in his series of cases. Nail changes seen in alopecia are interesting and quite common: 13 out of the 24 totalis and universalis cases showed them, and three other cases with simple patches had them in a minor degree. Leuconychia was not included, as this is not uncommon in normal subjects.

Nail changes fall into two groups: (1) longitudinal striations with a serrated nail edge, and (2) the pitted nail not unlike that of psoriasis. Sabouraud (1936) described these changes and said that when they are present the prognosis is hopeless.

Discussion

The aetiology of alopecia areata has been and still is the centre of considerable speculation. Early writers attempted to find one cause for all cases, which, as seen in this series, is a difficult task. There seem to be two likely causes.

The first, and probable, explanation is that the alopecia represents the reaction of the body to stress—i.e., it is, in modern terminology, a disease of adaptation. Barber (1950), in a discussion of psoriasis, included alopecia areata in the same group as psoriasis and thought that they were examples of diseases of adaptation. Stresses which may result in alopecia in a person with the hair as a "target area" are trauma, mental stress, and infection.

The other explanation, a possibility which we must still consider, is that of a virus infection. Since Sabouraud, opinions have been much against infection, but alopecia would agree well with a virus disease. We might visualize a virus which, like herpes simplex, remains dormant in the scalp and which with stress multiplies to cause the primary patch, this being followed in some cases by a general infection and an attack on all hairy parts and the nails. Attempts to infect subjects with alopecia have always failed, but I doubt if this can be taken as conclusive evidence. Epidemics of so-called alopecia areata have also been largely discounted in recent years.

For the present we must content ourselves with the knowledge of the precipitating causes only.

Summary

Alopecia areata was found in 2% of the 15,000 skin out-patients seen in a five-year period, and 2.5% of 320 orthopaedic patients had a past history of the condition.

The present series of 114 cases consists of 81 of simple alopecia areata, 24 extensive cases, and 9 of persistent areata.

The incidence seems to be the same in both sexes, and was not related to the colour of the hair. The disease occurs at all ages but is commonest in the younger age group.

There appears to be a difference in the position of the primary patch between the sexes—male: 60% occipital, 25% fronto-vertical; and female: 27% occipital, 56% fronto-vertical. A previous history of the disease was found in 28%.

A positive family history was present in 19%, but it is doubted if this is really significant of a familial tendency. Other members of the family were affected at the same time in 6% of cases.

Mental trauma was a precipitating cause in 23%. Focal sepsis is thought to play little part in the causation and was no more prominent in extensive cases than in those which recovered. In 27% the health, both physically and mentally, was excellent.

Vitiligo was present in 4% of cases. Nail changes are common in extensive alopecia.

The prognosis is difficult to give in an individual case, but probably less than 1% suffer permanent ill effects. The prognosis is graver when the disease occurs before 10 years of age, but is little affected by other factors in the history.

The aetiology is unknown; alopecia could be either a disease of adaptation or possibly a virus disease.

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TREATMENT OF THYROTOXICOSIS WITH 2-MERCAPTOIMIDAZOLE

CLINICAL IMPRESSIONS

BY

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The use of antithyroid drugs of the thiouracil series is undoubtedly established; however, as with all other treatments of thyrotoxicosis, relapse occurs in some cases and there is also the possibility of toxic effects. In many cases relapse is due to an aversion to continuing adequate treatment with a potentially toxic substance or to accepting its permanent use in maintenance doses in the same way as with thyroid substitution therapy in myxoedema. Thyrotoxic subjects treated with antithyroid drugs should be under supervision at regular intervals by units organized for long-term follow-up, with all the necessary facilities and attention, as with diabetes. In this way the patients would benefit from better control, and an opportunity would be provided for careful and concentrated study of thyroid disease.

With the use of some of the more recently introduced antithyroid drugs the toxicity factor has been much reduced, but not eliminated, and Stanley and Astwood (1948), by employing radioactive iodine tests, have been able to compare the potency of these newer drugs in man. They claim that 2-mercaptoimidazole is approximately five times more potent than methyl thiouracil; and Astwood (1949—personal communication) reports that methyl mercaptoimidazole is about 10 times more potent than 2-mercaptoimidazole.

