an anticoagulase antigenically distinct from either M₁ or D₂. It is apparent also that their clinical state does not depend on the serum-anticoagulase level, whether naturally or artificially induced; for whereas Patients F and G, who had titres of 320, were much improved, Patient C with a titre of 160 showed no improvement whatever. It was therefore demonstrated that the low alpha-haemolysin titres in untreated patients were not, as at first thought, accompanied by similarly low anticoagulase titres, for the titration of patients' sera with coagulase from their own organisms revealed some titres greater than 1 in 320. The situation is further complicated by the knowledge that a number of patients all infected with the same organism, phage type 80, showed no constant pattern of anticoagulase response, and it seems that the antigenicity of coagulase is almost strain-specific, so that the types of coagulase administered would be of benefit only to those few patients infected with the same antigenic types of staphylococcus.

TABLE V.—*Anticoagulase Titres on a Post-immunization Serum Sample from Seven Patients, Showing Discrepancy Between the Titres of the Different Antigenic Types, and Their Clinical Course. (Follow-up Results Expressed as Serial Figures According to the Scheme Detailed in Text)*

Patient	M ₁ Anti-Coagulase Titre	D ₂ Anti-Coagulase Titre	Own Staph. Coagulase Titre	Follow-up Result During Year	Clinical State During Year
A ..	0	0	7.5	2233	Not improved
B ..	40	20	0	0303	Improved
C ..	20	15	160	3333	Not improved
D ..	240	480	40	3333	Not improved
E ..	60	120	0	3322	Not improved
F ..	10	7.5	320	1003	Improved
G ..	40	80	320	0000	Cured

Conclusion

A high spontaneous-cure rate for furunculosis has been revealed, but neither alpha-haemolysin nor coagulase toxoids have proved better preventives than the placebo. There seems to be an essential similarity between the results of alpha-haemolysin and coagulase immunization in that both appear to give antitoxic rather than antibacterial protection. They both prolong the survival time in animals but do not give complete protection against staphylococcal challenge and afford no benefit when used as immunizing agents in chronic furunculosis. It is probable that no single protective antitoxic antigen exists, and that the answer lies in polyvalent somatic antigens such as those used by Greenberg and Cooper (1960) in animal experiments or in the teichoic acids, a new class of bacterial antigens discussed by Sanderson *et al.* (1961).

Summary

Alpha-haemolysin and coagulase toxoids and a placebo were given to three groups of patients suffering from chronic furunculosis and their subsequent clinical course was followed for one year.

Statistical analysis showed that neither form of treatment was better than the placebo. A high spontaneous-cure rate was observed.

The significance of alpha-haemolysin and coagulase antibodies before and after immunization and their relation to the clinical state are discussed. It is concluded that immunity to staphylococcal skin infection is independent of these factors, and that the antigenicity of coagulase is almost strain-specific.

It is suggested that antitoxic immunity is of no prophylactic value and that somatic antibacterial immunization may be more effective.

I wish to acknowledge my indebtedness to the late Dr. E. S. Duthie, of the Royal South Hants Hospital, Southampton, and the general practitioners of the Southampton area, where most of this work was carried out. I also thank Dr. J. Ungar, of Glaxo Laboratories Ltd., and his staff for their help and for supplying free of charge their staphylococcus toxoid and the placebo. Thanks are also due to Dr. C. H. Lack, of the Pathological Department, Royal National Orthopaedic Hospital, Stanmore, where this work was completed.

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POST-OPERATIVE HYPOTENSION DUE TO PAROXYSMAL ATRIAL TACHYCARDIA WITH BLOCK

BY

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AND

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In recent years attention has been drawn to paroxysmal atrial tachycardia with block (P.A.T.B.) as a particularly dangerous yet common and often unrecognized complication of digitalis therapy. Despite a description of this arrhythmia by Sir James Mackenzie (1910), it received little attention until the publications of Lown and Levine (1955, 1958).

In this paper we draw attention to possible difficulties in the use of digitalis post-operatively, and describe an example of digitalis-induced P.A.T.B. after gastric surgery in a patient with potassium depletion.

Case Report

The patient, a woman aged 82, had had intermittent dyspeptic symptoms for over 45 years.

