mouth ("elixir of myanesin") 1 fl. oz. (1 g.) five times daily, and 30 ml. of the 10% solution was added to each bottle of normal saline.

The dosage of mephenesin needed to control spasms rose day by day, and it is hardly surprising that, five days after starting mephenesin, haemoglobinuria occurred. This followed the administration of 21.5 g. of mephenesin in the preceding 24 hours (331 mg. per kg.). Within 24 hours of stopping mephenesin the urine was clear and there was no haemoglobin to spectroscopic examination. The blood urea was 36 mg. per 100 ml.—and the patient experienced no ill effects from the incident.

In place of mephenesin, gallamine triethiodide ("flaxedil") was now given into the drip tubing and was followed by immediate loss of spasm and pain with rather more tiredness and drunkenness than had occurred with mephenesin. The maximum single intravenous dose was found to be $\frac{1}{2}$ ml. (10 mg.), for on the occasion when 0.75 ml. was given complete paralysis of voluntary and respiratory muscles took place and the patient became deeply cyanosed. Oxygen was administered under pressure and artificial respiration maintained for a short time until normal respiration was re-established.

Coincident with the beginning of gallamine therapy the patient's temperature rose and he developed signs of patchy collapse at the right base. He was a little troubled at this time by the accumulation of secretions in his chest, which he was unable to cough up because coughing provoked generalized spasms. On March 27 striking improvement became apparent. Spasms diminished in intensity and frequency, and the amount of gallamine required to control them fell correspondingly. As the spasm diminished so the patient's respiratory condition improved, and he made an uneventful recovery.

Comment

The absence of respiratory depression with mephenesin makes this a highly useful drug in the treatment of tetanus. Intravenous administration gives maximal relief of spasm and is less disturbing to the patient than frequent intramuscular injections. It has the disadvantage that increasing dosage is required, and it is probably dangerous to press mephenesin therapy to the point of haemoglobinuria; indeed, Hewer and Woolmer (1947) report a death following its administration.

Gallamine triethiodide should be reserved for those cases which fail or cease to respond to mephenesin, since gallamine carries a very real risk of respiratory depression, and the borderline between relaxation and complete paralysis of all voluntary muscle is small. Again, intravenous administration is advisable, since intramuscularly its effect is difficult to control and it is a painful injection.

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The Central Youth Employment Executive has recently published three more booklets in the "Choice of Careers" series. These deal with the medical laboratory technician, the occupational therapist, and the physiotherapist respectively, and give an account of the technical qualifications, professional training, day-to-day work, and salaries and prospects in these three medical auxiliary services. The "Choice of Careers" booklets are intended primarily for young people who are deciding the type of work to take up, and also for those who are concerned in helping them to make a suitable choice of career. The booklets are obtainable from Her Majesty's Stationery Office, price 6d. each.

THE FLUORESCEIN CIRCULATION TIME IN THYROTOXICOSIS

BY

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A hyperkinetic circulation is an almost axiomatic feature of thyrotoxicosis. Blumgart *et al.* (1931) first demonstrated an increased speed of pulmonary blood flow in this condition. Wood (1950) stated that cardiac outputs of up to 12 litres a minute occur in thyrotoxicosis, and that increased outputs often do not subside for several weeks after the basal metabolic rate returns to normal. Goldberg (1938), in a study of 72 thyrotoxic subjects; demonstrated definite shortening of the circulation time in every instance. Unfortunately, the calcium gluconate method employed does not give an accurate end-point, and a control series of cases was not included. Moreover, other causes of circulatory acceleration were not considered.

In the measurement of circulation times the chief requisite is a method giving an objective and instantaneous "end-point." The fluorescein method described by Macgregor and Wayne (1951) fulfils these needs, and is safely and easily performed.

In this investigation the circulation times of 26 thyrotoxic subjects are compared with 14 euthyroid cases of thyroid enlargement and 20 cases of acute anxiety state. At the outset it was found that occasional cases of anxiety state had shortened circulation times when not sedated. Therefore, every case included in this investigation was given soluble amylobarbitone, 6 gr. (0.4 g.), one hour before the test was performed.

Technique

The technique used was a minor modification of Macgregor and Wayne's method. The test is briefly explained to the patient beforehand. This allays anxiety, and often evokes willing and interested co-operation. The requisites are: (1) A darkened, warm room. The ray-therapy room of a physiotherapy department was found to be ideal after fitting a blind to the window. (2) An ultra-violet lamp, fitted with Wood's diagnostic filter. This concentrated the radiation at a wave-length evoking the maximal fluorescence of fluorescein. (3) Ampoules of 4 ml. of sterile 20% fluorescein solution. (4) An equal mixture of histamine 0.1% (1:1,000) and procaine 2% solutions.

