longest survivor, a young woman alive and well in the sixteenth year, with two sons aged 8 and 5, has been reported several times before (Walton, 1950 ; Smithers, 1951 ; Kramer, Concannon, Evans, and Clark, 1955 ; Smithers, 1959a, 1959b) ; she was the first patient in this country to be successfully treated with radioactive iodine for disseminated thyroid carcinoma.

Table V shows survival for the whole group of 30 patients with distant metastases against the histology of the tumour ; Table VI shows survival against uptake of radioiodine ; and Fig. 5 shows the fate of each of these patients after their initial or ablative treatment with ^{131}I.

Summary

Thyroid carcinoma is not a common disease, and only a small proportion of cases benefit from radioiodine therapy. The variations in natural history and response to treatment make assessment difficult. Fifty-nine patients are reported who were treated with radioactive iodine for thyroid carcinoma.

A description is given of the physical measurements carried out to determine the pattern of retention of the administered radioiodine, and hence the radiation dose to the whole body, to the blood, and to functioning thyroid tissue. Preparation for treatment and rationale of the treatment dosage and schedule are discussed.

These 59 patients are analysed in two groups. The first comprises those in whom the disease was clinically confined to the neck, with persistent post-operative disease, with inoperable tumours, or with recurrent tumours. The second group comprises those with distant metastases, with no uptake, with limited uptake, or with good uptake of radioiodine in the tumour. Patients with anaplastic tumours, whether localized or generalized, all did badly. Good uptake of ^{131}I in a differentiated tumour may lead to regression and long survival, even in cases where wide dissemination has occurred.

A plea is made for the reporting in detail of similar series of patients with carcinoma of the thyroid treated with ^{131}I, so that experience can be accumulated and the value of this treatment assessed.

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Metabolic Changes after Aorto-iliac Occlusion

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The value of surgery for aorto-iliac disease is well established, but there remain a number of problems awaiting solution. Systemic hypotension following release of aortic clamps is often encountered (Brooks and Feldman, 1962 ; John and Peacock, 1963 ; Burton *et al.*, 1964), and although its cause has been attributed to the development of metabolic acidosis this relationship is uncertain. The metabolic consequences of circulatory exclusion of the lower limbs is poorly documented and forms the subject of this report.

Patients and Methods

Six adult white patients, four men and two women, have been studied. Two were suffering from aneurysms and the remainder had occlusive disease. The patients were premedicated with Omnopon 0.3 mg./kg. and atropine sulphate 0.015 mg./kg. One hour later anaesthesia was induced with intravenous sodium thiopentone 5 mg./kg. and relaxation obtained with tubocurarine chloride 0.5 mg./kg. Endotracheal anaesthesia was maintained with nitrous oxide and oxygen by intermittent positive pressure by means of a non-return circuit and a Pulmoflator.

The proportion of oxygen used in the inspired gases varied from 25% to 33%. The minute-volume was adjusted to maintain P_{CO_2} within the range 35–40 mm. Hg and was from 8 to 10 litres/minute. Additional curare was given as required. At the end of the operation any residual curarization was reversed with neostigmine, preceded by atropine, to minimize its muscarinic effects. In all the cases spontaneous respiration was re-established without difficulty.

The patients were conscious on return to the recovery ward, and were nursed in a semi-sitting position on a half-wedge, with the foot of the bed elevated. All the patients were given intranasal oxygen during the immediate post-operative period.

All six patients were treated by the insertion of bifurcation aorto-iliac grafts of woven Teflon, and in each case the lower anastomoses were made with the common iliac arteries. During the period from onset of the operation to release of the aortic clamp warmed blood was slowly infused ; this is routine policy in the vascular unit of the department of surgery and serves to produce a temporary increase in blood volume.

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This prevents a sudden drop in blood-pressure when clamps are removed, and obviates rapid alterations in acid-base status produced by such hypotension. It also permits assessment of changes in hydrogen-ion concentration and alteration of lactate/pyruvate values due to the administration of infused blood itself.

Measurements

Samples of blood were obtained from a radial artery and a femoral vein through indwelling cannulae. The mouth of the venous catheter was located 10 cm. below the sapheno-femoral junction. Arterial pressure was monitored directly by means of an N.E.P. transducer with oscilloscope display and recorded by pen-writer. Central venous pressure was also recorded by saline manometer connected to a jugular-vein cannula. The electrocardiogram was monitored throughout the procedure.

