pain which kills only sometimes, but which maims all the time unless under careful and wise supervision.

Miss E. M. Goldberg, of the medical research unit, and Miss M. E. Druett, almoner to the cardiac department, of the London Hospital, have given me great help in the interrogation of those patients who had passed through an attack of cardiac infarction.

THE THYROID AND THE HEART*

BY

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Both oversecretion and undersecretion of the thyroid hormone have serious effects on the heart. Those of oversecretion are better known because they are much the commoner. Many features of severe hyperthyroidism are historical because the picture has changed in the past decade or two as a result of earlier diagnosis and of more effective antithyroid treatment. Thus the more advanced changes formerly seen and the post-thyroidectomy thyroid crisis are never allowed to develop. In the first stage there is an increase in the heart rate, normal rhythm persisting. Under certain conditions—for example, any event which produces tachycardia in the euthyroid subject, such as an infection or operation—and particularly in the child and young woman, this increase may reach an extreme degree. As a hospital resident I saw a child of 13 with exophthalmic goitre, as we then called it, complicated by acute appendicitis. This had to be treated by operation, and it was followed by a mounting tachycardia which just before death reached the extreme figure for normal rhythm of 250 a minute. The tachycardia of hyperthyroidism is labile and shows an exaggerated response to emotion and, as mentioned, to infections. On the other hand, the heart rate may fall to normal in a few days with complete rest and medical treatment.

Occasionally toxic goitre can be diagnosed with a normal heart rate—that is, in the seventies. I think this may occur in subjects who normally have a bradycardia, and is therefore seen in the male; but it is also met with in the elderly woman who gets paroxysms of auricular fibrillation as evidence of thyroid toxaemia, but between these has sinus rhythm without tachycardia. Such a patient may have a B.M.R. not over the upper limit of the normal. Occasionally in younger women and girls the heart rate is high at times, though they have become fat, feel better, and seem generally to have lost their thyroid toxaemia. Here the tachycardia is probably nervous and not thyrotoxic in origin. Nearly all the abnormal rhythms occur in toxic goitre; and extrasystoles, more often ventricular than auricular, are the first to appear. Superimposed on a sinus tachycardia, they are of some diagnostic value, as this combination is commoner than in any other condition. When the extrasystoles are seen, auricular fibrillation is usually in the offing.

Auricular Fibrillation

Hyperthyroidism is one of the commonest causes of auricular fibrillation, and it is well to consider it, however inconspicuous the other symptoms of toxic goitre. If rheumatic, or coronary, or hypertensive heart disease is not the explanation, then toxic goitre may be. Unsuspected cases are treated solely with rest and digitalis when antithyroid treatment is essential. A clue to diagnosis is the absence of response to digitalis, as this drug has little effect on the ventricular rate until thyroid toxaemia is reduced; then it does appear to have some action. There is a close connexion between age and the incidence of auricular fibrillation in toxic goitre, with a rise in each successive decade, so that while extremely rare in those under 30—it used to be seen at this age after thyroidectomy—it is common in those over 70. This is true both of established fibrillation and of the paroxysmal form, either before or after thyroidectomy. Restoration of normal rhythm is evidence of good treatment.

It may be that the thyroid hormone plays a part in determining auricular fibrillation even when the secretion of the gland is physiological, as is suggested by the case of a woman aged 34 with mitral stenosis who had the whole of her thyroid gland, which was normal, removed for resistant heart failure. This was a form of treatment resorted to in the 1930's. Although she had been fibrillating for years, normal rhythm returned when she developed myxoedema after the operation. Spontaneous return of normal rhythm in a patient with advanced rheumatic heart disease who has had fibrillation for a long time is a most unlikely event and suggests that the thyroid hormone, even when present in normal amount, affects auricular function.

Other arrhythmias occur only rarely, but now and then there may be auricular tachycardia or flutter, usually alternating with auricular fibrillation. Mild heart block with prolonged A–V conduction time is occasionally seen, even in young subjects.

Blood Pressure

A raised pulse pressure is a cardinal symptom of hyperthyroidism; in fact, it should rank with tachycardia, goitre, eye signs, and tremor. Eye signs may be absent and a goitre not detected, but a diagnosis of toxic goitre in the absence of increased pulse pressure must be regarded as doubtful. This point is particularly important in the differential diagnosis between cases of goitrous tachycardia and those of diastolic hypertension in which tachycardia may be a feature. The first do not show increased pulse pressure despite their tachycardia. This is not to say that the diastolic pressure remains normal in hyperthyroidism. An investigation of 200 cases of toxic goitre showed a slight rise in diastolic pressure but a greater increase in the systolic as compared with 100 controls of the same age and sex distribution. Finally, there is the hypertension seen in middle-aged or elderly women many years after thyroidectomy. The operation has been successful in that thyroid function appears normal, but they show a severe degree of diastolic hypertension. The proportion who develop this seems too high to be accounted for by coincidence, but what connexion it has with toxic goitre in the distant past is obscure.

