest pain for two days, had complained of no other symptoms, and had failed to take the prescribed doses of prednisone for the previous 24 hours. Examination revealed a semi-comatose patient, responding to simple commands but not to questions. Temperature was 101° F. (38.3° C.), pulse rate 100 a minute, and systolic blood-pressure 60 mm. Hg. He appeared cyanosed, and gross rheumatoid arthritis was present. Examination of the chest revealed diminished air entry and scattered crepitations on the left side posteriorly. The cardiovascular, gastro-intestinal, genito-urinary, and central nervous systems revealed no other abnormalities. A radiograph of the chest showed linear atelectasis at the left basal region with consolidation of the left upper and lower lobes. The blood urea was 60 mg./100 ml., plasma CO₂ content 15.1 mEq/l., serum sodium 136 mEq/l., serum potassium 5.6 mEq/l., plasma chlorides 101 mEq/l., and blood sugar 108 mg./100 ml.

Shortly after admission 100 mg. of hydrocortisone (free alcohol) was administered intravenously, followed by an intravenous infusion of 1,000 ml. of 5% dextrose in 0.9% sodium chloride to which had been added 100 mg. of hydrocortisone. Penicillin, 1 million units, was given intramuscularly at six-hourly intervals for seven days. Within an hour of admission the systolic blood-pressure rose to 100 mm. Hg, and within three hours to 120 mm. Hg, at which stage full consciousness was restored. Oral prednisone was begun in a dose of 10 mg. thrice daily for two days. On the following day the blood urea had decreased to 23 mg./100 ml. and the serum electrolyte values were found to be normal. The prednisone was decreased to a maintenance dosage of 10 mg. daily. Within a week the chest had cleared both clinically and radiologically, and on the tenth hospital day the patient was discharged. When last seen, 18 months later, he was well.

Discussion

It is known that during the administration of corticosteroids suppression of endogenous adrenal cortical function occurs (Smyth *et al.*, 1960) and that with prolonged therapy, particularly in high dosage, atrophy of the adrenal cortex may supervene (Ingle and Kendall, 1937). Prolonged steroid therapy results in a slower response by the adrenal cortex to corticotrophin administration than does short-term therapy (Fredell *et al.*, 1955). However, cases have been cited in which adrenocortical suppression occurred after only five days of cortisone administration in a daily dose of 100 mg. (Salassa *et al.*, 1953). It has been suggested that in these and similar cases a state of subclinical latent adrenal insufficiency exists and that steroid therapy of

short duration suppresses the adrenal cortex sufficiently to provoke clinical adrenal failure (Capper and Moser, 1960).

Manifestations of adrenocortical insufficiency may occur after the abrupt withdrawal of steroid therapy, but these are rarely severe and usually subside spontaneously within two to five days (Smyth *et al.*, 1960). However, if steroid withdrawal and a stress situation coexist, symptoms of greater severity or even a frank adrenal crisis may ensue. Usually the stress situation cited in such cases is a surgical procedure, many examples of which are quoted in the literature (Fraser *et al.*, 1952; Salassa *et al.*, 1953; *Lancet*, 1957; *Brit. med. J.*, 1959; Smyth *et al.*, 1960). Other stress situations which have resulted in the same syndrome include parturition, burns, trauma, and a variety of medical illnesses (Capper and Moser, 1960). Stress may provoke an adrenal crisis even without the discontinuation of steroid therapy, and in these cases either an overwhelming infection (Jacobs and Rose, 1955; Medical Research Council, 1956; Pearson, 1959; Stevens, 1960) or a surgical procedure may be the precipitating factor (Smyth *et al.*, 1960). This probably results from the inability of the suppressed adrenal cortex to respond to the increased demand made upon it to meet the increased requirements of the body occasioned by the stress. An increased dosage of steroid immediately before and during an operation is therefore advised in patients on long-term therapy (Smyth *et al.*, 1960).

