heels. The nasal septum perforated. The previous day the heels and back were in perfect order. A radiogram taken on December 22nd showed necrosis of the bone of the os calcis. At this time both legs were markedly pigmented. The patient was discharged well on January 3rd, 1928.

CASE V.—Pulmonary Embolism.

This man was first seen on January 21st, 1927, with a primary syphilitic sore. He was treated at the London Hospital with seven weekly injections of novarsenobillon; the last six doses were 0.9 gram. Early in March he had some irritation of the neck, which he treated with iodine, and on March 6th he was admitted with exfoliative dermatitis. He became extremely ill with high fever, delirium, and albuminuria; he recovered from this, but his nasal septum perforated. On April 7th he complained of small boils on the left axillae and right groin. I examined him at 2 p.m. on April 12th, when he seemed fairly well, able to sit up in bed unassisted, tongue moist, pulse 80 regular, and exfoliation confined to the scalp, palms, and feet. At 10 o'clock that night he complained of distress in his chest, he became unconscious, cyanotic, and died within five minutes. No *post-mortem* examination was permitted, but the symptoms were sufficiently definite of pulmonary embolism from a clot dislodged from the iliac veins.

I have recorded uncommon but important ill effects following the administration of salvarsan remedies for syphilis. The knowledge of these possibilities makes it important that no practitioner should undertake the intravenous salvarsan therapy of syphilis without having facilities for immediate transference of his patients from an ambulatory clinic to a ward. The knowledge of these possibilities must be brought before the attention of the public if public support is to be sought for the compulsory treatment of venereal disease. Otherwise there will arise a feeling of resentment among the uninstructed should a severe accident or a fatality follow the compulsory administration of these most important but toxic remedies.

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THYROTOXICOSIS AND INDICANURIA.*

BY

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THIS paper embodies the results of an investigation undertaken to discover what relationship existed between the intestinal dissociation of aromatic amino-acids and thyroid hyperactivity. It is known that when tryptophane is decomposed in the intestine indole is eliminated in the urine as indican (potassium indoxyl sulphate), and as it is a simple matter to test for this substance it was thought that some light might be thrown on the question if the degree of indicanuria were estimated in a series of individuals suffering from thyrotoxicosis and compared with similar observations upon a series of non-thyrotoxic individuals.

It is possible, of course, that urinary indican may not be a true index of tryptophane decomposition, as the greater part of the indole may be eliminated in the faeces, but it seems reasonable to suppose that the urinary concentration of this substance will follow roughly the intestinal content. The degree of indicanuria, therefore, was measured in a large number of individuals. The technique adopted was a colorimetric one, the indican being estimated as indigo blue. To 2 c.cm.

of urine an equal amount of hydrochloric acid was added, then 0.5 c.cm. of hydrogen peroxide; the whole was shaken, and finally 1 c.cm. of chloroform was added. The colour

* An investigation of the hypothesis which ascribes thyrotoxicosis to an increased absorption of unchanged aromatic amino-acids from the intestine.

was estimated after standing for four minutes. It was assumed that the acid converted the indican to indoxyl and sulphuric acid, and the peroxide promoted the oxidation of indoxyl to indigotin, the chief constituent of indigo blue.

The individuals whose urine was examined comprised three groups. Daily observations were made and graphs prepared, with the degree of indicanuria as the ordinate and the day of the week as the abscissa. The groups were comprised as follows:

Group I consisted of seven normal healthy persons.

Group II consisted of fifty-seven patients suffering from various conditions, but without evidence of thyrotoxicosis, the series including two cases of non-toxic goitre.

Group III consisted of patients with exophthalmic and other varieties of thyrotoxicosis. Twelve cases were investigated, one, a case of exophthalmic goitre, at some length, to see whether there was any effect on the urinary indican output during the slight attacks of post-operative thyroidism following ligation of the thyroid vessels.