The electrocardiogram is of limited value in toxic goitre. It will provide an objective record of heart rate and the diagnosis of abnormal rhythms. In configuration the main change is a tall T wave, just the reverse of what happens in hypothyroidism.

Radiology of the Heart in Toxic Goitre

The apex beat is often felt outside the mid-clavicular line, giving an impression of enlargement, and is due to

*Read to the Section of Cardiology at the Annual Meeting of the British Medical Association, Birmingham, 1958.

the excited action of the heart and may not be borne out by radiology. In the first description of toxic goitre Parry in 1825 stated that the heart was enlarged, but he of course depended on clinical signs alone. However, there may actually be slight, moderate, or considerable enlargement, and certain changes in configuration which are to a certain extent characteristic. To take the contours in order, beginning at the left lower border, the left ventricular contour may be slightly prominent; immediately above this the border of the right ventricular conus is not affected (as it is in mitral stenosis); but higher still there is frequently a prominence of the main pulmonary artery. Above this the aortic knob is neither prominent nor small, as it often is in mitral stenosis, but the arch of the aorta may be unduly high. On the right border the superior vena caval shadow may be prominent, owing to lateral pressure on the vessel by the goitre, occasionally to congestive heart failure; possibly an increased venous return from the thyroid may be a factor. Of course the shadow of an intrathoracic goitre may be seen along the upper part of the vascular pedicle. The left auricle is not enlarged except when there is auricular fibrillation.

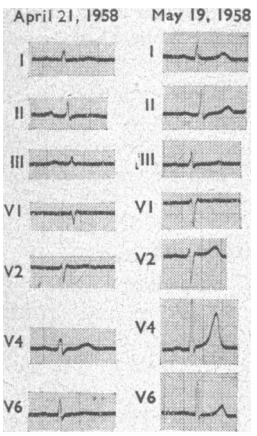

FIG. 1. — Electrocardiograms of woman aged 44 with a goitre and hypothyroidism. Left tracing shows normal rhythm, rate 68 a minute, low voltage, and slight increase in P-R interval, low T waves especially in the limb leads, and slight depression of the ST segments. The right tracing taken after four weeks' treatment with thyroid hormone shows reduced P-R interval and correction of the ST and T changes, the last shown best in lead V4.

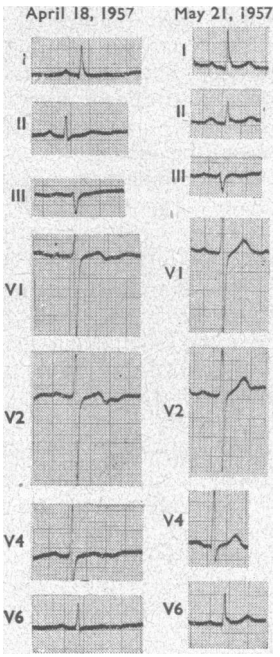

FIG. 2. — Electrocardiograms of woman aged 70 who developed severe myxoedema three months after radioiodine treatment for malignant goitre. Tracing on left taken at this time shows normal rhythm, rate about 70 a minute, T wave flat or biphasic, negative U wave; the right tracing, taken after one month's treatment with thyroxine, shows normal rhythm, rate 90 a minute, T wave normal, U wave just positive.

Anything more than slight changes in heart size do not occur unless there is auricular fibrillation, and especially if there is also failure. In its most characteristic form the goitre heart has a fairly straight left border with little alteration of the right profile, so that in shape it somewhat resembles a ham. The quick large pulsations of the left heart border and of the large arteries of the vascular pedicle are a striking feature.

The prominence of the pulmonary artery is probably due to several factors, increased cardiac output and increase in pulse pressure, causing an increased excursion and therefore stretching of the vessel wall, being the most important. The relatively thin-walled pulmonary artery is more affected by these factors than the aorta. In the cadaver with the heart *in situ*, distension of the pulmonary artery with fluid injected into the right ventricle causes the artery to bulge on the left profile so as to resemble the *x*-ray appearance of goitre heart.