Blood volume was measured with ^{131}I-tagged albumin, the dilution principle and the Volemetron apparatus being used. Body temperature was measured continuously during surgery with an Elab thermocouple, which has an oesophageal lead placed at cardiac level. A weighing bed was used to measure the body weight at the start and conclusion of the surgical procedure.

Samples of heparinized blood were taken simultaneously from the arterial and venous cannulae, and aliquots analysed immediately for *p*H, Pco_2, and standard bicarbonate (Astrup *et al.*, 1960). Po_2 was determined immediately by radiometer (Clark, 1956), electrode (Johnstone, 1965), and in one case oxygen saturation measurements were made on the Flik oxymeter. Lactate and pyruvate concentrations in whole blood were measured by the enzymatic methods of Scholz *et al.* (1959) and Gloster and Harris (1962) respectively. Care was taken to precipitate the blood immediately in a mixture of ice-cold trichloroacetic acid and hydrochloric acid prepared in a one-to-one proportion.

All specimens obtained during the operative period and so far as was possible afterwards were paired arterial and venous samples. At least two determinations were made before the aortic clamps were applied, and these served as control values. Two samples were taken during the period of occlusion, and then following release of the clamps at five-minute intervals for a period of 30 minutes, and then hourly up to six hours. Less frequent but timed samples were taken at intervals up to 24 hours after the start of the procedure.

Results

The first case studied was that of a 56-year-old woman with aorto-iliac occlusive disease producing claudication on walking 80 yards (73 metres). She was moderately obese and hypertensive, with a blood-pressure of 210/120, but no other abnormal features were found on clinical examination. Her blood volume measured 5.8 litres at the start and conclusion of the procedure, and her oesophageal temperature varied from 36.5° to 36° C. The metabolic data are shown in Fig. 1. There was a slight increase in hydrogen-ion concentration (*p*H 7.48 to *p*H 7.32), and a transient fall in standard bicarbonate from 26.4 to 24 mEq/l.

Blood lactate increased from 1.05 mEq/l. during the control period to 3.8 mEq/l. two and a half hours after release of the aortic clamp. Pyruvate increased from 0.18 to 0.35 mEq/l. during the same period. The concentration of both compounds appeared to be still increasing at the end of this period of observation. The oxygen saturation showed a reduction to 22% in the occluded limb, equivalent to a calculated Po_2 of 14 mm. Hg (Severinghaus, 1958).

Fig. 2 shows comparable data from Case 4 in our series. This patient was a 42-year-old man with bilateral aorto-iliac stenosis and complete occlusion of the left common iliac artery. Cardio-respiratory function was normal, as was his blood-pressure, but severe calf and thigh claudication limited his activity to 100 yards (90 metres). Blood lactate increased slightly during the control period before application of aortic clamps, coincident with the infusion of A.C.D. (acid, citrate, dextrose) bank blood. After restoration of circulation to the leg there was an increase from 1.05 to 2.2 mEq/l. in blood lactate. Pyruvate increased from 0.1 to 0.28 mEq/l. The values obtained for both these substances remained elevated for the next 6 to 12 hours. Oxygen tension was reduced in the leg to a Po_2 of 22 mm. Hg (calculated oxygen saturation=37%). Acid-base values followed the previously observed pattern with an increase of hydrogen-ion concentration (from *p*H 7.38 to *p*H 7.32) and reduction of standard bicarbonate from 22.2 to 21.5 mEq/l. The oesophageal temperature in this case remained steady at 36.2° C., and blood-volumes showed an overall increase from 5.85 to 6.05 l.

