Abbott and Schwab (1950), reviewing the toxic effects attributed to methoin and related drugs, suggest that all cases of blood dyscrasia develop gradually through three stages:

(1) Modified normal response in which the total white-cell count is normal but stained films show a fall in the proportion of neutrophils and monocytes and a rise in the proportion of lymphocytes and eosinophils:

(2) Controlled neutropenia in which the white-cell count is less than 3000 per c.mm. but there are no clinical abnormalities.

(3) "Runaway pancytopenia" with disastrous clinical signs.

They say that stage 1 is common, that stage 2 occurs in about 20% of patients, and that stage 3 occurs in 1% or 2% but is largely preventable if the earlier stages are recognised.

In most of the published cases of methoin toxicity, the drug was given continuously for several months before harm was evident; but it is now apparent that in sensitive persons severe reactions can develop after a very small dose and in a very short time. Plainly, routine blood examination cannot provide evidence on which these reactions can be prevented; and, if the use of methoin is contemplated, the following measures should be adopted to ensure that their incidence is minimal:

(1) Patients with a history of infantile eczema or other allergic diseases or of unexplained eruptions should be admitted to hospital and kept under observation for the first few weeks' treatment.

(2) Methoin should not be used until other drugs with less serious toxic effects have proved inadequate after thorough trial.

(3) Methoin should not be given in combination with other treatment known to depress erythropoiesis—e.g., X-ray therapy and troxidone.

(4) The initial dose of methoin should be very small and should be increased very gradually.

(5) The patient, or a responsible relation, should be warned to stop the methoin and report at once to his doctor if any rash, tremor, sore throat, fever, or other symptom develops.

(6) The blood should be examined at once if a patient taking methoin becomes pyrexial or unwell.

(7) If blood dyscrasia is discovered, treatment with antibiotics and hæmatinics should be started in full dosage at once, and continued for two weeks after all toxic signs have disappeared.

(8) Total white-cell counts and differential counts should be made before starting treatment and at intervals therafter.

SUMMARY

A case of agranulocytosis is described in a boy, aged 2 years, after seven days' treatment with methoin 0·1 g. twice daily. Blood dyscrasia is the only serious toxic effect so far attributed to this drug; 17 such cases, of which 7 were fatal, have previously been published. The case presented here is the second to be described fully in this country, and the second to be described in a child.

Attention is drawn to the potential toxicity of methoin, and measures are proposed to limit the dangers of methoin treatment.

I have to thank Dr. J. H. Hutchison for permission to use the records of this patient, who was treated in his wards at the Royal Hospital for Sick Children, Glasgow; and Prof. Stanley Graham and Dr. Hutchison for advice on preparing this article.

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PHYSIOLOGICAL ACTIVITY OF 3:5:3′-L-TRIIODOTHYRONINE

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THE synthesis of 3:5:3′-L-triiodothyronine and its identification in human plasma has recently been reported by Gross and Pitt-Rivers (1952), and the formation of the same compound during the iodination of 3:5-diiodothyronine has been described by Roche et al. (1952). This paper describes the biological assay of this compound by its effect in preventing goitre in animals treated with thiouracil.

METHODS

Male hooded rats weighing 80–120 g. were used. All the animals had 0·1% thiouracil in their drinking-water from the first day of the experiment and were injected subcutaneously each day with either the control solution A (solvent) or the test compounds. Each group contained 10 rats with 2 rats to each cage, and the rats of higher or lower weights were distributed as evenly throughout the groups as possible; the test lasted 10 days, and on the 11th day the rats were killed with chloroform and weighed; the thyroid glands were removed and weighed immediately, and the weight of gland per 100 g. body-weight was calculated (Cortell 1949).

Experiment 1.—Group A (controls) received daily injections of 0·1 ml. of 0·8% saline containing 0·00025*N* NaOH; group B received daily injections of 2 μg. L-thyroxine in 0·1 ml. of solvent A; group C received daily injections of 2·4 μg. L-triiodothyronine in 0·1 ml. of the same alkaline saline solution. The results are given in table I.