Heart Failure

There has been a long controversy about whether or not hyperthyroidism can by itself cause congestive heart failure. Certainly it is very rare under the age of 40 unless there is in addition some primary form of heart disease, but it is seen in middle-aged or elderly women with auricular fibrillation, and very rarely with normal rhythm. It is therefore contended that, but for the effects of age, coronary disease, and hypertension, failure would not develop. This is incorrect, but, even if it were correct, it is not of practical importance if toxic goitre is the exciting factor and its removal clears up the condition. Twenty-five to thirty years ago failure was seen in about 10% of cases, but the figure is very much less than this to-day. In the young middle-aged subject it is the high ventricular rate at the onset of

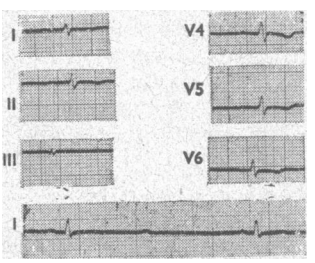

FIG. 3.—Electrocardiograms of girl aged 18 with hypothyroidism; thyroidectomy for toxic goitre at age 12. Tracing shows bradycardia, low voltage, and T wave just negative in all leads except III, where it is flat; P-R interval sometimes increased; lower strip of lead I shows 2:1 heart-block.

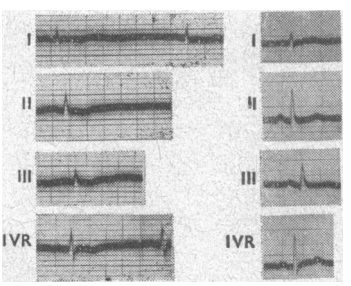

FIG. 4.—Electrocardiograms of man aged 57 with myxoedema. Left tracing shows normal rhythm rate 45 a minute; low voltage; digitalis-like depression of T and ST. Right tracing taken after treatment with thyroid extract, shows normal rhythm, rate 75 a minute; some increase in voltage; T and ST normal.

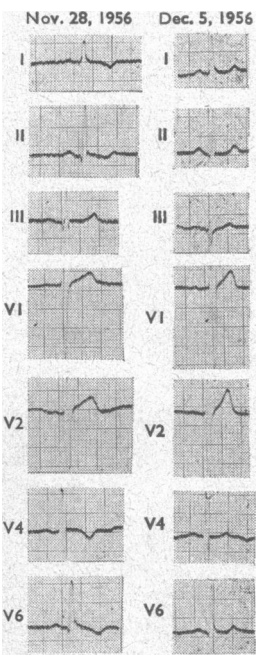

FIG. 5. — Electrocardiograms of woman aged 76 with spontaneous myxoedema. Tracing on left shows ST deviations and T inversions as in anterolateral coronary thrombosis; tracing on right, taken after one week's treatment with thyroxine, shows curve restored to normal.

fibrillation which leads to failure. For example, a woman aged 43 had a four-years history of loss of weight amounting to 70 lb. (32 kg.), palpitation, nervousness, and shakiness; a neck swelling had been noticed only six months before. When first examined her pulse was regular, rate 118 a minute, and B.P. 160/80 mm. Hg; later, auricular fibrillation developed with a ventricular rate of 150 a minute followed by congestive failure.

The treatment for failure with fibrillation is an antithyroid drug combined with the usual methods for failure, including digitalis and diuretics. The ventricular rate in the fibrillation of toxic goitre is resistant to digitalis, which, when given alone, may have little effect. However, when given with an antithyroid drug it seems to exert some activity. Failure of digitalis to slow the heart in auricular fibrillation usually indicates the existence of some extraneous factor, and toxic goitre is one of the first to be suspected. After a few weeks on an antithyroid drug and digitalis, normal rhythm can be expected to return. But, whether it has or not, thyroidectomy if contemplated can then be carried out provided failure has cleared up, the patient is well generally, and the ventricular rate is under control. After this, normal rhythm may return spontaneously; if it has not done so within a week or two an attempt may be made to restore it with quinidine.

Cardiac Pain in Toxic Goitre

In my experience cardiac pain is hardly ever a symptom in toxic goitre. Why it should be so exceedingly rare is a mystery, since at least half the patients are over 50 years of age. It is only partly accounted for by the predominantly female sex incidence of toxic goitre, while cardiac pain generally shows a moderate predominance in the male. Another small factor may be the presence of auricular fibrillation in the older women with toxic goitre; in some way this arrhythmia and the sensation of cardiac pain are antagonistic.