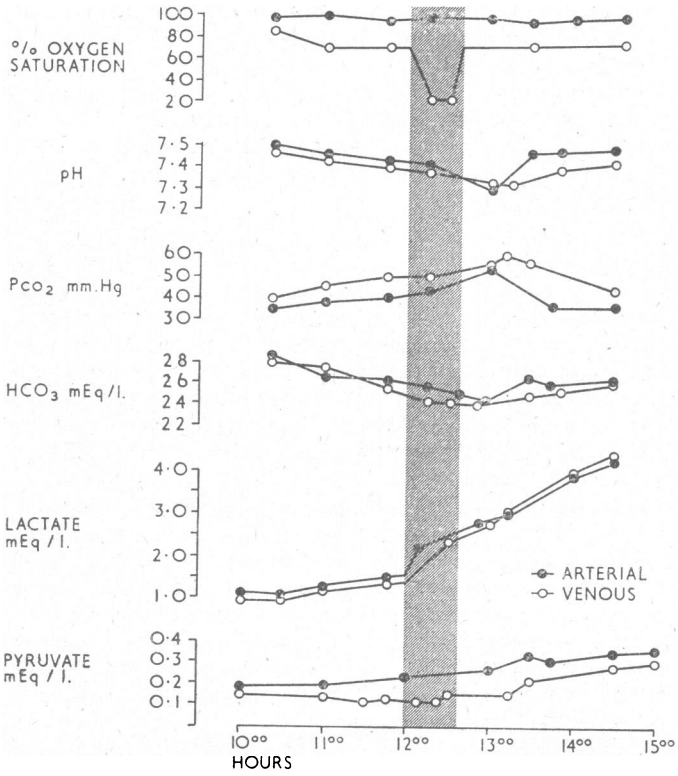

FIG. 1.—Metabolic data from Case 1. Hatched area indicates period of aortic occlusion.

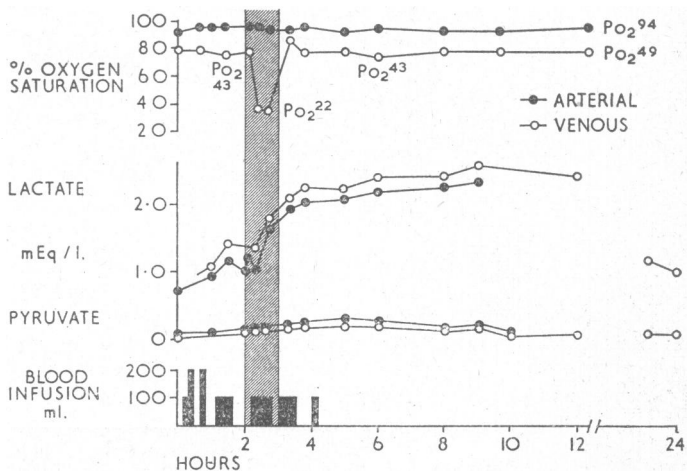

FIG. 2.—Metabolic data from Case 4. Hatched area indicates period of aortic occlusion.

The alterations in acid-base state for the group of patients as a whole is shown in Fig. 3. There is an overall increase in hydrogen-ion concentration after release of the aortic clamp. This is shown by reduction in *p*H and standard bicarbonate values. These changes, however, are not statistically different from control values (P>0.05), and they are seen to be transient.

Fig. 4 shows the mean values, with one standard deviation, for the observed changes in blood lactate and pyruvate. The hatched area indicates the period of aortic occlusion, and the sustained nature of the elevated levels is clearly shown. Arterial pyruvate is seen to be persistently higher than venous, whereas the converse is true of lactate values.

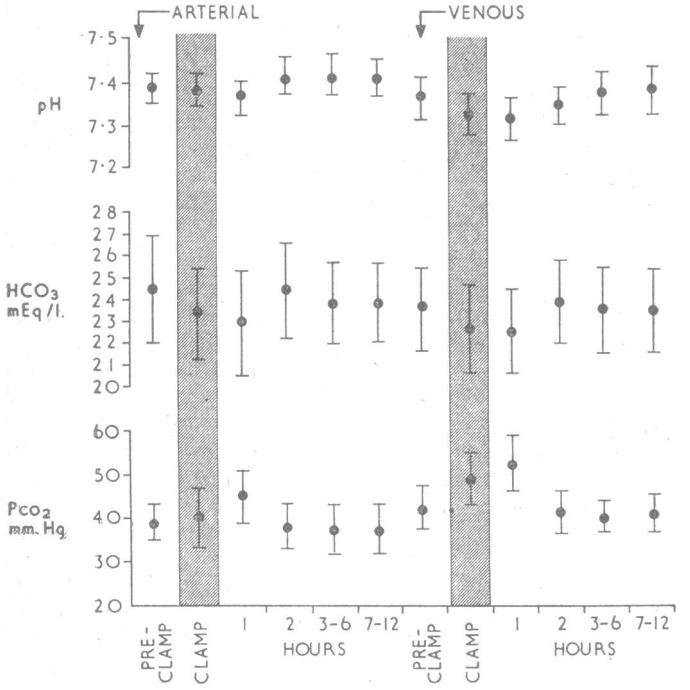

FIG. 3.—Acid-base values for entire group of patients. Values on left are for arterial blood and those on right for venous blood from the leg. Each dot represents the mean value of at least 12 determinations and the horizontal lines plus or minus one standard deviation. The time intervals shown are before, during, and 1, 2, 3–6, and 7–12 hours after release of aortic clamps, indicated by the hatched area.