Stanley and Astwood (1948) have briefly reported the efficacy of treatment with 2-mercaptoimidazole in a series of 20 patients with thyrotoxicosis; they found that 40–100 mg. daily was an adequate therapeutic dose. Even in severely thyrotoxic subjects a dose of 20 mg. sometimes produced nearly complete inhibition of hormone synthesis lasting as long as 11 hours. In others a dose of 20 mg. was only partially effective.

In May, 1949, 2-mercaptoimidazole became available for clinical trial in this country, and this paper reports the results of treatment of a small series of cases.

Toxicity of 2-Mercaptoimidazole in Animals

The acute toxicity of the antithyroid substances varies according to the experimental animals used, the strains selected, the diet, and other factors. Comparative data obtained in this way will not necessarily give the ratio for man. Astwood (1943a) stated that the minimal lethal dose (M.L.D.) of 2-thiouracil in rats was more than 100 times the dose required to produce a detectable thyroid effect. Toxic manifestations in rats were not seen with 2-thiouracil until a daily dose of 100 mg. per 100 g. body weight was exceeded (Astwood, 1943b). Although direct comparisons are unsatisfactory, owing to variations in techniques, it would seem that 2-mercaptoimidazole has an acute toxicity similar to that of thiouracil and that methyl mercaptoimidazole is about seven times more toxic, although much more active. If this is accepted, a comparative therapeutic index may be expressed as follows:

Thiouracil	Activity Toxicity	$\frac{1}{1} = 1$
2-Mercaptoimidazole	..	$\frac{10}{1} = 10$
Methylmercaptoimidazole	..	$\frac{100}{7} = 14$

These figures of activity are those given by Stanley and Astwood (1949).

After synthesis in this country both 2-mercaptoimidazole and methyl mercaptoimidazole, which in purity were equivalent to high-grade organic analytical reagents and free from contaminants, were subjected to toxicity trials. In female mice of Schofield strain the LD₅₀ by mouth of 2-mercaptoimidazole was approximately 2.2 g./kg. and of methyl mercaptoimidazole 0.3 g./kg. The former is of the same order of toxicity as thiouracil.

Method and Materials

A group of 18 unselected cases of thyrotoxicosis was used for this trial. Special medical record cards were prepared so that the detailed points in each case could be recorded serially. All the patients received a complete clinical examination followed by measurements of arm-head circulation time (theophylline with ethylenediamine), electrocardiography (E.C.G.), x-ray film of chest, blood cholesterol esti-

mation, and a radioactive iodine test. The latter was modified (Foss and Herbert, 1950) from that described by Stanley and Astwood (1948). Thyroxine synthesis was inhibited by 500 mg. of methyl thiouracil or 100 mg. of 2-mercaptoimidazole, administered one to one-and-a-half hours before a dose of 37.5 μ c. of ¹³¹I was given by mouth to the fasting subject. The percentage uptake of ¹³¹I by the thyroid and its dissolution after a dose of 1 g. of potassium thiocyanate by mouth, given at the time of maximum concentration, were plotted against time. Figures of 12% uptake or over have been taken as evidence of toxicity, the upper limit of normal controls under these conditions being 8%. All except four of these cases had not been treated previously for thyrotoxicosis.

Treatment with 2-mercaptoimidazole was usually started with a dose of 20 mg. three times daily, and the patients were seen at intervals of up to 28 days at first and, later, when stabilized, at intervals of six to eight weeks. Each time the general clinical impression was noted, together with records of heart rate and rhythm, blood pressure, weight, neck circumference, blood cholesterol estimation, and subjective and objective evidence of toxicity or myxoedema. When necessary, further E.C.G.s were taken. In this manner a consecutive impression of the patient's reaction to treatment was formed. After progressive control of the thyrotoxicosis on the initial dose, when the patient was in a state of normal or slightly subnormal metabolism, the dose of 2-mercaptoimidazole was gradually reduced. It was intended to follow up this group for at least two years in this manner, but owing to force of circumstances this was not possible.

