special facilities, special instruments, and special skill. Femoral thrombectomy requires none of these things.

The indications for femoral thrombectomy are: (1) when pulmonary embolism has occurred and mercifully the patient is yet in a fit condition to withstand operation, and (2) when phlebothrombosis decubiti has been diagnosed with some precision.

To endeavour to stimulate surgeons, house-surgeons, and practitioners to undertake a careful clinical examination for phlebothrombosis in relevant cases is my main object in writing this paper.

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TREATMENT OF THYROTOXIC HEART DISEASE BY METHYL THIOURACIL

BY

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While thiouracil has been employed in large numbers of cases of thyrotoxicosis, comparatively little attention has been paid to its use in the cardiovascular complications of that condition. It is the purpose here to survey this aspect of thiouracil therapy. Case histories are recounted, and these are reviewed in the light of the literature.

Patients suffering from cardiovascular disease to whom thiouracil may be administered may be grouped broadly into those in whom cardiovascular disease results from thyrotoxicosis and those in whom it originates independently. In the latter group thiouracil therapy has the same rationale as thyroidectomy has had in the past—that is, a lowering of the basal metabolic rate. It has been given with this aim chiefly to patients with angina pectoris and those with congestive heart failure.

Thyrotoxicosis is a common disorder, but few cases nowadays develop cardiovascular disease: timely operations have in so many instances remedied the condition in an early phase. Nevertheless, most of the published series of cases of thyrotoxicosis have contained several examples of such complications as auricular fibrillation. Thus Himsworth (1944) notes two cases of auricular fibrillation in 33 cases of hyperthyroidism. Grainger *et al.* (1945), reporting 29 cases of thyrotoxicosis, mentions two cases of patients with auricular fibrillation who reverted spontaneously to normal rhythm after treatment by thiouracil. Nussey (1944) mentions four cases of auricular fibrillation in a series of 29 cases of thyrotoxicosis. McGarack *et al.* (1945) reported the effect of thiouracil on 18 cases of auricular fibrillation in a series of 78 cases of thyrotoxicosis. Cookson (1945) mentions 10 cases of auricular fibrillation in 66 cases of thyrotoxicosis, and more recently Cookson and Staines (1947) reported eight patients out of 16 with

auricular fibrillation who reverted to normal rhythm. Wilson (1946) noted six cases of auricular fibrillation in 66 cases of thyrotoxicosis.

The material in the present series comprises 10 patients with cardiovascular disease associated with thyrotoxicosis—seven women and three men, whose ages ranged from 41 to 81. The longest history of symptoms was eight years, the shortest a few weeks. The increase in basal metabolic rate ranged from +14 to +55%, and the lowest blood cholesterol before treatment was 106 mg. per 100 ml. There were six cases of nodular hyperplasia and four cases of diffuse enlargement; the type of enlargement did not affect the response to treatment. They have been observed over a period of 8 to 18 months.

In four patients with established auricular fibrillation various complications caused failure in each case. There were two patients with paroxysmal auricular fibrillation, in both of whom treatment was successful. Of the two patients with hypertension and cardiac enlargement one showed only slight improvement, the other none. Striking improvement resulted in the patient with angina of effort, who was able to resume work after being completely incapacitated. One patient with premature contractions and gross diminution of cardiac reserve was much improved, and was able to do her housework.

Case Histories

Case 1.—A man aged 41 was diagnosed as suffering from thyrotoxicosis in 1940. In April, 1946, auricular fibrillation began. When seen six weeks later he showed typical thyrotoxic signs and symptoms. The thyroid was diffusely enlarged. There was no cardiac enlargement or any sign of valvular disease. Auricular fibrillation was present; the heart rate was 120 and the blood pressure 130/70. There was no cardiac failure. The basal metabolic rate was +45% and blood cholesterol 155 mg. per 100 ml. On methyl thiouracil therapy the B.M.R. fell to -10% and the blood cholesterol rose to 283 mg. Cardiac rhythm was restored to normal by 50 gr. (3.2 g.) of quinidine two weeks after starting thiouracil administration. After eight months methyl thiouracil had to be withdrawn because of granulopenia. The patient continued at work, against advice, from February to June, 1947, during which time he took sedatives, and then agreed to thyroidectomy. He has since been quite free from symptoms, the heart remaining in normal rhythm throughout.