Induced Hypothyroidism for Cardiac Failure and Cardiac Pain

In the 1930's many papers appeared in America on the total removal of the normal thyroid gland for chronic heart failure, of whatever aetiology, and for persistent cardiac pain. Very favourable results were reported, but nevertheless the method was rather suddenly dropped after a few years. With the development of other effective measures for heart disease the procedure is now chiefly of historical interest. Similarly, I have not found antithyroid drugs to induce hypothyroidism of any help in heart failure. In the few cases I have treated, the general state was made worse rather than better.

For severe effort or emotional angina the drawbacks of subthyroidism were again found to offset any temporary relief that might follow the operation. The antithyroid drugs have in my experience also been ineffective.

The Heart in Myxoedema

Spontaneous myxoedema is rare compared with hyperthyroidism, but, even more than in toxic goitre, shows itself in the female rather than in the male. However, as many cases occur as a sequel to treatment given for toxic goitre, and in these it is possible to study the disease in a milder form and usually free from the complicating effects of other types of heart disease. The clinical and electrocardiographic changes in myxoedema are in many ways the antithesis of those of toxic goitre: on the one hand, an animated, bright-eyed, thin subject with warm smooth moist skin; on the other, in severe cases of myxoedema almost lifeless immobility, expressionless puffy faces, and dry, rough, cold skin. Similarly, the electrocardiogram in the two conditions varies in opposite directions. It has been examined in three groups—patients who became hypothyroidic from antithyroid drugs, including one from radioiodine, cases following thyroidectomy, and spontaneous cases (Table I). There were 12, 7, and 18 cases respectively in the three groups (Tables II, III, and IV), making a total of 37 (36 female, 1 male).

TABLE I.—*Hypothyroidism and Myxoedema*

	No. of Cases
After thiouracil	11
,, radioiodine	1
,, thyroidectomy (and thiouracil)	7
Spontaneous (including 3 cases with goitre)	18

The electrocardiographic changes are unique in cardiography. The changes were similar in the three groups, varying only in degree. However, in the spontaneous cases, in which hypertension has often been present for many years, there will also be a left ventricular predominance pattern. It is generally accepted that the curve shows a slow rate, a low voltage, and in particular a flattening of the T wave. Exceptions to this are that, in the younger milder cases which are met with after they have had antithyroid drugs, the rate may be in the seventies; while in those with curves showing

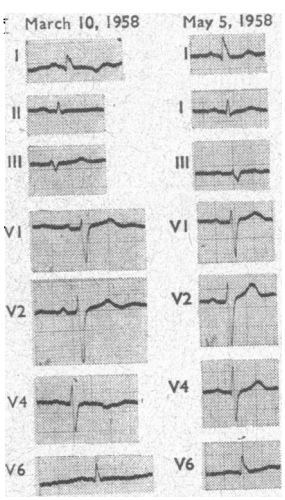

FIG. 6. — Electrocardiograms of woman aged 62 with post-thyroidectomy myxoedema shows combined effects of left ventricular predominance due to hypertension and myxoedema. Tracing on right taken after eight weeks' treatment with thyroid hormone shows only slight changes of left ventricular predominance.

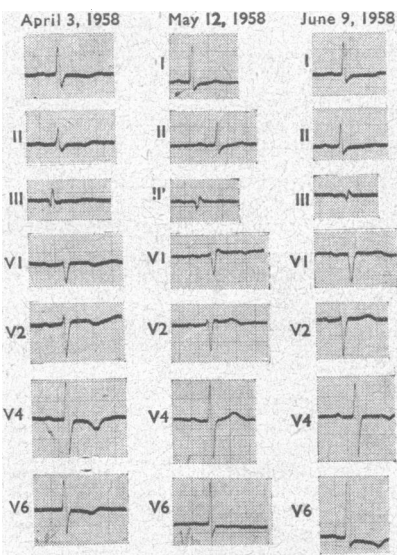

FIG. 7. — Electrocardiograms of woman aged 73 with spontaneous myxoedema. Left tracing shows T inversion in all leads; middle tracing, taken after five weeks on thyroid hormone, shows normal appearances, except that T is rather low. Right-hand tracing, taken four weeks after stopping thyroid, shows reversion almost to the original abnormal pattern.