The results were as follows:

Group I.—Five of the seven persons investigated gave varying concentrations (Fig. 1 shows an indican curve from this group), while two males, aged respectively 23 and 16, gave completely negative readings for over a month.

Group II.—Thirty-eight women and nineteen men were investigated; 971 observations were made—580 on women, 391 on men. It is interesting to note that of the observations on women 41 per cent. were negative and only 5 per cent. reached the highest degree of concentration, while of those on men only 23 per cent. were negative and 18 per cent. reached the maximum concentration (Figs. 2 and 3). In this group were two men and five women with urine completely free from indican.

Group III.—Several of the most toxic cases in this group had high concentrations of indican. The curves generally resembled those of healthy subjects, and in the case investigated to see whether the post-operative reaction following ligations had any effect on the urinary indican it was found that there was no constant effect, a slight rise occurring after two ligations, no change after one, and a slight fall after another. Furthermore, careful observations during the clinical course of cases of exophthalmic goitre failed to reveal any constant change in the urinary indican that could be correlated with an increase or decrease in the degree of intoxication (Figs. 4 and 5).

FIG. 1.—Healthy youth, aged 18.

FIG. 2.—Married woman, aged 28, with a tuberculous abscess in the abdominal wall.

FIG. 3.—Boy, aged 17, with large endemic goitre.

FIG. 4.—Man, aged 30, with acute exophthalmic goitre.

FIG. 5.—Married woman, aged 53, with severe exophthalmic goitre. The arrows mark points at which ligations were performed.

Since collecting the cases into groups, many more, particularly toxic and non-toxic goitre cases, have been investigated with similar results.

The findings may be summarized as follows:

(a) In healthy persons there may be little or no urinary indican without any evidence of thyrotoxicosis, and from

day to day the variations in the amount of indican are considerable.

(b) In patients without thyrotoxicosis there may be no indican present in the urine, or on similar diet there may be much indican.

(c) Goitre cases without thyrotoxicosis show no difference in the form of indican curve from that in toxic cases.

(d) Toxic cases show concentrations which do not vary inversely as the degree of intoxication. Some well-marked exophthalmic cases have much indican, some non-toxic cases little or no indican.

The foregoing results do not lend support to the view that thyrotoxicosis is dependent upon increased tryptophane absorption from the intestine, as advanced in 1923 by Mr. D. J. Harries.¹ It was at one time thought that thyroxine was derived from tryptophane, Professors Kendall and Osterberg regarding it as trihydro-tri-iodo-oxyindole propionic acid.² Dr. C. R. Harington,³ however, has since shown that it is derived from tyrosine, from which he has synthesized it as a diphenyl ether.

Further experiments were therefore undertaken to discover whether the absorption of unchanged tyrosine would result in thyrotoxicosis. Owing to the relative insolubility of tyrosine only small amounts could be injected intravenously, and, moreover, these experiments were limited to three volunteers. It is admitted that more experiments are desirable, but in the three performed there was no increase in the pulse rate following the injection, and no apparent effect on metabolism, as would be expected if thyroid activity depended upon the amount of unchanged aromatic amino-acids reaching the thyroid.

COMMENTARY AND CONCLUSIONS.

It would appear, in the first place, that urinary indican varies in amount from day to day both in normal people and in those suffering from various diseases, sometimes being absent in health, at other times highly concentrated, tending more often to reach high concentrations in men, and to be absent from the urine of women; secondly, in exophthalmic and other varieties of toxic goitre there is no constancy in the concentration of urinary indican, which may be absent or present in varying degree; and thirdly, the variations are independent of the degree of thyroid activity.

The urinary indican appears, therefore, to be of no value in determining whether a case of thyrotoxicosis is progressing or decreasing, and so enabling the surgeon to decide when to operate.