Of the 18 subjects originally started on this treatment three (Cases 8, 9, and 17) must be excluded, either for failing to take their tablets or for discontinuing attendance. They had all relapsed after previous courses and were not interested in further medical treatment. Brief summaries of the remaining 15 cases are shown in Table I.

Control of Thyrotoxic State**Ordinary Dosage Scheme**

Twelve patients were treated with 20 mg. of 2-mercaptoimidazole three times a day, and 10 (83.3%) of these were successfully controlled (Table II). These

TABLE I.—Case Summaries

Case	Age	Sex	Duration of Symptoms (Mths.)	Weight Loss lb.	Thyroid Enlargement	Heart Rhythm Rate	B.P.	Eyes		Tremor	Skin	Circulation Time (secs.)	Blood Cholesterol (mg./100ml.)	¹³¹ I % Uptake	Remarks
								E	LR						
1	61	F	3	27*	Slight	Reg. 130	170/100	+	+	++	H.M.	7.5	164	16	Anaemia. R.B.C. 3.6 mil. Hb 76%. Some myopathy; glossitis
2	25	F	12	7	Moderate	Reg. 90	140/80	+	N	±	C.M.	8	150	28	Irritable
3	40	F	9	0	Slight	Reg. 100	160/100	+	+	+	C.M.	10	184	20	Strong family history of thyrotoxicosis
4	54	F	18	52	Moderate	A. Fib. 270-300	230/120	N	N	+	H.M.	10	190	17.5	Irritable. Early failure
5	30	F	8	24	..	Reg. 100	150/80	++	+	±	C.D.	9	164	21	See full case history
6	46	F	3	14	..	Reg. 88	130/55	+	+	±	H.M.	14	75	16	Onset following hysterectomy
7	47	F	3	16	..	Reg. 90	130/80	N	+	+	H.M.	15	125	12	Loud bruit over thyroid
10	22	M	7	7	Slight	Reg. 88	145/65	N	+	+	H.M.	14	165	23.5	Suspect pulmonary tuberculosis. Chest x-ray film clear. Much psychic trauma
11	26	F	3	16	Moderate	Reg. 128	155/75	N	+	++	H.M.	9	200	23.8	Onset following examination for B.A.; involuntary muscle twitching
12	49	F	12	42	..	Reg. 134	195/90	+	+	++	H.M.	11	120	31	Early cardiac failure
13	44	F	48	35	..	Reg. 118	180/80	N	±	+	C.M.	8	205	28.6	Much psychic trauma. Thyroid bruit +
14	63	F	36	5	Moderate adenoma	A. Fib. 140	180/100	N	±	+	H.M.	18	180	19.3	Early congestive heart failure. Large heart. Goitre all her life
15	54	F	6	5	Slight adenoma	Reg. 100	160/85	N	+	+	H.M.	12	198	13	Slight oedema of ankles. Absent axillary hair. Menorrhagia
16	19	F	60	0	Very large	Reg. 110	170/80	N	±	+	H.M.	7	140	18.3	Medical treatment intermittent for 5 years. Several relapses. Mentally defective
18	33	F	6	14	Moderate	Reg. 130	150/90	+	+	±	C.M.	6.5	155	27.3	F.H. goitre and diabetes. Pregnant one month after starting therapy

E = Exophthalmos. LR = Lid retraction. H = Hot. M = Moist. C = Cool. D = Dry. N = Normal. * In conversion to metric equivalents, 1 lb. = 454 g.

