2-THIOURACIL IN THE TREATMENT OF CONGESTIVE HEART FAILURE

BY

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It has long been thought that removal of the influence of the thyroid gland might prolong life in cases of congestive heart failure. The theoretical purpose of such treatment is usually stated to be reduction of the total oxygen requirements of the body and decrease in the work of the heart (Blumgart, Levine, and Berlin, 1933; Fishberg, 1940). Total thyroidectomy has not proved entirely satisfactory, since the immediate mortality in severe cases was high (Cutler and Hoerr, 1941). The development of the goitrogenic substances for clinical use (Astwood, 1943) has indicated another possible method of diminishing thyroid activity, and this paper reports the effects of 2-thiouracil on cases of congestive heart failure which had failed to respond to ordinary methods of treatment and in which the immediate prognosis was poor.

Methods

The methods were similar to those published previously (McMichael and Sharpey-Schafer, 1944a; Howarth, McMichael, and Sharpey-Schafer, 1946), cardiac output and right auricular pressure being measured by cardiac catheterization. The observations were made with the patient's trunk elevated 45°. Right auricular pressure is about -7 cm. (sternal angle=0) in normal subjects in this position. The work of the heart is calculated arbitrarily from the product of the cardiac output and the blood pressure.

Results

Cases of severe congestive failure treated with thiouracil may be divided into two groups: low-cardiac-output heart failure (hypertensive and valvular heart disease) and high-cardiac-output heart failure (heart failure with emphysema). Initial data before thiouracil are shown in Table I. Cases 1, 3, 4, and 5 showed the usual response of their group to a fall in venous filling pressure—i.e., an increase in cardiac output. The slight fall in output after venesection in Case 2 indicated a less severe case. In the most severe cases, 6 and 7, little change in cardiac output was produced by a decrease in venous filling pressure. Starling's venous pressure-cardiac output curve has been suggested as a convenient concept for indicating the status of an individual heart (McMichael and Sharpey-Schafer, 1944b). In the emphysema group the usual status lies near the highest point of the curve, so that a fall of venous pressure results in a decrease in cardiac output (Cases 8, 9, 10, and 11). Only the most severe cases show an increasing output (Case 12) similar to the low output group. Several cases had a long period of treatment by ordinary methods—rest in bed, digitalis, and venesection in the low-output-heart-failure group and prolonged sojourn in an oxygen tent in the emphysema group. In some patients this treatment had caused little or no clinical improvement, the venous pressure remaining high.

Clinical Effects of Thiouracil.—The dosage of thiouracil and results of treatment are shown in Table II. No clinical benefit from thiouracil can be expected under a week or ten days. Fig. 1 (Case 1) shows an example of the fall of venous pressure

FIG. 1.—Case 1. Venous pressure fell and there was a diuresis after 10 days on thiouracil. V=Venesection. M=Mercurial diuretic.

and disappearance of oedema in a successful case. The long period of observation under treatment by ordinary methods in several cases makes spontaneous improvement unlikely. After several months on thiouracil signs of thyroid deficiency appear. The mental reactions and movements of the patient become slower. The skin becomes thickened, the hair dry, and the voice deeper and hoarser. In some cases the thyroid gland appears to increase in size; in others no enlargement is detectable. Agranulocytosis did not develop in any of these cases of congestive heart failure.

Effect on Oxygen Consumption.—Basal and resting oxygen consumption are reduced by thiouracil (Fig. 2). The basal

FIG. 2.—Case 2. Effect of thiouracil on basal oxygen consumption.

metabolic rate is usually increased in congestive heart failure. Prolonged treatment with thiouracil did not decrease the basal metabolic rate below -25% in any of these cases.