Two years ago she was admitted to hospital with acute abdominal pain; a straight film of her abdomen showed the presence of subdiaphragmatic gas, and she was presumed to have a perforated peptic ulcer. She made an excellent recovery on gastric suction and antibiotics. At that time she complained of minimal exertional dyspnoea but there was no history suggesting coronary insufficiency. She had multiple extrasystoles, her blood-pressure was 190/80, and she had a soft apical ejection murmur. There was no clinical evidence of

cardiac decompensation. Minimal enlargement of the heart was visible on chest x-ray examination; E.C.G. showed sinus arrhythmia and supraventricular ectopics (Fig. 1 A). Barium studies confirmed the presence of a chronic duodenal ulcer, and her response to a maximal histamine test of gastric secretion was 20.2 mEq HCl in one hour.

FIG. 1.—Electrocardiogram taken from lead V1.

She was readmitted in 1962 with acute abdominal pain, vomiting, and marked dehydration, and a history suggestive of duodenal ("pyloric") stenosis for about one year. Free gas was not visible under the diaphragm on this occasion, but she was again presumed to have had perforation of her ulcer and was again treated conservatively. She was noted to be in sinus rhythm with extrasystoles as before, and there was no evidence of cardiac failure.

One month later, while still in hospital, vomiting became more frequent, and a barium-meal examination showed a moderate degree of duodenal stenosis. At this stage she became dehydrated and required intermittent intravenous therapy; a mixture of normal saline and 2.5% glucose was used, as dictated by estimations of serum electrolytes.

When transferred to the gastro-intestinal unit for surgery, she was thought to have a moderate degree of potassium

FIG. 2.—Serum electrolyte levels before and after surgery.

depletion; she was extremely tired, weak, and apathetic. Her weight was 48 kg. She was still dehydrated, but her skin had a curious oedematous feeling; there was no peripheral oedema, however, or any clinical evidence of cardiac failure. Her heart rate was 90/min., and sinus rhythm with extrasystoles was present. Serum electrolytes (Fig. 2) were within normal limits, but her clinical state was thought to be due to potassium depletion in which intracellular potassium had been partially replaced by sodium; this impression was supported by a three-day balance study carried out during replacement of her potassium losses (Fig. 3). During this period intermittent gastric suction was carried out; she received a total of 11 litres of 2.5% glucose containing 234 mEq K^+ in the form of potassium chloride. Despite a complete absence of sodium

intake over this period she excreted a total of 310 mEq Na^+ in her urine.

She was now considered to be fit for operation, and in view of her age and the moderate acid secretion the duodenal stenosis was relieved by a simple posterior gastro-enterostomy.

Post-operative Course

The immediate post-operative course was satisfactory. She was given 1.5 litres of 2.5% glucose intravenously in the first 24 hours; no additional electrolyte therapy was used.

Eighteen hours after operation her condition suddenly deteriorated; she became unresponsive to questions and her blood-pressure fell (Fig. 4). Atrial fibrillation was present with a ventricular response of 150/min. (Fig. 1 B). She was given 0.5 mg. of digoxin intravenously and 0.5 mg. intramuscularly.

FIG. 3.—Metabolic balance of water, sodium, and potassium for three days before surgery; intake for the prior two days shown for comparison. Intake charted upwards from baseline and output downwards from intake level. Positive balance appears above the baseline (cross-hatched) and negative balance below the line (shaded). Contribution by gastric aspiration to the sodium and potassium balance is indicated by the lower segment of the output.

FIG. 4.—Blood-pressure in the post-operative period. The rise in blood-pressure is coincident with reversion of P.A.T.B. to sinus rhythm by intravenous potassium chloride.

Six hours later she had improved; her peripheral circulation was more effective and she responded to questions. The ventricular rate was still 120/130 min., and she was given a further 0.75 mg. of digoxin by intramuscular injection over the next 18 hours.

Thirty-six hours post-operatively her condition again deteriorated; she became unconscious and her extremities were cold and clammy. Her blood-pressure had fallen further; fibrillation was still occurring rapidly at 130/140 min. The administration of pressor agents and of more digoxin was considered. However, an E.C.G. at this point showed paroxysmal atrial tachycardia with a varying degree of AV block (Fig. 1 C). Despite a urinary output of 220 ml. for the previous 24 hours, and normal serum potassium levels, she was given 26 mEq K^+ intravenously in 40 minutes (in the form of 2 g. of potassium chloride in 300 ml. of 2.5% glucose). The cardiac rhythm immediately reverted to a regular sinus type, confirmed by electrocardiography (Fig. 1 D). At the same time the clinical signs of shock became less marked, the blood-pressure rose, and her peripheral circulation improved considerably (Fig. 4).

She was continued on intravenous therapy with 60–70 mEq of potassium daily for a further 48 hours, and then started on a light diet. The digoxin was continued in a dose of 0.25 mg. b.d. for a further four days. Apart from a transient episode of atrial fibrillation on the eighth post-operative day she remained in sinus rhythm. Her further progress was uncomplicated and she was discharged ambulant on the twenty-second day after operation.

