infrequently remains unsatisfactory (Wilkinson, 1948), and the neurological state is not prevented from deteriorating (Davidson, 1948 ; Israëls and Wilkinson, 1949). Since then Fuld (1950) and Schwartz *et al.* (1950) have reported poor haematological and neurological results with folic acid therapy. The latter reported 72 cases followed for three and a half years and treated with 5 mg. of folic acid daily: 23 cases developed cord degeneration, in 23 the red cell count and marrow showed relapse, and in 9 cases both occurred. Subacute combined degeneration of the cord has been reported as occurring with doses varying between 5 and 25 mg. daily. In the present case 3 mg. daily was enough to produce a considerable improvement in the blood condition, but did not prevent the rapid development of paraplegia.

In at least two large series folic acid has been given to normal subjects and to cases of anaemia other than pernicious anaemia (Weissberg *et al.*, 1950 ; Harvey *et al.*, 1950). There was no subsequent development of cord degeneration, and it is thus unlikely that folic acid has any direct toxic effect. The following reports of authors who have had the opportunity of observing large numbers of cases of Addisonian anaemia contain statements which suggest that they have not rejected the possibility that folic acid actually precipitates cord disease. Thus the explosive character of the onset of cord disease, as well as its rapid progression, have been more often noted after folic acid therapy, and have been contrasted with the more insidious disease previously described (Davidson, 1948 ; Wilkinson, 1948 ; Ross *et al.*, 1948 ; Jacobson *et al.*, 1948). The present case also showed these more acute features.

The experience of Conley and Krevans (1951) is interesting, being more akin to the present case. These authors saw 10 patients in 1950 who were suffering from undiagnosed Addisonian anaemia. Five had only neurological symptoms with no associated anaemia, and on this account various diagnoses, such as disseminated sclerosis and syphilis, were entertained. It was established that four out of the five had been given multivitamin preparations containing folic acid. The patients were not aware that they had received anti-anaemic treatment, and in two cases the physician prescribing the capsules was unaware that they contained folic acid. In all cases an excellent response to vitamin B_{12} was obtained. It was therefore suggested that in all doubtful cases a marked improvement in nervous system signs and symptoms following the injection of vitamin B_{12} provides strong support for a diagnosis of Addisonian anaemia.

The arguments against the inclusion of folic acid in polypharmaceutical preparations may be summed up as follows: (1) Folic acid temporarily improves the blood picture, and may restore it to normal. The physician is then faced with a disease of the central nervous system, the misdiagnosis of which is likely, as subacute combined degeneration of the cord without anaemia is very uncommon. (2) The relief of the general symptoms of pernicious anaemia often reassures the patient and the doctor, and masks the deterioration of the nervous system. (3) Folic acid deficiency occurs infrequently, and there is no need for this substance in multivitamin or iron preparations. (4) The question whether folic acid actually precipitates cord degeneration is still uncertain.

Summary

A case is described in which a proprietary preparation of iron containing folic acid was given to a patient with an anaemia which had not been accurately diagnosed. In fact, the patient was suffering from Addisonian anaemia. Deceptive improvement in the blood condition occurred, but was accompanied by the rapid development of combined degeneration of the cord.

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Medical Memoranda

Carbon Dioxide Retention Simulating Curarization

Numerous reports have appeared of persistent curarization after the use of one or other of the relaxants ; the following case therefore seems worthy of description.

CASE REPORT

The patient, a child aged 6, weighing 42 lb. (19 kg.), had undergone a laparotomy for the removal of a polyp from the sigmoid colon.

The premedication consisted of pentobarbitone sodium, 2 gr. (0.13 g.), and atropine, 1/100 gr. (0.65 mg.), following which the child arrived at the theatre asleep. Anaesthesia was maintained with nitrous oxide and oxygen and a trace of ether, a size 3 endotracheal tube having been inserted. The flow was at the rate of 3 litres of nitrous oxide and 2 litres of oxygen a minute. No absorber was incorporated. Just before opening the peritoneum 2 mg. of decamethonium iodide was given intravenously. After a brief period of apnoea respiration returned and was accompanied by a satisfactory degree of relaxation. (The respiration was assisted throughout.) Some 15 minutes after the first dose a second injection of 2 mg. of decamethonium iodide was given. This time the apnoea persisted for 15 minutes, and at the time of the skin closure only minimal diaphragmatic respiration was present.

After an interval of five minutes, respiratory activity, although minimal, appeared just sufficient to keep the child a good colour, provided pure oxygen was given through a T-piece connected to the endotracheal tube. The child was therefore returned to bed with a flow of 5 litres of oxygen a minute passing through the T-piece, and inflation by means of a bag was carried out for one-minute periods every five minutes.

Respiratory activity did not increase, although the child at all times remained a very good colour, there being no evidence of suboxygenation. After two hours it was noted that, if anything, respiratory activity was decreasing again, but that there was some improvement after each period of ventilation. There was no response at all to an intravenous dose of 2 ml. of nikethamide. The delay in recovery of respiration had until this time been attributed to a residual effect of the decamethonium iodide ; but it was noted that such respiratory effort as was present was not marked by any urgency, neither was it accompanied by a tracheal tug, both of which features are usually present in cases of residual curarization.

Three hours after the injection of the second dose of decamethonium iodide, on the supposition that carbon dioxide accumulation might be the underlying cause of the respiratory depression, the child was vigorously hyperventilated through an absorber for a period of three minutes. The absorber very rapidly became intensely hot, indicating considerable elimination of carbon dioxide. Promptly following this hyperventilation the child's respiration was noted

to be greatly increased in depth, and therefore a further three-minute period of hyperventilation through the canister was undertaken. At the end of this the child's respiration was noted to be normal in depth and character. The endotracheal tube was therefore removed, and an airway was substituted. No further oxygen administration was required.