Effect on Cardiovascular Dynamics.—Results in a case from each group are shown in Table III. In Case 1 cardiac output was the same after thiouracil as during the control period, for, although resting oxygen consumption was less, the arterio-venous oxygen difference had decreased in parallel. Since the blood pressure was the same, the work of the heart did not

TABLE I.—Circulatory Data Before Thiouracil

Case	Age	Sex	Diagnosis	Right Auricular Pressure cm. Saline above Sternal Angle	Cardiac Output litres per min.	Arterial O ₂ Saturation %	O ₂ Consumption c.cm./min.	Blood Pressure mm. Hg	Heart Rate per min.	Remarks
Low-output Heart Failure										
1	52	M	Hypertension	+20	3.1	87.5	287	190/160	100	C.O. increased after venesection
2	43	M	M.S., A.S., A.I.	+3.5	4.8	94	360	148/90	74	C.O. slight fall "
3	43	F	M.S.	+21	3.15	88	289	120/90	118	C.O. increased " digitalis
4	59	M	A.I.	+2	4.4	91	297	208/108	88	C.O. " " venesection
5	35	F	M.S., A.I.	+21	1.6	92	239	248/140	88	C.O. " " "
6	39	F	Hypertension	+5	3.7	90	233		92	C.O. no change after digitalis
7	72	F	M.S., A.I.	+6	2.6	92	230	140/90	120	C.O. slight increase after digitalis and theophylline
Heart Failure with Emphysema										
8	31	M		+16	8.4	66	327	140/92	100	C.O. fell after venesection
9	56	M		+8.5	9.0	48.5	320	98/60	102	C.O. " " digitalis
10	54	F		+1	5.0	71	280	85/60	108	C.O. " " "
11	52	M		+6	6.6	67.5	260	156/92	104	C.O. " " "
12	42	M		+5	6.5	42	203	118/68	104	C.O. increased after venesection

TABLE II.—*Effects of Treatment with Thiouracil*

Case	Probable Duration of Failure before Admission	Treatment before Thiouracil	Daily Dose of Thiouracil	Result
1	4 mon hs	B.D.M., 1 mon'h; no improvement	2 g. f. r 154 days	V.P. normal for 100 days. Died after 154 days
2	3 "	B.D.M., 2 months; slight improvement	2 g. " 28 "	Thiouracil stopped. Alive, working 18 months later
3	2 years	B.D.V.M., 6 months; no improvement	3 g. " 18 "	V.P. normal. Left hospital after 3 months. Thiouracil stopped. Died 170 days later
4	1 year	D., 1 year. Progressive deterioration	2 g. " 275 "	Slight improvement. Died
5	5 years	B.D.V.M., 7 days; no improvement	1 g. " 42 "	V.P. fell to +2 cm. Died 3 months later
6	6 "	D., 6 years; chronic failure	2 g. " 33 "	Initial improvement. Died
7	2 "	B.D., 4 days; no improvement	1 g. " 21 "	No improvement. Died
8	1 year	B.D.O ₂ , 2 months; no improvement	2 g. " 18 "	V.P. normal. Working. Arterial O ₂ saturation = 84%
9	3 months	B.O ₂ , 2 weeks; no improvement	1 g. " 94 "	V.P. normal up to 8 days before death (acute respiratory infection)
10	6 "	B.O ₂ , 6 weeks; slight improvement	2 g. " 36 "	V.P. normal. Thiouracil stopped. Died 169 days later
11	3 weeks	B.D.O ₂ , 10 days; slight improvement	2 g. " 61 "	V.P. normal. Thiouracil stopped. Died outside hospital of acute respiratory infection
12	1 year	B.D.V.O ₂ , 1 month; no improvement	2 g. " 37 "	No change. Died
			1 g. " 10 "	
			1 g. " 22 "	

B. = Bed-rest. D. = Digitalis. V. = Venesection. M. = Mercurial diuretics. O₂ = Oxygen tent. V.P. = Venous pressure.

TABLE III.—*Circulatory Data Before and After Thiouracil*

Case	Time	Right Auricular Pressure cm. Saline above Sternal Angle	Cardiac Output (litres per min.)	Arterial O ₂ Saturation (%)	O ₂ Consumption (c.cm./min.)	A.V. O ₂ diff. (c.cm./litre)	Blood Pressure	% Change Cardiac Work
1	Before	+20	3.1	87.5	287	92	190/160	} No change
	After	+12	3.1	91	199	64	198/155	
9	Before	+8.5	9.0	48.5	320	35.8	98/60	} 25% decrease
	After	-7	5.4	61	263	48.4	114/80	

change. In Case 9 the high initial output decreased to a normal level. This was due not only to a decrease in the oxygen consumption but to an increase in the arterio-venous oxygen difference.