Case 2.—A man aged 68 presented with sacral pain following an infected pilonidal sinus. On examination he was thyrotoxic, with slight exophthalmos and a nodular goitre. Auricular fibrillation was present. The heart rate was 124 per minute; the blood pressure 185/90 and there was marked arteriosclerosis. The heart was enlarged and the sounds weak; there was no evidence of valvular disease. He made steady improvement on methyl thiouracil for three months, when obvious chemosis and exophthalmos developed. He was admitted to hospital and treated with Lugol's iodine and 200 mg. of di-iodotyrosine daily; later, deep x-ray therapy to the pituitary gland was given. In two months the right eye developed an exposure keratitis and hypopyon, necessitating evisceration. After a very stormy convalescence he recovered, and eventually was discharged, still with fibrillation between 80 and 90 a minute and a blood pressure of 170/90.

Case 3.—A woman aged 46 presented with nervousness, depression, palpitations, and occasional irregularities of the heart. When seen in 1946 she was thyrotoxic and had an adenoma of the right lobe of the thyroid. There was no congestive failure; fibrillation was present at 140 a minute, with a radial pulse deficit of 16 a minute. Blood pressure was 130/80. Screening showed a typical heart of mitral stenosis. The electrocardiogram revealed auricular fibrillation with right ventricular stress. She made a good response to methyl thiouracil therapy, but on her return home various functional symptoms supervened and she decided to undergo operation.

Case 4.—A frail old lady of 81 presented with thyrotoxicosis and general slight thyroid enlargement. There was no cardiac

failure; rhythm was regular and blood pressure 205/100. X-ray examination revealed left ventricular enlargement and a prominent sclerotic aorta, with hilar engorgement. She was put on methyl thiouracil and after 13 days had improved somewhat; but she then developed drug fever to 103° F. (39.4° C.), which disappeared in 24 hours on stopping the methyl thiouracil. One week later fibrillation was noticed; at first it was intermittent, but in two days it had become persistent. Her condition deteriorated rapidly; she developed pneumonia, and died in coma two weeks later.

Case 5.—A woman aged 65, after a shock in December, 1945, noticed lack of energy and dyspnoea on effort, and later some swelling of the ankles. On examination she was thyrotoxic, with slight general thyroid enlargement. There were a few rales at the lung bases, the liver was enlarged by three fingerbreadths, and there was slight peripheral oedema. There was fibrillation on her first visit; but later the heart was regular at 96. It was not enlarged, and there was no valvular disease. Blood pressure was 150/80, with obvious arteriosclerosis. On methyl thiouracil she made excellent progress, which is being maintained on very small doses.

Case 6.—A woman aged 55 gave a history of prominence of the eyes and dyspnoea for 18 months, and palpitations for six months. On examination bilateral proptosis was present. The pulse was regular at 76, the blood pressure 150/95. There was a slight thickening of both lobes of the thyroid, but no thyrotoxicosis. On July 15, 1946, the blood cholesterol was 225 mg. per 100 ml. Radiographs of the pituitary fossa were normal. On Sept. 9 she was given hexoestrol, and two weeks later she presented with exophthalmos, enlargement of the thyroid, and thyrotoxicosis. Fibrillation was present. She responded rapidly to methyl thiouracil therapy, and the heart reverted spontaneously to normal rhythm.

Case 7.—A woman aged 52 gave a long history of nervous symptoms, which were exacerbated by the outbreak of war. In January, 1943, the thyroid was noticed to be enlarged. In July, 1946, she complained of lassitude, dyspnoea on effort, and palpitations. On examination she was thyrotoxic, and an adenoma of the right lobe of the thyroid was found. The heart was slightly enlarged, rate 90 a minute, and the blood pressure was 220/115. The arteries were normal for her age. She improved generally on thiouracil therapy, but her blood pressure fell only to 180/100.

Case 8.—A woman aged 60 gave a three-year history of loss of weight and excitability. On examination she was thyrotoxic and had a general nodular enlargement of the thyroid. The heart was slightly enlarged, with a soft apical systolic murmur. The blood pressure was 165/90, with general arteriosclerosis. The B.M.R. was +55% and the blood cholesterol 129 mg. per 100 ml. After seven days on methyl thiouracil (total dosage 4.6 g.) her temperature rose to 103.6° F. (39.8° C.). The next day fibrillation started, and continued for five days, remitting spontaneously. Thyroidectomy was performed later with excellent results. Her blood pressure, however, remained unchanged.

Case 9.—A man aged 45 had a coronary thrombosis in March, 1945, while in the Army, and was in hospital for three months. This was followed by angina of effort even on slight exertion. In May, 1946, paroxysmal nocturnal asthmatic attacks developed and he had to give up his work. Dyspnoea on effort was increasing, with ankle oedema in the evenings. In November, 1946, typical thyrotoxic symptoms started. On examination then he was obviously thyrotoxic. The thyroid was firm and easily palpable. The heart was not enlarged, and rhythm was regular at 120 a minute; there was no failure. Blood pressure was 145/90; arteriosclerosis was present. The B.M.R. was +39%, and the blood cholesterol 106 mg. Thiouracil therapy resulted in great improvement. He is now back at work, and has only a very mild chest pain after moderate effort.