Owing to the general similarity in structure of the molecules of thyroxine and adrenaline with that of tyrosine, and the fact that tyrosine is one of the essential amino-acids, it is reasonable to suppose that the hormones of the thyroid and suprarenal glands are ultimately derived from the tyrosine part of the ingested protein; but there is no evidence to show that the activity of these glands depends upon the amount of tyrosine available at any one moment from the alimentary tract, and without doubt the problem of the pathogenesis of thyrotoxicosis is more complex than merely a question of supply and demand, in which the supply is probably at all times very much greater than the demands made upon it.

SUMMARY.

1. Using a standard technique, colorimetric estimations of the concentration of urinary indican as indigotin were carried out for (a) healthy subjects, (b) non-thyrotoxic cases, and (c) cases of thyrotoxicosis.

2. Graphs (indicanuria curves) were made. There were no outstanding differences in the curves from each of these groups.

3. The urine of women is more often free from indican than is that of men. Higher concentrations of indican occur more frequently in men.

4. The concentration of urinary indican bears no constant relationship to the degree of thyrotoxicosis.

5. The hypothesis which ascribes thyrotoxicosis to an increased absorption of unchanged aromatic amino-acids from the intestine is not confirmed.

6. The statement that in all cases of well-established exophthalmic goitre there is no indican in the urine is not borne out. Several well-established cases gave high readings.

7. Three volunteers were injected intravenously with small quantities of tyrosine. There was no effect on their pulse rates.

8. The active principles of both thyroid and suprarenal are probably derived from tyrosine, but there is no evidence to show that the amount of these principles depends at any one moment on the quantity of tyrosine available from the alimentary tract.

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This research was carried out in the wards and laboratories of the Surgical Unit of the Welsh National School of Medicine, under the direction of Professor A. W. Sheen.

PAINLESS LABOURS:

THEIR OCCURRENCE, THEIR INTERPRETATION, AND THEIR ADOPTION AS A STANDARD.

BY

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PAINLESS labours are exceptional in occurrence, and are commonly regarded as being very rare, puzzling, and incomprehensible. A series was published in the *British Medical Journal* in 1906, and additional instances have been reported in previous issues of this year.

Reference to case reports and to the literature makes clear that such labours are commonly associated with uneventful recoveries and vigorous infants, with laceration rare and slight; the labours are often primiparous, and successive labours are usually painless also. The desirability of comfortable pregnancies, easy labours, and uneventful recoveries is undeniable, and it is surely worth while trying to explain their occurrence.

Before proceeding to a comparison of the painless with the usual form of labour it is necessary to mention certain features of average labour, all of which may be demonstrated in an analysis of a small series of cases. For instance, there is a great variation in the length of the first and second stages in different women, and also in the amount of suffering accompanying them; there is a definite rise in the forceps rate with the increasing duration of the first stage; and a short first stage tends to be followed by a short second stage, while a long first stage may be succeeded by a short, medium, or tedious second stage. The second stage is not uncommonly more endurable than the first stage, while its duration varies from two or three minutes to as many or more hours. The febrile puerperium is often related to an albuminuric or pyelitis pregnancy, as is also the prematurity and stillbirth rates.

The common symptoms of average labour are pain during the uterine contraction, sense of effort, sense of advance, sense of impending defaecation, bearing down, vomiting, cramps, and not uncommonly fatigue; these common symptoms vary from patient to patient, not all are present in every one, while the intensity of the pain may be trivial, moderate, extreme, or intolerable.

The first three of the cases recorded here demonstrate that the painless labour resembles the average labour in every respect except in the absence of the pain during the uterine contraction. The signs are just the same—"show," flow of waters, dilatation of os vagina and perineum, the "crowning," the delivery of infant and placenta, and the varying duration of the individual stages of labour. The characteristic symptoms are also the same—sense of pressure, sense of something to be expelled, sense of advance, sense of impending defaecation, strange feelings, and bearing down. In many painless or nearly painless labours the mother is the only one aware of the imminence of delivery; pain is so common that neither doctor nor nurse may pay sufficient heed to the mother's sensations, indicative as they are.

Is the absence of pain sufficient to brand such a labour as abnormal? It may be unusual, but it is not