The patient, well clothed and wearing woollen socks, is warmed with an electric blanket until sweating is induced, and, wrapped in several blankets, is then rapidly transported to the darkened room.

Using the histamine-procaine mixture, intradermal weals are made at the left antecubital fossa and at the lateral aspect of the base of each hallux. The patient is kept warm whilst the weals develop; when possible, it is a good plan to keep the feet exposed but heated by a radiant-heat lamp. The fluorescein ampoule is now opened and the contents are prepared for intravenous injection. An assistant stands by the electric-light switch with a stopwatch. He switches off and starts timing at the command "go," and records two times at the commands "now" and "stop." The commands are given by the operator at the beginning of rapid intravenous injection at the right antecubital fossa; at the first appearance of fluorescence at the left antecubital fossa; and at the first appearance of fluorescence at the feet.

The end-points are clear and instantaneous, being given by sudden bright fluorescence of the weals. In timing, fractions of a second were not recorded, but were counted to the following second.

The difference between the arm-to-arm and arm-to-feet times is the "foot-minus-arm" time and, eliminating the variables of pulmonary circulation, is normally constant between 8 and 13 seconds.

Side-reactions.—These are trivial, and consist of: (1) Momentary flushing. Nausea may occur immediately following the injection, and is rarely accompanied by vomiting. It is preferable not to perform the test less than one hour after food. (2) Local reactions; 20% fluorescein has a necrotizing effect if injected extraveneously. Thus the intravenous site of the needle should always be confirmed before extinguishing the lighting.

TABLE I.—Thyrotoxic Patients

Case	Sex	Age	Clinical Features	B.M.R.	Ancillary Investigations	Circn. Time Foot-minus-arm
1	F	50	Bilateral exophthalmos, weight loss	+56%	A.S.P. 82. S. chol. 90. S. creat. 0.9	4 secs.
2	F	51	Goitre, weight loss, tachycardia	+17%	A.S.P. 85. S. creat. 1.06	6 "
3	F	28	Goitre, hyperhidrosis, lassitude, weight loss	+36%	A.S.P. 94. S. chol. 98	3 "
4	M	26	Goitre, early exophthalmos	+56%	S. chol. 118. S. creat. 1.06. Histology positive	7 "
5	F	41	Exophthalmos (severe), minimal thyroid enlargement	+32%	A.S.P. 80	5 "
6	F	53	Goitre with vascular bruit, tachycardia, exophthalmos	+41%	A.S.P. 86. Histology positive	7 "
7	F	28	Goitre with vascular bruit, tachycardia, exophthalmos	+98%	A.S.P. 92. S. chol. 127. S. creat. 0.92	2 "
8	F	45	Goitre with vascular bruit, active rheumatoid arthritis	+21%	A.S.P. 86. S. chol. 92	6 "
9	F	31	Goitre with vascular bruit, tremor, sweating	+33%	A.S.P. 85. S. creat. 1.4. Histology positive	6 "
10	F	56	Nodular and retrosternal goitre, auricular fibrillation and congestive cardiac failure	+54%	S. chol. normal. Histology negative	6 "
11	F	24	Partial thyroidectomy 1946, loss of weight, tachycardia, recurrent goitre with vascular bruit	+91%	A.S.P. 80. S. chol. 125	2 "
12	F	62	Goitre, auricular fibrillation and congestive cardiac failure	+57%	Radioactive iodine uptake increased. Histology carcinoma	4 "
13	M	46	Goitre, exophthalmos, tachycardia	+43%	A.S.P. 80. Histology positive	5 "
14	F	32	Thyroid enlargement with vascular bruit, cachexia	+38% +35%	Radioactive iodine uptake increased	4 "
15	M	34	Goitre with vascular bruit, tachycardia	+51%	A.S.P. 84. Histology positive	6 "
16	F	24	Goitre, proptosis, hysteria	+22%	S. creat. 0.96	7 "
17	F	58	Goitre, lid-retraction, hysteria	+52%	A.S.P. 86. S. creat. 1.12	5 "
18	F	22	Exophthalmos, weight loss	+32%	S. chol. 72. Histology positive	4 "
19	F	41	Goitre with vascular bruit	+49%	A.S.P. 88. S. creat. 2.1. Histology positive	4 "
20	F	63	Thyroid "adenoma," exophthalmos and lid-retraction	+25%	A.S.P. 85. S. chol. 120	7 "
21	F	23	Goitre, exophthalmos, cachexia	+74%	A.S.P. 102. S. chol. 68	3 "
22	F	37	Goitre, dyspnoea, tachycardia, psychosis	+41%	S. chol. 122. Histology positive	13 "
23	F	39	Exophthalmos, auricular fibrillation	+62%	S. chol. 97. Histology positive	3 "
24	M	38	Goitre, obesity, tachycardia, lid-retraction	+40%	A.S.P. 86	7 "
25	M	40	Goitre with vascular bruit, exophthalmos, lid-retraction	+68%	A.S.P. 90. S. chol. 100. Histology positive	5 "
26	F	29	Goitre with vascular bruit, lid-retraction	+89%	A.S.P. 96. S. creat. 1.2	3 "

A.S.P. = Average sleeping pulse rate per minute. S. chol. = Serum cholesterol in mg. per 100 ml. S. creat. = Serum creatine in mg. per 100 ml.