TABLE II.—*Details of Dosage and Effects on Progress*

Case	Initial Daily Dose	Time Before Dose Reduced Below 60 mg./Day	Condition at this Time	Time Before Heart Rate Steady	Duration of Follow-up	Maintenance Dose at End of Follow-up	Remarks
1	60 mg.	121 days	Myxoedemic	21 days	10 months	10 mg. t.d.s.	Very well
2	60 "	98 "	Euthyroid	84 "	5½ "	10 mg. b.d.	" "
3	60 "	84 "	"	28 "	8½ "	5 mg. t.d.s.	" "
4	80 "	100 "	"	140 "	6½ "	5 mg. b.d.	Very well. Auricular fibrillation changed to normal rhythm permanently after two days
5	60 "		Thyrotoxic				Treatment stopped owing to toxic signs. See full case history
6	60 "	56 "	Early myxoedema	28 "	9½ "	5 mg. daily	Very well
7	60 "	28 "	Euthyroid	21 "	6½ "	2.5 mg. b.d.	" "
10	60 "	82 "	"	98 "	6½ "	10 mg. t.d.s.	Uneventful progress
11	60 "	168 "	"	168 "	6 "	20 mg. b.d.	Very well
12	100 "		Early myxoedema	56 "	5 "	20 mg. t.d.s.	Additional therapy with L-thyroxine sodium 0.3 mg. daily
13	60 "	84 "	Euthyroid	28 "	11½ "	2.5 mg. b.d.	Very well
14	80 "	56 "	"		2 "		Thyroid adenoma removed. Owing to flutter treatment stopped
15	60 "	84 "	Myxoedemic	28 "	8½ "	10 mg. b.d.	Very well
16	60 "		Hyperthyroid	252 "	11 "	20 mg. t.d.s.	60 mg. daily inadequate with big goitre; 80 mg. daily produced euthyroid state
18	60 "	56 "	Euthyroid	56 "	8½ "	10 mg. b.d.	Very well. Pregnancy progressing. Exophthalmos appeared less with pregnancy

subjects were in a state of euthyroidism (7) or definitely early myxoedema (3) when the initial dose was reduced after 28–168 days (mean 86 days). Of the two remaining patients, Case 5 was treated for only 47 days, when the drug was stopped owing to a toxic febrile illness, but during this time no real change had occurred except for a slight fall of resting heart rate from 106 to 98 a minute. A full account of this case is given under the heading of toxic effects.

Case 16 was treated ineffectively for four months on this dosage, but rapid control was established by increasing it to 80 mg. daily, when a rise of blood cholesterol from 185 to 320 mg./100 ml., and a gain of 2 lb. (0.9 kg.) in weight occurred in a month. At this time the patient showed signs of early myxoedema. She had a very large goitre and had previously received three courses of thiouracil with relapse.

Other Initial Doses

In the following three cases 80 mg. or 100 mg. daily was given.

Case 4.—A married woman aged 54 was seen on September 15, 1949. She complained of attacks of palpitation for four months, loss of weight during the preceding 18 months, nervousness and irritability for two months, and increased perspiration for five weeks; about this time she had sudden attacks of dyspnoea at night. Her appetite was small and she was languid and tired. She was well nourished, weighing 130 lb. (59 kg.), but previously had been rather obese, weighing 182 lb. (82.5 kg.). Her face was expressionless and there were no eye signs. Her skin was fine, hot, and sweaty. She had firm generalized thyroid enlargement but a loud bruit, and a neck circumference of 13½ in. (34.2 cm.). There was a coarse vibrating tremor of her hands and face, and reflexes were brisk. Heart: apex beat in sixth space in the mid-clavicular line, and first sound loud; rapid fibrillation; B.P. 230/120. There was no congestive failure. E.C.G. revealed auricular fibrillation of 270–300 a minute. X-ray examination showed the heart size to be within normal limits and the lung fields clear. Theophylline-ethylenediamine circulation time was 10 seconds; blood cholesterol, 190 mg./100 ml. Radioactive iodine test showed a toxic curve—17.5% uptake of ¹³¹I.