COMMENT

The remarkable features of this case appear to be: (1) Persistent respiratory paralysis, apparently due to the residual effect of a relaxant, seems to have been caused by carbon dioxide retention. Possibly an increased carbon dioxide tension is capable of producing myoneural block. (2) The child did not recover consciousness for some four hours, although recovery would normally have been anticipated within one hour after operation; it therefore seems likely that the degree of carbon dioxide retention was sufficient to produce narcosis.

It is unfortunate that carbon dioxide estimations were not possible in this case. The difficulty of the treatment of prolonged respiratory depression is illustrated. Such depression has been attributed to hyperventilation: it now appears that underventilation also may perpetuate respiratory depression. It is possible that an electronic apparatus may in future be devised which, by means of an electrode inserted into the tissues, may give continuous measurement either of *p*H or of carbon dioxide concentration. Such an instrument would obviously be of the greatest value in cases requiring controlled ventilation.

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A Possible Method of Pre-operative Anticipation of Thrombo-Embolic Episodes

In recent years major advances have been made in the preparation of patients for the stress and eventualities of surgical procedures, and many previously fatal secondary factors can now be evaluated and corrected pre-operatively to prevent a fatal outcome. Not so post-operative thrombo-embolic episodes: the majority still occur apparently unexpectedly and in spite of increasing awareness of the condition and diligent attempts to anticipate its occurrence.

Ochsner has shown that approximately 50% of pulmonary emboli occur in patients without recognizable preceding peripheral stigmata. Sulamaa and Pentti (1949) reported 170 cases of thrombo-embolic disease, 20 being fatal pulmonary emboli: of the latter, 14 were not diagnosed or were not suspected before their occurrence. Felder (1949) reported 27 cases of pulmonary emboli; in 10 the chest and peripheral signs occurred simultaneously and in 11 cases the chest signs were the first indication. In 78% of his cases treatment began after the chest signs were manifest.

Active prophylactic therapy, excluding routine use of anticoagulants, has not lowered the incidence; 0.57% of patients are liable to pulmonary infarction and 0.22% to fatal pulmonary emboli. A perusal of gastrectomy fatalities shows that about 20% are due to pulmonary emboli.

It is thus the more apparent that pre-operative diagnosis of the thrombophilic type of patient would present a major advance in the selection of those patients who require post-operative anticoagulant therapy. At present it would be unwise to adopt routine anticoagulant treatment owing to its cost, its sequelae, and the labour involved.

It seems reasonable to postulate that clotting *per se* is a normal physiological accompaniment to wound-healing, and that in association with any trauma, definitive or accidental, there is a general and a local mechanism which ensures clotting at the breaches in vascular continuity; likewise, this process is graded in degree to meet the local requirement, and its duration should be proportional to the initial lesion. This effector mechanism has already been discussed in detail by many authors, and no useful purpose will be served by repeating their observations.

Previous attempts have been made to prevent patients from developing thrombo-embolic episodes—the construction of a coagulation graph post-operatively and detection of fibrinogen B in the plasma (Cummine and Lyons, 1948). Ochsner also propounded the theory of a lowered antithrombin titre, and advocated the use of alpha-tocopherol and intravenous injections of calcium to raise a lowered titre. No case selection was made, and such a method, even if it proved to be effective, would be costly and, like coagulation-graph charting, could be conducted only in well-staffed institutions. If it could be foreseen which patients were liable to thrombo-embolic phenomena, active measures could be taken with this smaller group.

It is possible that an increased post-operative clotting tendency is a function of the general response of the body to the strain applied to it by a surgical operation and that the degree of clotting is an indication of adrenal cortical function. During recent years there have been increasing records of spontaneous thromboses and embolic phenomena occurring during cortisone therapy. Cosgriff (1951) recorded the increased coagulability of the blood during treatment and an unexpectedly high incidence of thrombo-embolic complications. The patient liable to post-operative thrombotic episodes may thus respond abnormally to stress or prolongation of the post-operative state.

Godlowski (1951) demonstrated that changes in the eosinophil count could be modified by the administration of heparin, and this suggested that such changes may bear some relation to blood coagulability. Post-operative eosinophil counts were charted on several cases, but the results were not uniform.

An effective reproduction of stress to the body can be secured by the adrenaline test, as used extensively in America to ascertain the resistance to stress of a patient about to undergo a given major operation.

Adrenaline hydrochloride, 0.3 mg., was given to pre-operative patients, and their clotting-times and eosinophil counts were recorded half-hourly during the next four hours. It was found that varying results were obtained. These same patients had coagulation graphs taken post-operatively and were examined clinically for thrombotic stigmata. In all, about 50 patients have been examined and a certain pattern is developing.

The majority of those patients examined showed a rapid shortening of their coagulation time during the first hour and then a fairly quick return to normal time inside the four-hour period of examination. Six of them showed a shortened coagulation time, but it persisted at a low level and was still present after six hours. They also were followed up post-operatively, and all six developed thrombotic episodes, two of a major nature and one fatal. The other patients demonstrated shortening of their coagulation time for four days and then elongation to normal.

All patients were treated identically: pre-operative and post-operative physiotherapy, early rising, and routine examination for tender calf muscles and calf-muscle spasms. The duration of stay on the operating table was almost identical, and the operative procedures were of a similar magnitude and location.

Application.—Given forewarning of subjects who are likely to develop post-operative thrombotic episodes, it is possible to provide selective treatment with anticoagulants 24–48 hours after operation; and, in the event of the discovery of a more innocuous replacement therapy on the lines of the antithrombin hypothesis, treatment could be given post-operatively to those subjects showing a suggestive adrenaline response and liable to undergo major surgery.

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