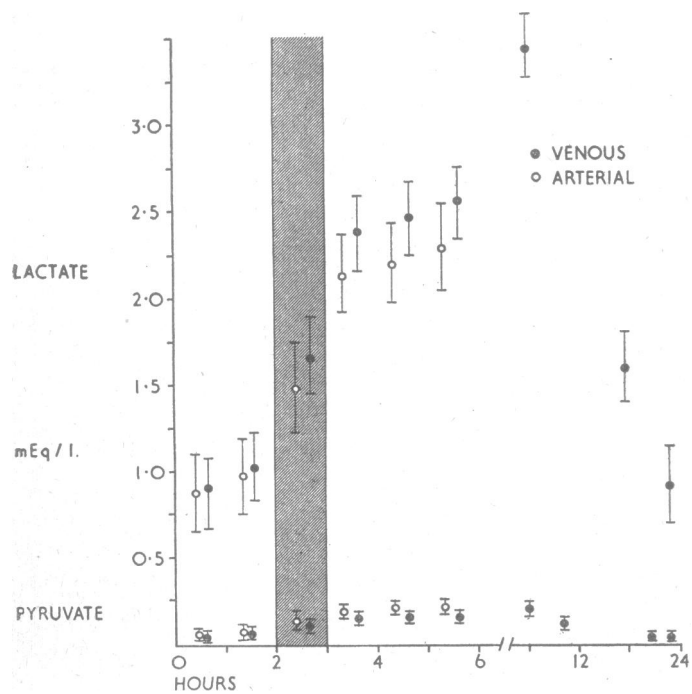

FIG. 4.—Mean values plus or minus one standard deviation for observed changes in blood lactate and pyruvate.

Discussion

The hypotension encountered after release of aortic clamps was attributed by Brooks and Feldman (1962) to release of metabolites from the anoxic lower limb. This problem was studied by Burton *et al.* (1964), who could find little evidence for production of significant acid metabolite ; they attributed changes observed by them to rapid transfusion of A.C.D. bank blood. It is difficult to interpret the significance of metabolic data obtained on patients undergoing major aortic surgery, when hypotensive conditions prevail, since the very parameters under review are largely affected by such changes in pressure. Relative over-transfusion during the preliminary stages of such surgery is of help in limiting the rate at which blood needs to be given and nullifies the effects of temporary leaks and distal vasodilatation after release of the aortic clamps.

The arterial pressure in all cases studied was monitored continuously, and in no case was a reduction of more than 10 mm. Hg observed when the clamps were removed. The data obtained demonstrate an increased hydrogen-ion concentration in the lower limb as reflected by the fall in *p*H and standard bicarbonate. As expected, this change was somewhat more pronounced in the limb than in the blood obtained from the radial artery. In all cases studied, however, the change was slight, transient, and not of statistical significance in comparison with control values. No alteration of hydrogen-ion concentration could be ascribed to blood transfusion. This reflects the relative slow nature of the infusion, and also supports observations of Drucker *et al.* (1961) that the metabolism of citrate is rapid and complete when normothermic conditions prevail.

During infrarenal aortic occlusions there is a profound fall in oxygen tension in the lower limb. The Po_2 of venous blood taken 10 cm. below the sapheno-femoral junction varied between 14 and 26 mm. Hg, compared with control values of 48–58 mm. Hg. It is probable that oxygen tension at sites more distal than this would be even lower. The arterial Po_2 throughout each investigation remained in the range 96–116 mm. Hg. Huckabee (1958) showed that oxygen lack leads to the production of lactic acid, due to the progressive failure of oxidative mechanisms. Hence the equilibrium of the reaction

$$\text{Pyruvate} + \text{NADH}_2{}^{1} \overset{\text{LDH}^3}{\rightleftharpoons} \text{Lactate} + \text{NAD}^2$$

is altered to favour the production of lactate. It is of interest that in our cases there seemed to be a conversion of pyruvate to lactate in the limb, since venous lactate was higher than arterial and pyruvate showed the reverse trend. The ratio of lactate to pyruvate remained constant up to two hours after the release of the aortic clamp, but after this period an increased value was observed. This resembles the so-called "excess lactate" of Huckabee (1958), although doubt has been expressed regarding the validity of such a concept (Harris *et al.*, 1962 ; Olson, 1963).