Reduced adrenocortical function may persist for some years after discontinuing steroid therapy, and an adrenal crisis has been described in a stress situation in a patient whose steroid therapy of six months' duration had been discontinued three years previously (Capper and Moser, 1960). There is therefore no apparent correlation between the advent of an adrenal crisis and the period of time that steroid therapy has been withheld. This is particularly interesting in the light of histopathological studies which have indicated that regenerative changes are evident in the human adrenal cortex as early as 17 to 51 days after steroid withdrawal (O'Donnell *et al.*, 1951). However, it is difficult to evaluate whether the restoration of functional activity corresponds with the structural improvement. It would appear, therefore, that the dose of steroid used is probably not as important a factor in influencing the production and severity of adrenocortical suppression as is the duration of therapy. Moreover, any patient who has received, or is receiving, steroids is liable to the hazards associated with the resultant adrenocortical suppression.

The main features of the Addisonian crisis are symptoms of severe weakness, vomiting, diarrhoea, and sometimes abdominal pain, with a fall in blood-pressure and the development of circulatory collapse. Loss of consciousness has rarely been cited as a manifestation except as a pre-terminal event (Soffer, 1956), and does not appear to have been recorded previously as a presenting manifestation.

The three cases described above are unusual in that loss of consciousness was the presenting manifestation. Prompt recovery followed hormone replacement in these cases and it is therefore reasonable to assume that adrenocortical insufficiency was present and was responsible for coma. In an adrenal crisis coma might be expected to be associated with severe circulatory collapse or with a state of hypoglycaemia, but neither of these factors appeared to have operated in at least

two of the above cases, and in the third case it is doubtful whether circulatory collapse was severe enough to be wholly responsible. To explain the onset of coma, a cerebral electrolytic and metabolic disturbance may possibly be incriminated. In this connexion the influence of the adrenocortical hormones on the central nervous system has been extensively studied (Timiras *et al.*, 1954; Hoagland, 1955; Woodbury, 1958).

In adrenalectomized animals the plasma sodium level decreases and the plasma potassium level increases, whereas the total brain sodium concentration increases greatly with no change in potassium concentration; thus the ratios of extracellular to intracellular sodium and of intracellular to extracellular potassium are decreased. The accompanying increased brain excitability which has been noted might account for spontaneous seizures which may occur in adrenal crises. The E.E.G. (Engel and Margolin, 1942), which is characterized by diffuse slow activity with frequencies of 2 to 6/sec. and voltages higher than those of alpha-waves, may revert to the normal pattern after administration of corticosteroid. The cerebral metabolic rate is decreased, and this, too, appears to be related to the E.E.G. changes. In addition, the central conduction time is decreased. In the cases described above relatively normal serum electrolyte values were found, and it is therefore difficult to relate the coma, in these cases, to the electrolytic and metabolic disturbances which have been observed, although these serum values might not be a reflection of brain electrolyte changes.

Experimental and clinical investigations indicate that corticosteroid administration results in suppressed secretion of endogenous A.C.T.H., and it has been suggested that this is a factor in the production of the steroid withdrawal syndrome (Holub *et al.*, 1959; Amatruda *et al.*, 1960). It is of interest that, in contrast to primary adrenocortical failure, hypopituitarism is often associated with coma. Hypopituitary coma is probably due to a variety of factors, most of which can be ascribed to lack of thyrotrophin and corticotrophin, with resultant suppression of thyroid and adrenocortical function (Caughey, 1958). Shock invariably precedes coma in most adrenal crises described in the literature, whether these be due to primary adrenocortical disease or to iatrogenic adrenocortical insufficiency. In hypopituitary coma, however, hypotension does not usually appear to be an important factor (Caughey, 1958; Blau and Hinton, 1960). In the light of these observations, it may be postulated that in Cases 1 and 2 pituitary failure might have played an important part in the production of coma since both these cases were characterized by the early onset of coma with no associated hypotension at any time.

