It was felt that reflux was the most likely cause of oesophagitis in the cases here described. Since both cases showed a complete achlorhydria, it was thought that acid or peptic digestion was unlikely to be the operative factor. On the other hand, the conditions for tryptic activity were ideal. It was therefore felt necessary to prevent jejunal contents from reaching the lower end of the oesophagus. The obvious means of attaining this end was to convert the Polya gastrectomy into a Billroth type. If reflux did thereafter occur, the contents would be gastric, achlorhydric, and free of jejunal content.

In both cases this manœuvre was successful. The oesophagitis and dysphagia cleared up rapidly, and though review has taken place at frequent intervals for the past two years, no evidence of recurrence of stricture has occurred. This seems to confirm that reflux of jejunal content, and probably tryptic activity, were the cause of the oesophagitis which led to stenosis.

Summary

Two cases of an unusual complication of subtotal gastrectomy are described.

The possible causes of this complication are discussed.

It is suggested, on theoretical grounds and as a result of the line of treatment adopted in these cases, that the reflux of the jejunal contents, and possibly tryptic activity, may be the operative factors in causing the oesophagitis which led to stenosis.

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ADRENALINE IN HYPERTHYROIDISM AND INSULIN HYPOGLYCAEMIA

BY

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AND

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There are many similarities between the features of acute insulin hypoglycaemia and of hyperthyroidism. Tachycardia, weakness, finger tremor, sweating, and flushing can occur to a similar extent in both conditions. Furthermore, the similarity between the features of hyperthyroidism and those of phaeochromocytoma is striking; indeed, these disorders are not infrequently confused. All three conditions are known or thought to be related to an increase of secretion of adrenaline from the adrenal medulla. Cannon *et al.* (1924) reported an increase of adrenaline secretion in cats in response to insulin hypoglycaemia and showed that this was a mechanism for raising the lowered blood sugar. It has been suggested that adrenaline is responsible for many of the symptoms of hypoglycaemic reactions (Bell *et al.*, 1956). Similarly, in man, von Euler and Luft (1952) and French and Kilpatrick (1955) demonstrated a considerable increase in urinary adrenaline excretion following hypoglycaemia.

An association between hyperthyroidism and changes in adrenaline metabolism has long been suspected. Hyperthyroid subjects have a striking increase in sensitivity to adrenaline and noradrenaline (Rosenblum *et al.*, 1933; Peltola, 1951; Schneckloth *et al.*, 1953; Brewster *et al.*, 1956). Many observers have noted changes in adrenaline content of adrenal glands in animals in which hyperthyroidism was produced by giving thyroxine (Goodall, 1951; Hökfelt, 1951; Pekkarinen *et al.*, 1951; Durlach *et al.*, 1955). Accordingly, urinary catechol excretion has been measured in a number of patients with hyperthyroidism and the results are compared with those found in insulin hypoglycaemia and in normal subjects.

Methods

The urinary catechol excretion was measured in 12 euthyroid subjects, in 17 patients with hyperthyroidism of varying degree, and in two patients with hypothyroidism. The estimation was repeated in two patients previously hyperthyroid who had become euthyroid following treatment with radioiodine.

In all but one of the patients with hyperthyroidism the estimation was performed while they were in-patients and thus at rest in bed. The normal subjects, who were mainly hospital and university staff, were performing their usual duties. Urine was collected for 24 hours into a dark bottle containing hydrochloric acid.

Two methods of extraction were used, either aluminium hydroxide (von Euler and Hellner, 1951) or aluminium oxide (von Euler and Orwen, 1955). The latter method required modification as our assay was done on the rat-uterus preparation (Diller, 1958). Recovery by both methods varied between 65 and 90%. No correction was made for this.

Adrenaline assays were performed, using the oestrous rat uterus stimulated by carbachol (Gaddum and Lembeck, 1949). Values are given as L-adrenaline. The assay was checked in two ways. Firstly it was shown that all adrenaline-like activity was destroyed by boiling an aliquot of the extract at alkaline *p*H. Secondly, addition of known amounts of adrenaline to the extract after measurement produced only additive effects and no potentiation or masking was found. If either of these requirements was not met another extract was prepared from a further urine collection.