TABLE II.—*Myxoedema (Therapeutic)*

Case No.	Age	E.C.G. Rate	ST	T Wave	Low Voltage	Other Features	Heart Size	B.P.	Treatment Result
1	60	75	Depressed. Digitalis-like	Bi. and Neg.	Yes		Sl. +	150/90	Sl. ST depression only left
2	57	90	Not depressed	Flat	Reduced		,,	160/115	High T
3	39	72	,, ,,	,,	Yes		Not +	130/100	Normal
4	65	65	Depressed. Digitalis-like	Neg.	,,		Sl. +	125/80	V. sl. ST depression
5	61	75	Depressed	Flat	,,		,,	—	Normal
6	67	70	Not depressed	Flat. Neg. Bi.		Neg. U	Normal	170/110→140/100	,,
7	75	70	,, ,,	Pos.	Yes	P–R sl. +	Sl. +	240/120	,,
8	44	70	Depressed ,,	Just neg.	,,		Not +	170/100	E.C.G. normal. Rate unchanged; increased voltage
9	53	68	Not depressed	Flat	,,	P–R +	Sl. +	—	T normal
10	50	70	,, ,,	Low	,,		Not +	—	Normal E.C.G.
11	36	80	Depressed ,,	,,	,,		—	—	,, ,,
12	59	78	Not depressed	,,	No		Sl. +	170/100	,, ——

Bi. = Biphasic.

TABLE III.—*Myxoedema (Post-operative)*

Case No.	Age	E.C.G. Rate	ST	T Wave	Low Voltage	Other Features	Heart Size	B.P.	Treatment Result
1	73	85	Depressed	Pos.	No		Sl. +	220/105	Thyroid extract omitted. E.C.G. unchanged in 2/12
2	29	68	,,	Neg.	Yes		Not +	130/90	E.C.G. normal after 15/52. E.C.G. relapse in 2/52
3	34	85	Sl. depression	Pos.	,,	Mitral stenosis	+++	145/90	Died. 24 oz. (680 ml.) pericardial fluid
4	62	65	,, ,,	Neg.	,,	L.V.P. pattern. Cholesterol 317→170	Sl. +	190/130→185/115	Less T inversion, then T pos. Increased rate and voltage
5	18	65	,, ,,	,,	,,	Heart-block	Not +	115/65→130/100	E.C.G. normal apart from P–R
6	27	75	Normal	,,	No		,,	120/80	Normal—later some relapse
7	40	95	Sl. depression	,,	Yes		,,	160/110 (prev. 170/90)	E.C.G. normal

L.V.P. = Left ventricular predominance.

TABLE IV.—*Myxoedema (Spontaneous)*

Case No.	Age	E.C.G. Rate	ST	T Wave	Low Voltage	Other Features	Heart Size	B.P.	Treatment Result
1	64	62	Depressed	Neg. all leads	Sl.	L.V.P. Oedema Cerv. vs. +	+++ →sl. +	170/120→170/85	Converted to L.V.P.
2	76	55	Deviated	Neg. as in ant. lat. infin.	No		Sl. +	110/70	E.C.G. normal in 17 days
3	73	68	Sl. depression	Neg.	Yes	Oedema	,,	110/60	E.C.G. normal. Heart size normal
4	76	78	Depressed	,,	,,		,,	130/80	P.M. cereb. haem. Pul. emb.
5*	57	40	,,	Flat	,,	Sl. oedema	,,	120/75	E.C.G. normal
6	46	75	Sl. depression	,,	,,	Goitre. Oedema	Not +		,, ,,
7	69	62–80	Depressed	Neg.	No	Oedema	++	265/145→175/100	Slight change in T
8	42	68	Not depressed	Low	Yes	Exophthalmos	Not +	120/70	Increased rate and voltage
9	44	80	,,	Flat	,,			120/80	E.C.G. normal
10	65	65	Depressed	Neg.	Sl.		Sl. +	130/70→180/110	,, ,,
11	74	78	,,	,,	No		+	275/160	Rate unchanged; incr. L.V.P.
12	44	68	Not depressed	Low	Yes	Goitre. P–R +	Not +	135/95	Increased T; P–R reduced
13	40	68	,, ,,	Sl. low	,,	Goitre	Not +. Left mid-arc. sl. +	130/85	Increased voltage only
14	63	90	,, ,,	Flat	Sl.		++	230/130	P. 85. T and voltage increased
15	68	<60	Sl. depression	Flattened	Yes		+	230/85→205/100	E.C.G. normal; P–R reduced
16	60	60	Isoelectric	Flat	,,	P–R +	++	160/105	P–R reduced; A.P.C.; rise in B.P. L.V.P.
17	73	65	Depressed	Neg.	No	P–R sl. +	Sl. +	225/130→170/80	Increased voltage and rate. T pos. Relapse in 3/52
18	41	55	Not depressed	Sl. neg. chest only	Yes		Not +; pulsn. very small	140/100→125/70	E.C.G. normal

L.V.P. = Left ventricular predominance. Cerv. vs. = Cervical veins. A.P.C. = Auricular premature contractions. *Male.