The patient was admitted to hospital and treatment started with 2-mercaptoimidazole 20 mg. four times daily on September 20. After two days she felt much better and the rhythm was restored to normal, the E.C.G. showing sinus tachycardia, rate 190 a minute. At this stage a punctate irritating erythematous rash developed on the forearms. After 20 days the dose of 2-mercaptoimidazole was reduced to 60 mg. daily, and at the end of a month her weight had increased by

9%, the cholesterol to 240 mg./100 ml., and the heart rate was 108. After 77 days the bruit over the thyroid had disappeared, steady progress had been made, and her weight had increased by 15%—that is, 19 lb. (8.6 kg.). After 100 days her skin was cool; the heart rate was 96, and B.P. 205/115, so the dose was reduced to 20 mg. twice daily, and later to 5 mg. twice daily. The only possible evidence of toxicity was the rash after two days.

Case 14.—A woman aged 63, with an adenoma in the right lobe of her thyroid, auricular fibrillation, and congestive failure, was treated in hospital. After three weeks in bed on 80 mg. daily her failure was controlled; she had gained 2 lb. (0.9 kg.) in weight in spite of loss of slight oedema, and the blood cholesterol had increased from 180 to 260 mg./100 ml. When she was discharged home her skin was cool, dry, and rough, and the dose was reduced to 20 mg. three times daily. After two months treatment was stopped owing to the development of auricular flutter with a 2:1/3:1 auriculo-ventricular block. Later the adenoma was removed surgically.

Case 12.—A woman aged 49 was given 20 mg. five times daily, as she was very toxic, having lost 42 lb. (19.1 kg.) in three months, and had sinus tachycardia of 134 a minute without congestive failure. After 10 days' rest in bed on this dose her heart rate fell to 80 a minute, but she developed an acute confusional state with rapid recovery and transient amnesia. Treatment was stopped for a few days, being then continued with a dose of 20 mg. three times daily. A few more "blackouts" and brief spells of amnesia occurred, but by 84 days there was definite general improvement, a gain in weight of 13 lb. (5.9 kg.)—that is, 9%—and early signs of myxoedema, an increase in thyroid size, and a cool dry skin.

Maintenance Dose

Once a definite euthyroid or early subthyroid state was achieved doses were gradually reduced, but no rigid level can be stated. When this follow-up ceased some patients were adequately controlled after 11½ months by 2.5 mg. twice daily, whereas others—for example, Case 16—still needed 20 mg. three times daily after 11 months, and in Case 12 the dose was reduced from 100 mg. daily to 60 mg. daily with the addition of L-thyroxine sodium, 0.3 mg.

Effects of Treatment

Heart Rate and Rhythm.—The time for restoration to a normal rate was variable, being only one month in six cases but in two others five and six months. With an initial dose of 80 mg. daily one patient (Case 4) with rapid auricular fibrillation of 270–300 a minute was restored to normal sinus rhythm of 190 in two days, but it required 140 days' treatment to reduce the rate to normal. In

TABLE III.—Showing Changes in Weight and Blood Cholesterol

Case	Age	Initial Weight lb.	Initial Cholesterol mg. %	Months After Starting Treatment																		
				1	1½	2	2½	3	3½	4	4½	5	5½	6	6½	7	7½	8	8½	9	9½	10
1	61	99	164	102 310		114 350		115			121 490		117 235		121 265			121				118 180
2	25	109	150	112 225		114 210		117 219		118 215			119 175									
3	40	98	184	107 285		108		110 315		108 265		109 220			108 230			108 220				
4	54	130	170	142 240	143	149 215			153 218			157 190			165 186							
5	30	137	164	139 170		131 160		130 200														
6	46	134	75	143 145		152		156 144		154		154					154	153		153	104	
7	47	121	125	128 360		130 220		133 277			133 235				133 305							
10	22	140	165	145 220		145 195			149 180			152 160			154							
11	26	103	200	115 240			118		119 215		123			124 185								
12	49	140	120	145 185		145 190		153 185		161 210		164 100										
13	44	105	205	105 220		111		116 285		111 200		112		114	210	115		116		117 200	120 340	
14	63	128	180	130 260																		
15	54	105	198	117 270		124		127	310		129 205			127	163		129		129 205			
16	19	108	140	108 160		109 174		112 170		114 185		115 320		113 220		107 179		108 175		107 120		
18	33	116	155	120 185		126		129 200		134		140 350		144 275					158 185			

this case the dose was reduced to 60 mg. daily after 100 days as the patient had in general regained a euthyroid state.