Discussion

The association of potassium deficiency with chronic duodenal stenosis is well recognized (Black and Jepson, 1954). In the case described here a probable deficit of total body potassium was aggravated by prolonged intravenous therapy with a saline/dextrose mixture based on serum electrolyte levels. This was confirmed by the metabolic balance (Fig. 3). Over a period of 72 hours of potassium replacement the patient retained 111 mEq of potassium from a total of 234 mEq administered; the urinary loss over this period was 86 mEq, and 37 mEq was lost by aspiration; no faeces were passed throughout this period. On the day prior to operation she continued to retain potassium, and it seems likely that surgery was undertaken after inadequate correction of the potassium deficit.

The relationship between potassium metabolism and digitalis sensitivity has been clarified by Lown *et al.* (1960). The use of potassium salts to counteract cardiac arrhythmias was described by Sampson *et al.* (1943); it was noted that their action was more effective when the disturbance of rhythm was caused by digitalis. At first this was thought to be a non-specific pharmacological effect; however, from recent work it appears more probably a physiological restitution of a myocardial potassium depletion.

Lown and Levine (1955) demonstrated that in a group of uraemic patients extraction of body potassium by haemodialysis in subjects on maintenance digitalis therapy was sufficient to induce signs of toxicity, including atrial tachycardia with heart-block. In a control series such complications did not ensue. The use of chlorothiazide and similar diuretics, which are easily administered and have a powerful potassium-losing effect, has been blamed for the apparent increase in frequency of P.A.T.B. (Harris *et al.*, 1960). Other causes of potassium loss in which caution in the use of digitalis has been recommended (Oram *et al.*, 1960) include vomiting, diarrhoea, blood loss, renal disease, the diuresis of uncontrolled diabetes, and the use of steroid therapy. Lown *et al.*

(1951) stated that increased sensitivity to digitalis was found after acute myocardial infarction and pulmonary embolism, and during acute infections. They concluded that this was probably due to the negative potassium balance arising in these conditions as part of the body response to acute stress.

A metabolic stress response is an invariable effect of operation. There are no reported human or animal studies of the complex effects of operation on the digitalized patient (Lown *et al.*, 1960). Despite this, certain deductions are possible. The metabolic response to operations includes a phase of sodium retention and of increased potassium loss in the urine, often maximal on the first post-operative day (Moore and Ball, 1952); these effects are, in general, more marked in chronically ill patients. They are accompanied by hyponatraemia and a tendency to elevation of the serum-potassium level which may indicate shift of potassium out of the cells and its intracellular replacement by sodium.

Digitalis interferes with active ionic transport across the muscle cell membrane. Where there is no electrolytic imbalance this action of digitalis is of little moment (Draper *et al.*, 1962). However, it may be inferred that when the intracellular concentration of potassium is low any such toxic action might be critical, in that it interferes with an already overloaded cell-membrane-restoring mechanism; hence a state of so-called digitalis sensitivity ensues which should be theoretically offset by the restoration of the ionic gradients across the membrane, in particular potassium. Serum-potassium levels are no index of this gradient, and even a complete metabolic balance of intake and loss allows only conjecture about the values at a cellular level. In the case reported the pre-operative potassium deficit and the intracellular potassium loss induced by the metabolic response to trauma combined to leave the myocardium in a state of digitalis sensitivity.

Lown *et al.* (1951) measured the urinary loss of potassium after mercurial-induced diuresis in patients with cardiac failure. The response to a standard dose of acetyl strophanthidin (a rapidly acting cardiac glycoside) was contrasted before and after the diuresis. After potassium losses of 80–85 mEq they found the dose of strophanthidin required to produce signs of toxicity was approximately halved. These workers made no attempt to determine the overall potassium balance before the artificially induced diuresis. However, a negative balance of this magnitude is frequently observed a few days after trauma (Moore and Ball, 1952). It must be expected that digitalis sensitivity may occur after major surgery due to potassium loss.

The treatment of choice when this arrhythmia is due to digitalis intoxication would appear to be the administration of potassium chloride. Lown and Levine (1955) state that P.A.T.B. not due to digitalis will not respond to potassium; in the case described the prompt return to sinus rhythm after intravenous potassium is further evidence that the arrhythmia was induced by digitalis. The maintenance of digitalis therapy after control of P.A.T.B. was considered advisable in view of the patient's cardiac status during the period of atrial fibrillation. Although most authorities advise complete withdrawal of digitalis therapy when P.A.T.B. appears, we concluded that elevation of the myocardial threshold to the glycoside by potassium supplements would enable satisfactory digitalization to be maintained until the immediate post-operative period was passed.