TABLE I—RESULTS OF EXPERIMENT 1

Animal no.	Group A		Group B		Group C	
	Body-weight (g.)	Thyroid weight (mg.)	Body-weight (g.)	Thyroid weight (mg.)	Body-weight (g.)	Thyroid weight (mg.)
1	102·5	21·9	133·5	26·3	110·0	7·2
2	99·15	17·7	117·8	17·2	162·0	10·2
3	117·9	31·1	171·3	31·2	94·9	8·0
4	113·5	21·3	122·0	24·8	105·8	7·7
5	162·2	33·3	107·1	18·7	135·4	8·5
6	95·4	30·2	88·6	15·4	111·6	8·5
7	163·4	34·2	151·6	30·7	136·0	10·0
8	110·5	24·7	146·2	23·6	93·2	7·0
9	101·5	23·1	130·6	25·8	87·3	8·9
10	119·4	22·7	100·6	14·9	102·9	9·1

Experiment 2.—Group A animals were treated as in experiment 1; group B received 2·3 μg. L-thyroxine daily; group C received 2·0 μg. L-triiodothyronine hydrochloride daily (an equimolecular dose to the thyroxine); group D received 0·5 μg. of L-triiodothyronine hydrochloride daily, all doses being administered in 0·1 ml. of solvent A. The results are shown in table II.

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DISCUSSION

There is a significant difference (t on 17 degrees of freedom is 3·06—i.e., P = 0·001–0·1) between the thyroid weights (expressed as a fraction of the body-weights) of the rats given equimolecular doses of L-thyroxine and L-triiodothyronine (experiment 2). The difference between the thyroid weights (expressed as a fraction of the body-weights) in the animals receiving thyroxine and 0·25 equivalent of triiodothyronine is not significant (t on 18 degrees of freedom is 0·63—i.e., P = 0·5–0·6). It is estimated from these experimental findings that the potency of L-triiodothyronine is 3–4 times that of L-thyroxine in the goitre prevention assay.

TABLE II—RESULTS OF EXPERIMENT 2

Anime lno.	Group A		Group B		Group C		Group D	
	Body-weight (g.)	Thyroid weight (mg.)	Body-weight (g.)	Thyroid weight (mg.)	Body-weight (g.)	Thyroid weight (g.)	Body-weight (g.)	Thyroid weight (mg.)
1	123·0	29·7	94·7	7·7	129·2	8·2	108·5	13·3
2	151·5	42·6	132·1	15·1	123·0	8·9	105·8	8·2
3	147·3	31·1	169·1	21·1	131·0	9·0	127·2	14·6
4	148·2	33·2	134·1	7·8	157·7	10·7	104·8	10·8
5	132·4	20·4	126·8	11·1	130·7	9·3	100·0	10·1
6	111·2	28·4	183·9	24·6	116·0	12·3	119·7	8·5
7	142·6	29·2	128·6	13·2	123·8	8·8	132·8	24·1
8	150·0	29·9	170·0	20·6	133·0	11·1	108·2	12·8
9	94·7	18·7	121·2	11·8	112·5	7·3	113·2	8·2
10	120·0	21·7	113·3	10·2	1 dead		122·8	15·9

These results suggest that the formation of triiodothyronine from thyroxine may be yet a further step in the biological synthesis of the thyroid hormone as described by Harington (1944). The stages at present assumed are :

(1) Oxidation of iodide to iodine.
(2) Iodination of tyrosine to diiodotyrosine.
(3) Coupling of 2 molecules of diiodotyrosine to give 1 molecule of thyroxine.

We now have to consider the possibility of :

(4) Deiodination of thyroxine to give triiodothyronine.