A yellow appearance of the skin may be disturbing, but the subject should be reassured and told that the fluorescein will be rapidly excreted in the urine.

Thyrotoxic Cases

Table I shows some details of 26 thyrotoxic patients; in every case thyroid enlargement was present. Thyrotoxicosis was diagnosed clinically, before detailed investigation, in 23 cases. Apart from classical physical signs of thyrotoxicity, considerable diagnostic value was attached to the presence of a to-and-fro vascular bruit on auscultation over the thyroid gland. This sign was present in 10 of the thyrotoxic cases, but was not found in any of the 14 euthyroid cases of thyroid enlargement listed in Table II.

The following routine investigations were performed in the assessment of thyroid function: (1) Basal metabolic rate (B.M.R.). This is shown as a plus or minus figure, representing percentage deviation from average normal. (2) "Average sleeping pulse rate" (A.S.P.). This is the average of five nightly estimations, each taken from the temporal pulse during deep sleep, without waking the patient. Boas (1932) first drew attention to the value of this simple often-neglected investigation—which is of considerable use if common-sense precautions are taken in its execution. An A.S.P. of 80 a minute or more was regarded as supporting a diagnosis of thyrotoxicosis. (3) Serum cholesterol values of under 120 mg. per 100 ml. were regarded as supporting a diagnosis of thyrotoxicosis. (4) Serum creatine was estimated by the method of Peters (1942), and values of over 0.5 mg. per 100 ml. were regarded as supporting a diagnosis of thyrotoxicosis. (5) Thyroid histology, when available post-operatively or at post-mortem examination, was studied by the same pathologist on each occasion. Appearances suggestive of thyrotoxicosis are shown in Tables I and II as "histology positive"; in all cases in which the histological appearances were indefinite this is shown as "histology negative." (6) The radioactive iodine uptake was estimated in only two cases. With the exception of the B.M.R., which is tabulated separately, all investigations

TABLE II.—First Control Series. Euthyroid Patients

Case	Sex	Age	Clinical Features	B.M.R.	Ancillary Investigations	Circn. Time Foot-minus-arm
1	F	38	Partial thyroidectomy for "toxicity," 1943. Weight loss, nervous symptoms, and migraine. No thyroid enlargement	+24	Negative	10 secs.
2	F	26	Thyroid enlargement. Tachycardia and nervous symptoms	-1	"	12 "
3	F	19	Goitre and nervous symptoms	+15	Negative, save S. creat. 0.64	12 "
4	F	32	Goitre; loss of weight, lassitude	-9	Negative	15 "
5	F	18	Goitre; dyspnoea	-3	"	9 "
6	F	32	Partial thyroidectomy for "toxicity," 1943. Persistent exophthalmos	+22	"	14 "
7	F	47	Goitre. Dyspnoea with stridor	+14	Negative. Histology negative	10 "
8	F	69	Dyspnoea. Retrosternal goitre on radiography	+6	" "	17 "
9	M	25	Goitre with recent increase size	-9	Negative	9 "
10	F	53	Goitre; paroxysmal dyspnoea, severe hypertension	+12	"	13 "
11	M	32	Dyspnoea, lassitude, tachycardia, tremor	+11	"	14 "
12	F	33	Paroxysmal tachycardia. Minimal thyroid enlargement	-2	"	8 "
13	F	57	Loss of weight, tremor, dyspnoea	+15	"	15 "
14	F	30	Goitre, loss of weight, and tracheal compression	-6	Negative. Histology negative	9 "

are included in the section headed "ancillary investigations." Only results relevant to a diagnosis of thyrotoxicosis are shown in this column.

Of the 26 cases, 25 showed a shortened circulation time, the curious exception (Case 22) having a psychosis (agitated depression) necessitating certification some two weeks post-operatively.

In eight cases the circulation time was re-estimated after apparent restoration to euthyroidism following medical or surgical treatment. In two cases a hyperdynamic circulation persisted—one six months after partial thyroidectomy and another after 22 months' thiouracil treatment.