Total catechols were measured in the same extract on the cat's blood pressure, and the noradrenaline content was found by using the adrenaline value from the uterus assay (Burn *et al.*, 1950). Values are given as DL-noradrenaline.

Attempts were also made to measure adrenaline and noradrenaline by a fluorimetric method (von Euler and Floding, 1955), so that the number of estimations could be increased. However, it was found that there was much non-specific fluorescence in all the urines that were studied. This produced more inaccuracy when the level of catechols was in the physiological range. Similar results with fluorimetric methods are described by Pitkänen (1956).

Radioiodine tracer studies were performed in all of the patients with thyroid disorders. They were given 25 μc. of ^{131}I and the thyroid uptake was measured after 4 and 48 hours. Protein-bound ^{131}I was measured at 48 hours, using trichloracetic acid as protein precipitant (Goodwin *et al.*, 1951).

Results

The clinical diagnosis of hyperthyroidism was confirmed by radioiodine studies; in all of them the four-hour uptake was more than 40% of the dose and the 48-hour protein-

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bound ^{131}I more than 0.4% of the dose per litre of plasma (Wayne, 1954).

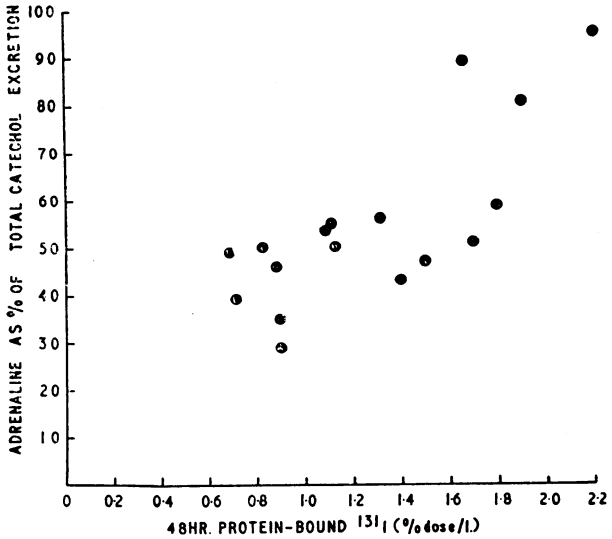
The values for adrenaline and noradrenaline in normal subjects and patients with thyroid disease are shown in the Table. In normal subjects the mean daily adrenaline excretion was 2.8 μg. (range 1–7 μg.) and the mean daily noradrenaline excretion 22.6 μg. (range 9.4–50 μg.). No significant difference was found between the two methods of extraction.

Urinary Catechols in Hyperthyroidism and Hypothyrodism

	No.	No. of Estimations	Mean Daily Output of		
			Adrenaline (μg. ±S.E.)	Noradrenaline (μg. ±S.E.)	Adrenaline (Percentage of Total Catechols ±S.E.)
Normal ..	12	16	2·8 ± 0·5	22·6 ± 3·1	12 ± 1
Hyperthyroid ..	17	20	25·0 ± 6·8	15·8 ± 2·3	55 ± 4
Hypothyroid ..	2	3	0·8	14·3	5

A striking difference is apparent when the mean daily adrenaline excretion in the patients with hyperthyroidism is considered. This is 25 μg. (range 7.5–130 μg.) and is significantly greater than the mean in normal subjects ($P<0.05$). The mean excretion of noradrenaline is lower, but this difference is not significant. The high adrenaline excretion in hyperthyroidism is emphasized when this is expressed as a percentage of the total catechol excretion. In hyperthyroidism this is more than four times that found in normal subjects.

The protein-bound ^{131}I values reflect the rate of turnover of iodine by the thyroid and probably give an indication of the severity of hyperthyroidism, provided that the thyroid gland has not been disturbed by previous treatment. In this series all the patients with hyperthyroidism were studied before any treatment had been given. The 48-hour protein-bound ^{131}I values have been plotted against the daily adrenaline excretion, expressed as a percentage of the total catechol excretion (see Chart). The excretion of adrenaline apparently rises with an increased concentration of labelled hormone.