Case 10.—A woman aged 45 had had increasing dyspnoea on effort for nine months, and when seen in July, 1946, could walk only a short distance on the level. She was thyrotoxic, with nodular swelling of the right lobe of the thyroid. There was no failure, the heart was not enlarged, and there was no valve affection. Pulse rate 100, with frequent premature con-

tractions. Blood pressure was 145/70; the arteries were normal for her age. She improved on thiouracil, and manages her housework and has no cardiac symptoms. She is still on 50 mg. of methyl thiouracil daily.

Comments on Results

Auricular Fibrillation.—In the present series six patients had established or paroxysmal auricular fibrillation. Three reverted to normal rhythm; two of these were suffering from paroxysmal auricular fibrillation and in one it had been established only a few weeks. The latter patient developed a granulopenia, and treatment had to be abandoned; but normal rhythm was held, and continued after thyroidectomy. In McGarack's (1945) series there were 18 cases of auricular fibrillation; 12 of these reverted to normal rhythm spontaneously on treatment with thiouracil, and three others were successful when digitalis was given. In none of these cases was there any other cardiovascular disease, the fibrillation being due entirely to the thyrotoxicosis. In Cookson's (1945) cases normal rhythm was restored in three out of 10 cases of auricular fibrillation. Of the remaining seven, one was treated only six days before death, and one also had mitral stenosis. In Wilson's (1946) series five out of six cases of auricular fibrillation reverted to normal rhythm spontaneously, and here again no other cardiac lesion was mentioned. Similarly, Grainger's two cases reverted to normal rhythm spontaneously. Of Nussey's four cases two were restored to normal rhythm—one spontaneously and one after the administration of quinidine. In the other two, of one and five years' standing, no attempt was made to restore normal rhythm.

Hypertension.—Grainger *et al.* (1945), noting the effect of thiouracil on hypertension not associated with thyrotoxicosis, found that little or no response occurred. Two of our cases had hypertension as the only cardiovascular abnormality and two more had established auricular fibrillation with hypertension. Of the first two, one responded well so far as her toxic symptoms were concerned, but showed only a slight fall in blood pressure. The other developed a drug fever, and treatment had to be abandoned. Thyroidectomy was performed; her blood pressure, however, remains at its former level. Of the other two, one developed malignant exophthalmos, and his fibrillation and hypertension persisted; the other reverted to normal rhythm, but the blood pressure rose from 150/95 to 170/95.

Angina.—One patient with angina pectoris gave an excellent response to thiouracil. The toxic symptoms completely disappeared, and instead of an attack of anginal pain occurring after walking half a mile (0.8 km.), he is now hardly troubled during the whole day. Raab (1945) states that the treatment of angina pectoris unassociated with thyrotoxicosis proved effective in seven out of 10 cases, the clinical improvement coinciding closely with the fall in the basal metabolic rate. Ben-Ascher (1947) found thiouracil beneficial in 25 out of 37 patients with angina pectoris. In a former paper Ben-Ascher (1945) reported on eight cases of angina pectoris with favourable results in all of them. The basal metabolic rate fell from -8% to -20% at the time of the maximum improvement. Di Palma and McGovern (1946), however, reporting eight cases of angina pectoris, found that treatment had to be abandoned in four instances, and two of the others became myxoedematous. One patient had symptoms of coronary occlusion during treatment.

Cause of Failure of Thiouracil Therapy.—Failure in five cases in the present series was due to a variety of reasons. In two cases drug fever prevented further administration; in another, psychological inability to face the long treatment necessary in thiouracil therapy was the cause, and

one was due to development of granulopenia while on a maintenance dose of thiouracil. One patient developed a malignant exophthalmos which necessitated evisceration of an eye.

Thiouracil Therapy v. Surgery

Thiouracil interferes with the production of thyroxine by the thyroid gland and, as shown by Himsworth *et al.* (1947), after the first three weeks there is no difference between the condition of patients so treated and those treated by thyroidectomy; and the risk of thyroidectomy is removed. With expert surgeons the mortality rate is 1% or less, and is probably nearer 4-5% when overall figures are taken. *A priori*, in cases with cardiovascular disease complicating thyrotoxicosis the figure is higher. In patients who refuse operation outright thiouracil provides an effective alternative method of treatment.