Weight.—The increase in weight was rapid in these patients, and all except two (Cases 13 and 16) showed gains in the first month. After stabilization of the toxic state the weight either remained at a steady level or continued in a few subjects to increase by as much as 20% (Table III).

Blood Cholesterol.—Although single estimations of blood cholesterol are of little clinical value, serial readings were useful in assessing the progress of these cases during treatment. In all these subjects there were significant increases after one month, and the level became high only during the development of frank myxoedema (Table III), but the early onset of the condition was best recognized clinically.

Myxoedema.—It was usual to continue the initial dose of 2-mercaptoimidazole until a euthyroid state was maintained or there was early evidence of myxoedema. After some experience, recognition of these early signs was not difficult. Patients complained of a return of tiredness and loss of energy, a feeling of depression or irritability, sometimes nausea and sickness, or an aching in the thyroid: often a gritty sensation in the eyes, with lacrimation, was noticed. They began to feel cold, and found that hair came out easily when combed. The menstrual loss occasionally became heavier. The diagnosis of the early myxoedemic state was perhaps more readily apparent to an observer who saw the patients at regular intervals. There was slight puffiness of the face, suffusion of the conjunctivae and lacrimation, dryness of the skin, and very soon a husky timbre to the voice. Often the heart rate took several weeks to reach normal after this clinical state was evident. The hair tended to become thin and the nails were sometimes brittle.

Toxic Effects

When considering signs of toxicity one had to be cautious of symptoms due to the thyrotoxic state itself, symptoms

referable to cardiac arrhythmia or early failure, anxiety, early myxoedema, or some other unrelated condition. Twelve patients were free from any complaints due to drug toxicity; many of these, however, showed symptoms of early myxoedema at some stage of observation, and one had nausea, which proved to be due to pregnancy. None of this small series complained of sore throat, nor was drug fever seen in any of those treated as in-patients. From the clinical aspect the likely toxic effects can be divided into:

1. *Possible Toxic Effects* (two cases=13.3%).—**Rash:**—Case 4, described above, had an irritative erythematous rash over the forearms, while she was sweating profusely on the second day of treatment in bed. When the dose was continued the rash cleared. **Arrhythmia:**—Case 14, described above, had auricular flutter with an adenoma. This patient had previously had fibrillation. It was thought advisable to stop treatment, and later the adenoma was removed.

2. *Probable Toxic Effects* (two cases=13.3%).—**Confusional state and transient amnesia:**—In Case 12, described above, the episodes lasted for only a few hours while the patient was taking 100 mg. daily, with briefer "blackouts" later when on 60 mg. daily. As she had not previously complained of similar phenomena it was presumed that the drug was responsible.

Case 5: Polyarteritis Nodosa

A married woman aged 30 was seen on July 14, 1949. She had always been nervous, and had noticed prominence of both eyes nine months previously, during which time she had lost 14 lb. (6.35 kg.). She was extremely active and was always busy. Her appetite was very large; she preferred cold weather, but did not perspire unduly, and had only occasional attacks of palpitation. She had had scarlet fever as a child. Her menses had become scanty, lasting four days every 28–30 days. She had a daughter aged 2 years. There was no family history of thyroid disease.