Urine adrenaline excretion in patients with hyperthyroidism, and the protein-bound radioactivity of serum at 48 hours.

In two patients with hyperthyroidism, who had become euthyroid some months after treatment with radioiodine, the daily adrenaline excretion had fallen from 30 and 20 μg. to 5 and 7 μg. respectively. These latter results are within the range of normal.

Only two patients with hypothyroidism were studied; both had low values for adrenaline excretion (see Table).

These results of adrenaline excretion in hyperthyroidism may be compared with those found in insulin hypoglycaemia. French and Kilpatrick (1955) found that the mean adrenaline excretion in three patients during the three hours preceding the injection of insulin intravenously was 5.1 μg., and 46.1 μg. during the three hours following it. As hypoglycaemia occurs acutely, it is difficult to compare with the daily adrenaline output in hyperthyroidism. However, the rise in output during the three hours following the induction of hypoglycaemia and for 24 hours in hyperthyroidism is approximately tenfold compared with the control results.

Discussion

The results for adrenaline and noradrenaline excretion in normal subjects agree with those of von Euler and Floding (1955) and of Bischoff and Gray (1956), using biological assay.

It seems that adrenaline excretion in urine is much increased when hyperthyroidism is present, and the correlation of adrenaline excretion with the amount of labelled thyroid hormone is suggestive evidence that this excretion is related to the degree of thyroid hyperactivity. It has been shown (von Euler and Hellner, 1952) that activity increases adrenaline excretion, and thus the adrenaline values in hyperthyroidism are even more striking, as these patients were in bed, whereas the normal subjects had no restriction on activity. If it is assumed that renal clearance of catechols remains unaltered, this suggests that the blood adrenaline level is also raised in hyperthyroidism. This may be due either to increased production or to decreased destruction. There is no direct evidence for or against the first, though many observers have noted changes in histology and adrenaline content of adrenal glands in experimental hyperthyroidism in animals (Herring, 1917; Goodall, 1951; Hökfelt, 1951; Pekkarinen *et al.*, 1951; Durlach *et al.*, 1955).

There is some evidence that there may be decreased destruction of adrenaline in hyperthyroidism. Spinks and Burn (1952) and Trendelenburg (1953) found a fall in liver amine oxidase content in rabbits when thyroid extract was given and a rise in the content of the enzyme following thyroidectomy in rabbits and rats. Kawamoto *et al.* (1952) noted a fall in adrenaline dehydrogenating enzyme in hyperthyroidism. Burn and Marks (1925) revealed this decreased destruction by showing that following thyroid feeding there was an increase in the hyperglycaemia produced by adrenaline and a decrease following thyroidectomy. They also showed that there was an inverse relationship between hyperglycaemia produced by adrenaline and hypoglycaemia produced by insulin. Thyroidectomy increased the fall in blood sugar following insulin, and thyroid feeding decreased it.

The insulin-tolerance test may show prolonged hypoglycaemia after insulin in patients with hypothyroidism (Fraser and Smith, 1941). These results are in accordance with the evidence that adrenaline is released in response to insulin hypoglycaemia (von Euler and Luft, 1952), even though this release appears to cause very few of the symptoms of hypoglycaemia (French and Kilpatrick, 1955). Adrenaline and insulin can be regarded as physiological antagonists for many of their actions, and thus the secretion of adrenaline in response to hypoglycaemia may be regarded as compensatory. However, this is not so with thyroxine and adrenaline. It is surprising, therefore, that the blood level of adrenaline appears to increase when hyperthyroidism is present. Direct measurement of circulating adrenaline, and if possible in adrenal vein blood, is required for final confirmation.

Summary

The daily urinary excretion of adrenaline and noradrenaline has been measured in patients with hyperthyroidism and in normal subjects.

A large increase in adrenaline excretion was found in hyperthyroidism, but no change in noradrenaline excretion.

There was a correlation between adrenaline excretion and severity of hyperthyroidism, as measured by output of labelled hormone following a tracer dose of ^{131}I.

Possible mechanisms for these changes and relationship to insulin hypoglycaemia are discussed.