Thiouracil may also be used to assess the effect of thyroidectomy on the cardiovascular condition generally, and to bring the patient into a better state pre-operatively. This is so especially in cases in congestive heart failure. It is given for at least three weeks; it is then stopped seven to 10 days before operation, and iodine is substituted. This reduces the friability and vascularity of the gland resulting from the use of thiouracil, and substantially facilitates the surgical procedures. In patients who are sensitive to iodine, however, thiouracil may be used alone as a pre-operative measure.

Thiouracil may be used in the younger age groups in whom auricular fibrillation has occurred secondarily to the thyrotoxicosis alone. The heart in most cases will revert to normal rhythm spontaneously, and almost all of those which do not will do so when quinidine is combined with thiouracil therapy. The thyrotoxicosis may remit in time, and after adequate treatment over 12 to 18 months the thiouracil may be stopped with a fair chance of complete recovery.

Whenever thiouracil is used the risk of allergic or toxic complications arising is very real. The drug is stored in the bone-marrow in concentrations up to 16 times that in the blood, and it is this which causes the most lethal of all the ill-effects attendant on its use. Fowler (1946) has shown that of 1,573 cases collected from the literature toxic reactions of one kind or another occurred in 13.7% and serious complications in 4%; the mortality was 0.57%, and was decreasing. With the smaller doses needed when using methyl or propyl thiouracil complications are less likely to occur.

In cases with rheumatic, hypertensive, or arteriosclerotic heart disease neither thiouracil nor thyroidectomy will have any effect on the original heart condition. It will, however, improve prognosis by removing the toxic effect and the added load imposed on the already damaged heart by the thyrotoxic state.

Some cardiologists of repute have entirely abandoned the use of thiouracil as being too toxic and dangerous, and regard thyroidectomy as an equally safe method of treatment, with a more immediate and better cosmetic result.

Thiouracil should never be used when the gland is so enlarged or so placed as to cause tracheal obstruction; nor in cases in which there is the slightest suspicion of malignancy. In elderly people thyroidectomy is to be preferred. There is always a possibility of relapse on ceasing treatment or of complications, and such people will then be in a worse condition for thyroidectomy and their myocardium less well able to withstand either operation or thyrotoxicosis. In those whose temperament or economic condition will not permit them to face the long treatment with thiouracil under adequate supervision thyroidectomy is best performed at once.

Summary

An account is given of the use of methyl thiouracil in 10 patients with thyrotoxic cardiovascular disease.

The value of this treatment in auricular fibrillation, hypertension, and angina pectoris is discussed and the results are compared with those of other observers.

Treatment failed in five cases, the causes of failure being drug fever (2), malignant exophthalmos (1), granulopenia (1), and neurosis (1).

The considerations governing the choice between surgical treatment and thiouracil therapy in thyrotoxic cardiovascular disease have been reviewed.

I am much indebted to Dr. K. Shirley Smith for his encouragement and help and for permission to refer to his cases; also to Dr. H. A. Dunlop for permission to include two of his patients in this series.

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PENICILLIN AND GONORRHOEA

AN ANALYSIS OF 150 CASES TREATED BY THE SINGLE-INJECTION METHOD

BY

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It is now common knowledge that penicillin injected intramuscularly affords the best means of curing gonorrhoea. Like other treatments it has, however, certain disadvantages, and an analysis of 150 cases seen at the male V.D. clinic of the Cardiff Royal Infirmary may prove of interest. The cases were treated between October, 1946, and June, 1947. All except three showed typical signs and symptoms of acute gonococcal urethritis. In each case the diagnosis was confirmed by a microscopical examination of the discharge.

Details of the Cases

Their nationality was: British, 144; Greek, 3; Maltese, 3. 101 were single, 44 married, 3 married but separated, and 2 were widowers.

Age Incidence

16-20 years	..	..	9	36-40 years	..	..	8
21-25 "	..	..	50	41-50 "	..	..	7
26-30 "	..	..	44	51-60 "	..	..	Nil
31-35 "	..	..	31	61-70 "	..	..	1

The greatest number of cases occurred during the age group 21-25, and altogether 125 out of the 150 men were from 21 to 35 years old. The youngest patient seen was a boy aged 16 years and 11 months whose case is described below, and the oldest was a widower aged 63, who gave a history of having had gonorrhoea 30 years previously. This man was first seen on Nov. 11, 1946, after infection by a prostitute. He was free from discharge and other signs of gonorrhoea in 10 days after one injection. He then ceased attending. On Jan. 2, 1947, he returned, admitting to further coitus, and was found to have become reinfected. Again a single injection of penicillin cleared