TABLE V.—*Effects of Thyroid Hormone Controls*

Case No.	Age	E.C.G. Rate	ST	T Wave	Low Voltage	Other Features	Heart Size	B.P.	Treatment Result
1	47	58	Not depressed	Pos.	Sl.	Cholesterol 262→172 in 10 days	Sl. +	130/70	Rate 62. Increased voltage, especially T. B.P. 120/80
2	73	80	,, ,,	,,	Yes	Raynaud's disease	Not +	170/90	Rate 80; T only increased
3	66	60	Depressed	Flat or pos.	,,	Leukaemia	,,	110/75	A.F.
4	54	75	,,	Neg.	No	Hypertension. Colitis	Sl. +	190/125	Rate 90; less ST depression
5	77	75	,,	,,	Yes	B.P.	Not +	145/80→150/75	Rate 84. T more normal
6	62	48	,,	,,	No	Hypertension	,,	230/100	Rate 85. T more normal
7	77	50	Sl. depression	,,	,,	Old cardiac infarction. A.P.C.	Sl. +	170/90	Rate 60. V.P.C. T reversal and more pos.
8	30	88	,,	Pos.	,,	Goitre	Not +	130/85	Rate 110. More S–T depreciation. T. less pos.
9	50	50	Not depressed	,,	,,	R + in V1	,,	130/85	Rate 55; no other change

left ventricular predominance there need not be low voltage. A mild spontaneous case is illustrated by the tracing from a woman aged 44 with a goitre (Fig. 1). The curve shows a rate of 68 a minute, low voltage, and a slight increase of P–R interval, low T waves, especially in the limb leads, and very slight depression of the ST segments. It is a feature of the myxoedema cardiogram that the abnormalities are shown in all leads, both limb and chest leads, though sometimes more pronounced in the one, sometimes in the other. Slight increase in the A–V conduction time is not uncommon. After four weeks' treatment with thyroid hormone the tracing shows a reduced P–R interval, and correction of the ST and T changes, the last shown especially in lead V4.

A negative U wave has been seen once or twice, as shown in the tracing from a woman aged 70, who developed myxoedema after radioiodine treatment for a malignant goitre (Fig. 2). The curve became normal after a month's treatment with thyroxine; it is noteworthy that there is no change in the voltage. Heart-block of a higher grade than prolonged conduction time was seen only once; this was in a girl of 18 who developed hyperthyroidism six years after thyroidectomy for toxic goitre (Fig. 3). The three standard limb leads and chest leads show the P–R interval sometimes prolonged; low voltage and T wave just negative in all except lead III, where it is flat. Another strip of lead I shows 2:1 block which produced syncopal attacks. Occasionally the effect on the ST segment and T wave resembles that of digitalis, as shown in the tracing from a 57-year-old man (Fig. 4). The right-hand tracing shows a return to normal after treatment. He became psychotic, and was in a mental institution until it was recommended that he should have thyroid hormone, after which his mentality quickly became normal.

In more severe cases, as seen in those arising spontaneously or after thyroidectomy, the curve may resemble that of an antero-lateral infarction. Fig. 5 is a tracing from a woman of 76 with low blood pressure (110/70). The pattern resembles an antero-lateral ischaemic injury, but after seven days' treatment the curve has become normal. Her blood cholesterol fell from 680 to 145 mg. per 100 ml. in five weeks. The time taken for a tracing to be restored to normal depends in part at least on the dose of thyroid hormone prescribed, and the time in this case was the shortest observed. This shows how quickly the abnormal curve can be corrected, but it is usually wiser to adjust the treatment so that it takes several weeks.

In some cases there was at first a left ventricular predominance pattern. This might be entirely restored to normal or partially corrected. Fig. 6 shows correction of T inversions, but a wide slurred QRS and slight ST deviations persist. In a few cases there was correction of some T inversions, but an increase occurred in others, thus leaving a more ordinary left ventricular predominance pattern. The T-wave reversal can occur with no change in heart rate and little change in voltage.