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AETIOLOGICAL FACTORS IN PRIMARY RAYNAUD'S DISEASE

BY

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The term "idiopathic," or "primary," Raynaud's disease is currently applied to those patients who present with intermittent attacks of digital pallor or cyanosis in whom careful examination fails to reveal either a local contributory cause or an associated systemic disease in which the digital symptoms might be considered to represent a single feature of a more generalized disease process.

The use of the term primary is in many ways open to individual interpretation by the clinician. This is not only due to the gradually increasing number of diseases with which the digital syndrome is now associated, but is also dependent on the care and accuracy taken to exclude systemic disease and to establish aetiological factors on which such a diagnosis may be accepted or rejected.

Apart from the influence of heredity and the frequent appearance of symptoms during childhood or at puberty (Lewis and Pickering, 1934), little is known about endogenous influences which may affect either the appearance of symptoms or the severity of the disease, and the purpose of this paper is to draw attention to certain features in the histories of a group of patients with this disease which suggest that they should be regarded as aetiological factors in the evolution of the vascular abnormality of primary Raynaud's disease.

Clinical Material

The 21 cases recorded form part of a group of 42 patients diagnosed as having primary Raynaud's disease. Their symptoms were intermittent attacks of digital pallor or cyanosis of the upper extremities of such severity as to constitute a serious disability in their normal way of life. All were females, aged 23 to 52 years, who had been referred either for upper-limb sympathectomies or because of recurrence of symptoms following previous operations. All fulfilled both the criteria laid down by Allen and Brown (1932a) of a diagnosis of primary Raynaud's disease and those suggested by Hunt (1936) for primary Raynaud's phenomenon. They were otherwise in good general health, and with the exception of one case (No. 10) were non-smokers.

Clinical examination failed to reveal either a local cause for their symptoms or any associated systemic disease. All peripheral pulses were normal and the blood pressure ranged from 110 to 140 mm. Hg systolic and 65 to 80 mm. Hg diastolic. A careful investigation of the E.S.R., serum proteins, and blood excluded the presence of the collagen disease group.

Clinical Histories

Analysis of the clinical histories of the patients obtained by careful questioning of the patients themselves and their close relatives indicated that symptoms either arose for the first time, or pre-existing mild symptoms became greatly exacerbated, following three main events in the patient's life: (1) childbirth; (2) the onset of the menopause; and (3) a period of severe mental stress.

Aetiological Factors in Primary Raynaud's Disease

Case No.	Hereditary History	Age of Onset of Digital Symptoms	Age of Onset of Disability	Aetiological Factor	Progression to Nutritional Lesions
1	+	32	32	Parturition	Yes
2	+	15	29	,,	,,
3	+	Child	36	,,	No
4	+	26	26	,,	,,
5	+	Child	18	,,	,,
6	+	35	35	,,	,,
7	Not known	17	33	,,	,,
8	+	15	23	,,	,,
9	+	Child	45	Menopause	,,
10	+	,,	47	,,	,,
11	+	Teens	35	Hysterectomy and unilateral oophorectomy	,,
12	+	,,	34	Hysterectomy	,,
13	−	33	33	,,	,,
14	−	42	42	,,	,,
15	+	40	40	Mental stress	,,
16	+	28	28	,, ,,	,,
17	+	42	42	,, ,,	,,
18	−	30	30	,, ,,	,,
19	+	35	35	,, ,,	Yes
20	+	Teens	37	,, ,,	No
21	−	25	25	,, ,,	,,

Childbirth.—In eight patients symptoms severe enough to make them seek medical treatment arose within six months of the birth of a child, the time period between parturition and the onset of symptoms being related to the interval between parturition and the onset of cold weather. In three cases it was following the birth of the first child, in four the second, and in one the third. Two of these cases progressed within a period of five years to nutritional lesions of the digits and sclerodactyly. In three patients the symptoms arose *de novo* and there was no evidence to suggest that previous mild attacks had occurred. In five cases occasional digital pallor had been present for many years, and it was the severity of the attacks that had been modified. These had been converted from occasional and mild to severe and prolonged, with marked pain and disability.

Menopause.—In four of the six patients in this group the digital symptoms followed within a few months of subtotal hysterectomy for fibroids. In only one case (No. 11) was