Summary

A case of post-operative hypotension due to paroxysmal atrial tachycardia with block is described. It was due to digitalis intoxication in the presence of potassium deficiency, and the possible aetiological factors include the normal metabolic response to trauma.

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PITUITARY-ADRENAL FUNCTION IN CASES OF PITUITARY TUMOUR

BY

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The technical difficulty of measuring adrenocorticotrophin (A.C.T.H.) accounts to a large extent for the paucity of reliable information on the incidence of impaired pituitary-adrenal function in patients with pituitary "chromophobe" adenoma† despite its obvious clinical importance. Clinical and biochemical differences between primary and secondary adrenal insufficiency, possibly complicated by abnormalities of gonad, thyroid, and somatotrophic function, make interpretation of standard laboratory procedures for adrenal function difficult or impossible.

Adrenal insufficiency may develop as part of the syndrome of panhypopituitarism, but this is uncommon with pituitary chromophobe adenoma. Most patients with pituitary adenoma first present with visual failure; clinical evidence of endocrine dysfunction, either objective or symptomatic, is seldom pronounced (Younghusband *et al.*, 1952; Nurnberger and Korey, 1953; Troen and Rynearson, 1956). More particularly, the classical features of Addison's disease—that is, cutaneous pigmentation, muscular weakness and wasting, anorexia, gastro-intestinal upsets, cramps, asthenia, hypotension, hypoglycaemia, and abnormalities of electrolyte balance—are rare. Tests of carbohydrate metabolism and measurement of urinary steroids are often normal, but water diuresis, a more sensitive but non-specific index of pituitary-adrenal function, is frequently impaired (Jefferson, 1957b; Heimbach, 1959). At post-mortem examinations the adrenals more often appear normal in size or large than small and atrophied (Russfield *et al.*, 1956).

In an attempt to obtain more specific information concerning pituitary-adrenal function in cases of pituitary adenoma we have used a metyrapone ("metopirone"; SU 4885) test. Our results in 15 patients with pituitary tumour and in five with suprasellar tumours are recorded here.

Material

Fifteen patients with intrasellar-space-occupying lesions were investigated (Table I). The youngest was aged 13 years and the oldest 69. All but three (Cases 13, 14, and

15) were previously untreated. In 10 the histological examination of the tumour confirmed the diagnosis of pituitary adenoma. In the remainder the presumptive diagnosis of pituitary adenoma was made on the physical signs and demonstration of typical changes in the x-ray picture of the skull and by air-contrast radiography. Admission to hospital of 14 patients was dictated by the onset of neurological signs and symptoms—generally visual failure; endocrine features were not a major cause of symptoms. Patient No. 15 was admitted to hospital for assessment of endocrine status prior to replacement therapy after treatment by partial pituitary adenectomy two years earlier.

Patients with pituitary tumour were classified on physical appearance as suggested by Mogenson (1957): those whose physical appearance is normal are called "normocrine"; those with characteristic skin pallor, absent pubic, axillary, and body hair, and in males scanty facial hair, are called "hypocrine." In the present series 11 patients were normocrine, two hypocrine, and two acromegalic.

Five patients with suprasellar-space-occupying lesions and chiasmal compression were investigated (Table II). Prior to diagnosis by exploration, or by air-contrast radiography, pituitary adenoma was in each case considered in the differential diagnosis.

Fourteen control subjects studied were hospital in-patients of comparable age, with varying degrees of debility, but without pituitary disease or other primary endocrine disorders (Table III).

Metyrapone Test

The test (Marks, 1962) was carried out in hospital, though subjects were not confined to bed unless this was otherwise indicated. Consecutive 24-hour urine samples were collected for seven days, using 2–5 ml. of chloroform as preservative. Urine samples were analysed for creatinine (King and Wootton, 1956), neutral 17-keto-steroids (17-KS) and 17-ketogenic steroids (17-KGS) (Norymberski *et al.*, 1953), and total 17-hydroxycorticosteroids (17-OHCS) (Appleby *et al.*, 1955). Mean daily creatinine excretion during the period of observation was designated a creatinine day. Daily urinary steroid excretions were expressed as milligrams of steroid per creatinine day. Despite certain theoretical objections, this method of

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†Pituitary adenomas are traditionally classified on histological grounds as chromophobe, eosinophil, or basophil. The chromophobe adenomata are now recognized as being a heterogeneous group; many appearing not to be "chromophobe" with new staining techniques.