The effects on the tracing of giving and stopping thyroid hormone are illustrated in the case of a woman of 73 with spontaneous myxoedema (Fig. 7). She was sent with a diagnosis of myxoedema, and, although she was not typical in appearance or demeanour, her electrocardiogram showed T inversion in all leads, B.P. 225/130, heart a little enlarged, and cholesterol 245 mg. per 100 ml. Thyroid hormone was given, and after five weeks the electrocardiogram became normal, the heart rate increasing from 62 to 75; the voltage was

FIG. 8.—Photograph of woman aged 64 with spontaneous myxoedema.

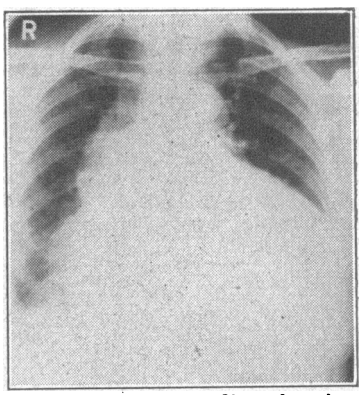

FIG. 9.—Chest *x*-ray film of patient shown in Fig. 8; great cardiac enlargement.

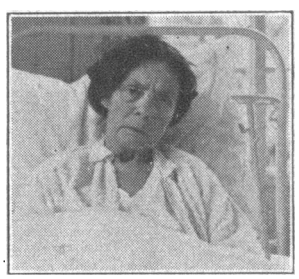

FIG. 10. — Photograph of patient shown in Fig. 8 after five weeks' treatment with thyroid hormone.

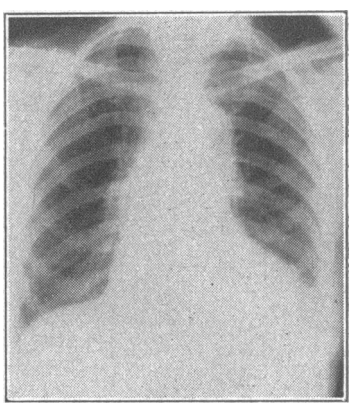

FIG. 11.—Chest *x*-ray film of patient shown in Fig. 10 taken at same time; great reduction in heart size.

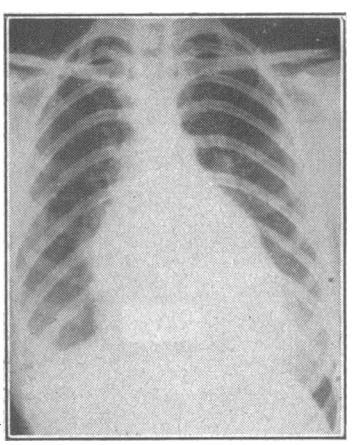

FIG. 12.—Chest *x*-ray film of patient with mitral stenosis.

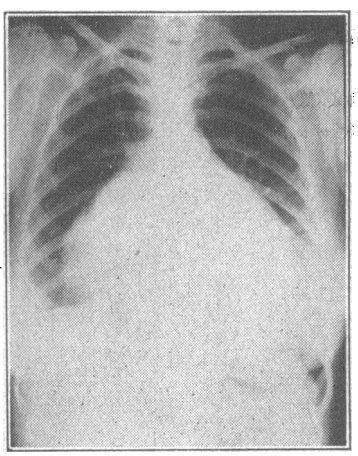

FIG. 13.—Chest *x*-ray of patient shown in Fig. 12 taken when myxoedema had developed after a therapeutic total thyroidectomy; great increase in cardiac silhouette due to pericardial effusion.

unchanged; the B.P. had fallen to 170/95; and the cholesterol was 210 mg. per 100 ml. However, the patient did not feel so well. Treatment was then stopped, and after four weeks the tracing had returned almost to its original normal pattern, the B.P. had risen to 210/105, and the cholesterol to 300 mg. The patient felt better for a time but then deteriorated; she finally improved on a smaller dose of thyroid.

The blood pressure, especially the diastolic, was slightly raised in mild cases. In the severe spontaneous cases it was very high in one half. Nearly always it fell to near normal as the myxoedema was corrected by thyroid hormone. The possibility that the disappearance of the electrocardiographic abnormalities under treatment could be due to fall in blood pressure might be put forward. This cannot be accepted, however, because the T-wave changes in myxoedema are more widespread than in hypertension; they can be corrected very much more quickly than in primary hypertension; and, moreover, they revert just as readily when an initially low blood pressure rises with treatment.