A point of interest in the above cases is the fact that the infection was not particularly severe. In fact, the infection in Case 1 was of a relatively mild type and in Case 2 was probably in a very early stage when the patient first presented. It is extremely unlikely that steroid withdrawal alone would have produced an adrenal crisis in these patients in the absence of acute infection. This serves to emphasize the fact that a minor illness which ordinarily would give little cause for concern can cause an alarming presentation when the functional activity of the adrenal cortex is in a state of suppression. It would be fair to assume that early recognition and treatment of the condition probably prevented the development of the more classical features of an adrenal

crisis. The use of the steroids is such common practice to-day that in cases of unexplained coma the possibility of adrenocortical insufficiency due to steroid withdrawal and an accompanying infection should be suspected.

Summary

Loss of consciousness was the presenting manifestation in three patients who while being maintained on long-term steroid therapy developed an acute respiratory infection and concomitantly discontinued their medication.

Prompt recovery occurred after corticosteroid administration, and it is postulated that the loss of consciousness was due to acute adrenal insufficiency occasioned by steroid withdrawal and the stress of infection.

It is suggested that in cases of unexplained coma the possibility of adrenocortical insufficiency due to withdrawal of steroid therapy and a concomitant stress situation should be suspected.

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A survey made to study the fate of the radioactive waste discharged into the River Thames from the Atomic Energy Research Establishment at Harwell shows that a significant amount of the caesium-137 so released is absorbed on the river bottom. This effectively reduces the concentration of this radionuclide in London's drinking-water. Enhanced activity on the river bed exists for many miles below the outfall but is not sufficient to raise radiation levels in air significantly above background at any point. (H.M.S.O., price 4s. net.)

MANAGEMENT OF THE SECOND TWIN

BY

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Argument continues unabated on whether the second twin is at greater risk than the first. Confusion arises because of conflicting reports from various eminent centres. Bender (1952), of Liverpool, and Potter and Fuller (1949), of Chicago, stated that there was no increased risk for the second twin, and Chassar Moir (1956) wrote that there was no increased stillbirth rate among second twins in Oxford. On the other hand, many authorities reported a second-twin loss up to twice that of the first (Munnell and Taylor, 1946; Corston, 1957). Tow (1959), of Belfast, and Little and Friedman (1958), of New York, found neonatal deaths more than twice as common among second twins.

There is also dispute about the management of the second twin, particularly as to the best delivery interval. Greenhill (1955) advocated waiting an hour before rupturing the membranes in the absence of complications, but in 1960 he reduced this to 15 minutes. A tendency to shorten the delivery interval is seen throughout the current literature except in a report by Danielson (1960), who thought it acceptable to wait two hours.

The present investigation was undertaken to see if there was any increased risk for the second twin, and also to find out the best way of managing the second delivery. A series of 500 consecutive twin deliveries at the Royal Maternity Hospital, Glasgow, from 1953 to 1958 have been analysed (497 patients with twin pregnancies were delivered in the hospital during that time, and the first three cases from 1959 were taken to make up the 500). Every case-sheet was studied individually by me, and the paediatric reports were also consulted where necessary, in order to make the assessment as uniform and accurate as possible.

Incidence and Mortality

A total of 20,369 patients were delivered in the hospital during the same period, giving an incidence of twin deliveries of 1 in 41, a figure which emphasizes the high rate of abnormal cases in the hospital. The vast majority of patients belonged to social classes III to V and approximately 80% were booked.

There was no maternal death in the series and the gross perinatal mortality, including infants born alive before 28 weeks, was 12.5% (cf. 8.3% for the hospital as a whole). This compares with 9.2% (Little and Friedman, 1958), 28.1% (Munnell and Taylor, 1946), 14% (Potter and Fuller, 1949), 11% (Bender, 1952), and 12.3% (Tow, 1959).

Table I shows the stillbirths and neonatal deaths of the first and second twins. For mechanical reasons macerated babies seem more likely to come second, and, in fact, on two occasions in this series the macerated

TABLE I.—Stillbirths and Neonatal Deaths

	First Twin	Second Twin
Fresh stillbirth	13	14
Macerated	15	24
Neonatal	26	33