First Control Series

Table II shows details of 14 cases with thyroid enlargement and associated symptoms, or with persistent symptoms following partial thyroidectomy for thyrotoxicosis. All were clinically adjudged euthyroid. In Cases 7, 8, and 14, thyroidectomy was subsequently performed—one for retrosternal extension and two for tracheal compression. In one case (No. 1) cautious medical treatment was undertaken, in deference to a raised B.M.R. reading, associated with a past history of partial thyroidectomy. It is noteworthy that no case in this group had vascular bruit over the thyroid gland. All members of this group had normal circulation times.

Second Control Series

Table III shows some details of 20 patients in whom a psychiatric diagnosis was eventually established. None had thyroid enlargement, and in no instance was a diagnosis of

TABLE III.—*Second Control Series*

Case	Sex	Age	Clinical Features	Circulation Time (Foot-arm)	Remarks
1	F	54	Agitated depression	20 secs.	Marked improvement on E.C.T.
2	M	40	Cardiac neurosis	8 "	B.M.R. +6. Improved on sedation and reassurance
3	M	25	Hysterical hyperpnoea. Early schizophrenia	6 "	Transferred to psychiatric hospital
4	F	47	Menopause. Cardiac neurosis	11 "	B.M.R. -2. Improved on sedation and reassurance
5	F	18	Hysterical hyperpnoea	10 "	Recovery on sedation and psychotherapy
6	M	28	Acute anxiety. Attacks of tachycardia and sweating	9 "	B.M.R. +5. Improved after sedation, cardiac investigation, and reassurance

Cases 7 to 20 were out-patients with acute anxiety state. All of these showed "foot-minus-arm" circulation times within a range of 9 to 17 seconds.

thyrotoxicosis made on clinical grounds. All were followed up for short periods of up to three months. Most of these were cases of acute anxiety state in whom dyspnoea, tachycardia, or loss of weight featured prominently. For obvious reasons it was not desirable to admit all cases to hospital for detailed investigation.

The circulation time was within, or above, the normal range in 19 instances, the only case with a hyperdynamic circulation (No. 3) having a psychosis.

Discussion

Several causes of hyperkinetic circulation are now recognized, and it is therefore necessary to exclude them before a shortening of circulation time can fairly be attributed to thyrotoxicosis. These causes include pregnancy, anaemia, aortic incompetence, Paget's disease of bone, advanced hepatic failure, arteriovenous aneurysm, beriberi. These conditions are easily separated from thyrotoxicosis, and their exclusion rarely creates a problem, with the possible exception of vitamin-B deficiency.

Williams *et al.* (1943) found biochemical evidence of thiamine deficiency in 75% of a group of 40 unselected

thyrotoxic subjects, and regarded this as being due to a combination of increased requirement and excretion of thiamine.

Since Wenckebach (1934) and other investigators have demonstrated a hyperkinetic circulation in beriberi, it is possible that vitamin-B deficiency of subclinical degree may be a factor in the circulatory acceleration of thyrotoxic subjects. This may explain some discrepancies in either degree or duration of hyperkinesis, but does not affect the first finding of this investigation—that virtually all thyrotoxic subjects have some degree of circulatory acceleration.

The second finding is that psychogenic disturbances, under amylobarbitone sedation, do not result in hyperkinesis. Thus a relatively simple test can be used to resolve the differential diagnosis of thyrotoxicosis and uncomplicated anxiety state.

Summary

The circulation time, calculated by the method described, is considered to be a valuable ancillary investigation in the diagnosis of thyrotoxicosis, provided other causes of hyperdynamic circulation are recognized and excluded.

The method used is regarded as safe and easy; in several instances it was performed on out-patients.

In a group of 26 thyrotoxic cases, 25 had a circulation time below normal limits.

In a group of 20 psychiatric cases, only one case had a shortened circulation time.

In a group of 14 euthyroid patients with thyroid enlargement, all cases had normal circulation times.

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TREATMENT WITH INSULIN ZINC SUSPENSIONS

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Further evidence regarding the results of insulin zinc suspension therapy is provided by the series of 52 patients reported here. Treatment was given in the wards in 36 of these cases, the remainder being treated throughout as out-patients. This trial has been in progress for the past nine months.

Results were classified as good if the fasting, noon, and evening blood sugars (estimated by King's method) were within normal limits, such results being confirmed by further satisfactory urine and blood-sugar tests.

The quantity of carbohydrate in the diets varied from 140 to 250 g. a day, generally divided into approximately equal rations at the four main meals, with snacks at mid-morning and bedtime. In some cases in which the noon blood sugars remained high as compared with those later in the day, the carbohydrate was reduced at breakfast, more being given at lunch and/or the later meals.