To test the effect of thyroid hormone on the electrocardiogram of patients with normal thyroid function, nine subjects were given triiodothyronine in doses of 40 to 90 μg. daily. The results are given in Table V. In those with a left ventricular predominance pattern there was some lessening of the depression of the ST segment and increase in the voltage of T; there were similar effects on the tracings of two patients with old coronary thrombosis. In one with a normal tracing thyroid hormone had no effect beyond a slight increase in rate. These effects are in keeping with the usual high T voltage in toxic goitre, for when thyroid hormone is given to a subject whose thyroid is functioning normally a mild degree of hyperthyroidism is produced. This raises the T wave and, with it, lessens the depression of the ST segment. The changes are, however, trivial in comparison with what occurs in myxoedema using the same dose of hormone.

Arrhythmia.—Abnormal rhythms are conspicuously absent. Apart from heart-block, the only one recorded was an occasional extrasystole, either ventricular or auricular. While an excess of thyroid secretion promotes auricular fibrillation, lack of this seems to prevent it.

Heart Size.—There was no enlargement in 14 out of 36 cases. However, pulsation was small even in these. Enlargement when present varied from slight to very great. Its amount was not always proportional to the severity of the hypothyroidism as judged by clinical, cardiographic, blood pressure, or cholesterol findings. It is probable that great enlargement is always due to pericardial effusion (Figs. 8 to 13). This is suggested by the shape of the very large heart and by the rapid shrinkage with treatment; as the face and body lose their puffiness the heart goes down at the same time.

Simulation of Congestive Heart Failure.—In a severe case with cardiac enlargement there is pitting oedema of the feet and legs and engorged cervical veins. Yet the *x*-ray picture of the lungs does not show congestion, and the patient can lie flat in bed and walk at her ordinary slow pace without dyspnoea. There are usually no cardiac murmurs, the pulse rate is slow, and digitalis is of no value. It is probable, therefore, that there is no congestive failure, the oedema and cervical vein engorgement being accounted for by anaemia, fluid retention, immobility, and pericardial effusion. There was no instance of cardiac pain before treatment was started, and in the two necropsies obtained the coronary arteries were entirely free of atheroma.

ORAL METHYLTESTOSTERONE AND JAUNDICE

BY

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Androgen therapy can be given by injection using single esters of testosterone such as the propionate, phenylpropionate, or oenanthate, or mixtures of esters such as the propionate, valerianate, and undecylenate; by injection of microcrystalline suspensions of testosterone or of testosterone isobutyrate; and by implantation of pellets of fused testosterone or testosterone propionate. Treatment can thus be planned to give temporary high-level doses with an injection every three to four days, or a long-lasting action for three to four weeks, using the oenanthate. After implantation, continuous absorption of small amounts of hormone will last for three to six months.

However, oral therapy is efficient, simple, rapid in action, and can obviously be stopped at once, if necessary. Methyltestosterone was introduced to clinical medicine by Foss in 1939, and since that time must have been used for its androgenic and protein anabolic effects in thousands of cases.

The effect of methylating testosterone was to protect it from deactivation in the liver after its absorption into the portal system, whereas free testosterone was largely inactivated by the liver.

By using the route of oral absorption, steroid hormones are absorbed through the buccal mucosa, when held either under the tongue or between the upper lip and the gum. Much of the hormone is then absorbed direct into the systemic circulation, thus bypassing the liver. When applied in this manner, methyltestosterone is, in fact, hardly more effective than by ingestion (Foss, 1956). Testosterone is of little value when swallowed, but is effective by buccal mucosal absorption (Escamilla and Gordan, 1950).

The metabolism of testosterone and methyltestosterone is different. Both hormones are powerfully anabolic and androgenic, but after mucosal absorption in the mouth testosterone produces an increased excretion of 17-ketosteroids, but has no effect on the excretion of creatine in the urine. Methyltestosterone, however, does not materially alter the excretion of 17-ketosteroids, but it does cause creatinuria.

Creatinuria can be produced also by other methylated steroids such as methylandrostenediol and methylandrostanediol. Methyltestosterone causes an increased excretion of glycocyamine along with creatinuria, which suggests that the synthesis of creatine is increased (Dorfman and Shipley, 1956). Samuels, Sellers, and McCaulay (1946) believe that the kidney is the primary site of action of methyltestosterone on creatine metabolism. In severe liver disease methyltestosterone was able to produce increased quantities of creatine, but this was not possible in nephrosis.

From the practical point of view, patients who have to continue substitution treatment for many years dislike the sublabial route. Designed for slow absorption, the