Roche et al. (1951) have shown that sheep thyroid slices can deiodinate I^{131}-labelled diiodotyrosine to give monoiodotyrosine, and have postulated a dehalogenating enzyme in the thyroid gland. It may well be that this or a similar enzyme plays an essential rôle in thyroid hormone synthesis by effecting the deiodination of thyroxine to triiodothyronine. There is, moreover, evidence that such an enzyme occurs in other parts of the body ; Gross and Leblond (1951) found that in thyroidectomised mice the administration of thyroxine labelled with I^{131} led to the appearance in the plasma of their compound, unknown 1, now identified (Gross and Pitt-Rivers 1952) as triiodothyronine.

At present, it is not possible to do more than speculate on the rôle of triiodothyronine in thyroid function, but the possibility clearly exists that it is the form of the thyroid hormone that is active in the tissues. Further experiments on the activity of triiodothyronine in the whole animal and also in isolated tissues are being carried out.

SUMMARY

3:5:3′-L-triiodothyronine has been assayed in rats by its effect in preventing goitre in thiouracil-treated rats. In this test its activity is about three times that of L-thyroxine.

We wish to thank Dr. W. L. M. Perry for help in the calculations of the results.

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STRANGULATED FEMORAL HERNIA IN A YOUNG BOY

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UNCOMPLICATED femoral hernia is uncommon in children under 10 years of age, occurring once in about every 250 cases of all types of hernia in this age-group (Stiles 1904, Rutherford 1927, Herzfeld 1938). Three-quarters of these children were girls. Strangulation of a femoral hernia in a child appears to be very rare, and I have found only three other published cases (Biasini 1936, Shepler and Smith 1940, Innocenti 1946).

A boy, aged 3 years 9 months, was admitted to the West Middlesex Hospital on Oct. 28, 1950, under the care of Mr. John Scholefield. He had been quite well until he awoke early that day with abdominal discomfort and pain in the right groin. A swelling was noticed in this region by the parent for the first time. There was no vomiting.

On examination the child did not appear ill. Temperature 99·2°F, pulse-rate 128. The tongue was moist and clean. The abdomen was soft and not distended ; bowel sounds were present and of normal quality. In the right groin there was a firm tender swelling, about 1 in. in diameter, below and lateral to the pubic tubercle ; it did not transmit a cough impulse. The overlying skin was not reddened, and no evidence of recent infection was found in the right lower limb, perineum, scrotum, or back.

Operation was carried out the same afternoon under general anæsthesia. Through an incision below and parallel to the right inguinal ligament the swelling was explored and found to be a femoral sac containing bloodstained fluid and a portion of strangulated omentum. It proved impossible to return this into the abdomen through the neck of the sac, which was very narrow, and it was therefore ligated and excised. The sac was freed from below and removed after ligation, but no repair was attempted.

The boy made an uninterrupted recovery and was discharged home on the 8th postoperative day.

The problem of diagnosis is well illustrated by this case. The family doctor had sent the boy to hospital as a case of inguinal lymphadenitis, but the admitting medical officer thought he had an irreducible right inguinal hernia. The lump was in the position of a femoral hernia ; but, in view of the rarity of this condition in childhood, lymphadenitis seemed to be the most likely diagnosis. Because of the absence of a primary focus of infection and the nearly normal temperature with a raised pulse-rate it was thought wise to operate. Biasini's (1936) patient, a girl of 6 had a raised temperature and was treated for some time with poultices before operation. Inguinal adenitis is fairly common in children without any obvious source of infection ; in adults it is notoriously difficult to distinguish from strangulated femoral hernia and may be tuberculous in origin. The importance of avoiding the conservative treatment of strangulated femoral hernia under the mistaken diagnosis of inguinal adenitis needs no emphasis.

Two other conditions which should be easy to exclude are femoral ectopia of a maldescended testis and psoas abscess.

I am grateful to Mr. Scholefield for permission to publish this case.

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