Effect on Thyroid Gland.—Detailed histological studies will be reported elsewhere on two surgical biopsies and ten post-mortem specimens (Doniach and Sharpey-Schafer, to be published). Clear-cut evidence of stimulation was present in cases receiving more than 70 g. The average weight of hyperplastic glands was not significantly greater than that of control untreated cases. Colloid re-formed and follicular epithelium was reduced in height within a few months of cessation of thiouracil treatment.

Discussion

"Clinical improvement" in patients with severe chronic congestive failure may be defined as a change which shows itself by a fall of venous pressure towards normal levels and an increase in exercise tolerance, which allows the patient to get about or to leave hospital. This definition covers both the high-output and the low-output groups. The data presented in this paper suggest that some cases which have reached a chronic state on ordinary methods of treatment will show "clinical improvement" when the activity of the thyroid gland is depressed by thiouracil. No benefit can be expected in cases which are becoming rapidly worse, since there is probably little effect on thyroid activity under ten days.

The exact mechanism by which induction of a hypothyroid state results in improvement is still uncertain. It involves the nature of the changes producing "congestive heart failure"—a subject on which our knowledge is as yet scanty. When the venous filling pressure is lowered by venesection or digitalis in cases of low-output heart failure, the cardiac output increases, and "clinical improvement" is associated with increased work of the heart (McMichael and Sharpey-Schafer, 1944b; Howarth, McMichael, and Sharpey-Schafer, 1946). In these cases, however, the oxygen consumption is unchanged as an immediate result of treatment.

Case 1 shows that the work of the heart may not change after thiouracil, and it is probable that some cases of low-output heart failure may show increased work in the hypothyroid state. In cases treated with thiouracil, although cardiac output may be unaltered it is maintained at a lower filling pressure and in relation to the oxygen consumption of the individual it is relatively increased.

Detailed studies on cases of heart failure with emphysema will be reported elsewhere, but in view of the poor prognosis in this group it is encouraging that even a few cases can be improved sufficiently to leave hospital.

Summary

Cases of severe congestive heart failure showing no response to usual therapy (bed-rest, digitalis, and mercurial diuretics) were given 2-thiouracil 1 to 2 g. a day over long periods. Life may be prolonged both in the low-cardiac-output cases (valvular and hypertensive heart disease) and in the high-cardiac-output cases (heart failure with emphysema).

In the low-output group the arterio-venous oxygen difference may decrease as well as the resting oxygen consumption. The work of the heart may be unchanged, but output is maintained at a lower venous pressure, and in relation to oxygen consumption cardiac output is relatively increased.

Cases of high-cardiac-output heart failure with emphysema may improve sufficiently to leave hospital in spite of permanent reduction of arterial oxygen saturation.

There is histological evidence that the thyroid returns to normal after stopping thiouracil.

These observations were made in collaboration with Dr. John McMichael and Dr. Sheila Howarth. The Medical Research Council defrayed some of the expense.

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Assistant nurses who have been enrolled by virtue of two years' whole-time nursing experience acquired since Sept. 3, 1939, may be granted a remission of six months in the normal three-year period of training for State registration. This concession is already available to men and women who have had suitable nursing experience in the Forces or as members of the Civil Nursing Reserve, the British Red Cross Society, or the St. John Ambulance Brigade, and the Minister of Health has now informed hospital authorities of its extension to assistant nurses. Applications should be made to the hospital at which the applicant wishes to train. A concession in the period of training for the Tuberculosis Association's certificate is also announced.