The reason for prolonged production of lactate is difficult to see, since in all cases release of the aortic clamps was associated with good restoration of pulsatile blood-flow to all parts of both limbs, which became pink and warm. The adequacy of peripheral perfusion is supported by the normality of all post-release acid-base values. One possible cause for the phenomenon is temporary damage to the cellular enzyme systems which renders the cell unable to utilize available oxygen. Hypothermia and hypotension are seen to play

[1] Dehydro nicotine adenine dinucleotide.
[2] Nicotine adenine dinucleotide.
[3] Lactic acid dehydrogenase.

no part in the genesis of this lactate, and infusion of A.C.D. bank blood had been stopped previously.

The quantities of lactate and pyruvate circulating during the immediate post-operative period amount to 4 mEq/l. at maximum. No significant change occurs in hydrogen-ion concentrations as a result of these metabolites, and although the reason for their continued production is at present obscure they do not appear to be harmful *per se*.

Summary

Six cases have been studied during reconstructive surgery for aorto-iliac disease. Infrarenal aortic occlusion produces severe desaturation of blood in the lower limb, leading to anaerobic production of lactate. The change in hydrogen-ion concentration produced is small, transient, and not significant at normothermia.

Alterations in hydrogen-ion concentration due to release of anoxic metabolites does not appear to be the cause of systemic hypotension after release of aortic clamps.

We would like to express our thanks to Mr. G. Slaney and Mr. F. Ashton for allowing us to study patients under their care, and for their help and advice in the preparation of this paper.

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Eczema and Keratoconus

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A series of 100 patients with keratoconus (conical cornea) were examined to test the significance of the occasionally reported association of eczema and this rare eye disease. Eczema has been recorded with keratoconus in 19 patients (François, 1961) since Hilgartner *et al.* (1937) first noted the coincidence. The reported incidence varies widely: all six patients with atopic eczema (Spencer and Fisher, 1959) had keratoconus, and, according to Roth and Kierland (1964), out of 492 with atopic eczema only one had keratoconus. But cataract (Brunsting *et al.*, 1955 ; Rosen, 1959), and perhaps keratoconjunctivitis (Hogan, 1952 ; Thygeson, quoted by Spencer and Fisher, 1959), are accepted accompaniments of atopic eczema.

Investigation

All the patients were attending the Contact Lens Department at Moorfields Eye Hospital, High Holborn. A history was taken. This included details of the following: age at onset of keratoconus, family history, and treatment of keratoconus ; inquiry about types of trauma and habit of eye-rubbing ; right- or left-handed ; past and family history of eczema, asthma, and hay-fever, with age at onset, type, severity, and treatment. Every patient was examined, attention being paid to the following: whole of skin for eczema, particularly of the face and eyelids ; congenital defects of the teeth, hair, finger-nails ; vitiligo, ichthyosis, naevi ; mucous membranes of mouth and conjunctivae ; connective-tissue disorders (Marfan's disease, Ehlers-Danlos syndrome, and cutis laxa).

Findings

Fifty-eight of the patients with keratoconus were males. The age at onset of deterioration of vision which resulted in the diagnosis of keratoconus is shown in the Table ; in 81 patients it was 10 to 25 years. Over half of the series were technicians or professional people, and half appeared to be above average in intelligence ; 85% were Caucasian, 10% Jews, and the remainder Asian or West Indian. There was a family history of keratoconus in six patients.

Age at Onset, Sex, Presence of Eczema in 100 Patients with Keratoconus. Sex Incidence of Eye-rubbers was Approximately Equal

Age at Onset	Males		Females		Eye-rubbers
	Total	With Eczema	Total	With Eczema	
Under 10 ..	4	1	1	—	5
10–20	43	9	22	8	47
21–25	7	1	9	5	8
Over 25 ..	4	3	10	5	11
Total ..	58	14	42	18	71

Eczema.—Thirty-two patients had either signs or a past history of eczema. Fifteen (perhaps 16) of these had *atopic eczema*—among them were three with seborrhoeic distribution of eczema, dandruff, and blepharitis yet with strong past and family histories of atopy. Five had *seborrhoeic eczema* particularly affecting the eyelids. The remainder were more difficult to classify ; three had *lichen simplex chronicus*, with episodes of eye-rubbing, and mild eczema of the eyelids or hay-fever ; two had dyshidrotic eczema or pompholyx (one of whom was probably an atopic) ; three had *contact eczema*, including one patient with nickel allergy and hay-fever. In all patients the eczema preceded the keratoconus ; the interval varied by many years. In six of those with atopic eczema there was a definite history of the eczema spreading to the face and eyelids and being followed in one to two years by the diagnosis of keratoconus. Nine of the eczematous group had hay-fever and six a family history of it. Three of the eczematous patients emphatically denied rubbing their eyes.

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