She was fairly well nourished, weighing 137 lb. (62.1 kg.). There was considerable bilateral exophthalmos and lid retraction. Her thyroid was full and soft; neck circumference 14½ in. (36.8 cm.). Her skin was cool and dry, with pigmentation of the

upper lids. The reflexes were brisk and a trace of coarse tremor of the hands was seen. Heart: apex beat in fifth space in the mid-clavicular line, first sound forceful; rate 100 a minute; rhythm regular; B.P. 150/80. E.C.G. and x-ray film were normal; theophylline-ethylenediamine circulation time 9 seconds; blood cholesterol 184 mg./100 ml. Iodine, which had been given for seven months by her doctor, was stopped and a radioactive iodine test was carried out a month later. This gave a toxic curve; also the clinical signs of toxicity were now exaggerated. Uptake of ^{131}I = 21%.

Treatment as an out-patient was started on August 15 with 2-mercaptoimidazole, 20 mg. three times a day. After four weeks she had gained 1% in weight, with slight general improvement; heart rate 106.

After 47 days she had a pyrexial attack with generalized aches, pain in her legs, and some swelling of the ankles. Her doctor stopped 2-mercaptoimidazole and kept her in bed for 14 days. When seen after 73 days she had lost 8 lb. (3.63 kg.) in weight. The heart rate was 98 and regular, no abnormalities were found, and there was no oedema. In view of the complaint of previous pain in the legs, her reflexes and sensation were tested and found to be normal. The E.C.G. was unchanged. Treatment was resumed with 2-mercaptoimidazole, 20 mg. three times a day.

On the 87th day her condition was unchanged subjectively; her weight was the same; her neck measured $13\frac{1}{4}$ in. (33.7 cm.); the heart rate was 90, rhythm regular, and the first sound was quieter; B.P. 130/75. She complained of slight swelling of her ankles at night. Reflexes and sensation were normal. Her urine was clear; the blood cholesterol was 200 mg./100 ml. Owing to temporary shortage of 2-mercaptoimidazole, she was given methyl thiouracil, 100 mg. three times a day, which she took for two days and then developed tingling in her fingers. Four days later she was admitted to hospital obviously ill. She had signs of peripheral neuritis, with paraesthesia of hands and feet, and some weakness of the small muscles of the hands with diminished reflexes. Her thyrotoxic symptoms were, however, under control: the thyroid was normal in size, the neck circumference $12\frac{1}{4}$ in. (32.4 cm.), and the exophthalmos unchanged. Examination showed: E.S.R., 45 mm. in one hour; Hb, 90% (13.3 g.); W.B.C., 26,000 per c.mm. (neutrophils 82%). Urine contained a trace of albumin with one or two red cells and a few granular casts. She had some pyrexia and tachycardia. A diagnosis of polyarteritis nodosa was made. The peripheral neuritis progressed rapidly and there was considerable wasting of both arms and legs, with bilateral foot-drop and loss of sensation.

No definite nodules were felt and a muscle biopsy failed to show conclusive evidence of polyarteritis. She was afebrile after three weeks, and the tachycardia settled from 110–160 to 80–90 in four weeks, but by this time her B.P. was 150/120.

When she was discharged from hospital on the 184th day (91 days after admission) there was little improvement in the motor or sensory changes. Heart rate was approximately 110; W.B.C. normal. Her thyroid was normal in size and exophthalmos was definitely less. She was last seen on the 248th day, when she had increased slightly in weight and was able to walk with aid. Her neck measurement was $13\frac{1}{4}$ in. (34.3 cm.); thyroid bruit was absent; heart rate 120; rhythm regular; B.P. 170/110. There was no definite evidence of thyrotoxicosis.

White Cell Counts.—White blood cell estimations were not made as a routine, but only if patients complained of any symptoms that might be attributable to the drug, and in no case was a leucopenia found.

Discussion

The number of cases in this series is too small and the duration of treatment too short for one to form more than an impression of the efficacy of 2-mercaptoimidazole in the doses used to control the thyrotoxicosis. In most patients a dose of 60 mg. daily would seem to be adequate, 10 out of 15 cases (66.6%) were successfully controlled. In three other subjects control was achieved by 80 mg.

daily, and another patient required 100 mg. daily. The remaining case was not long enough on the drug for the adequacy of 60 mg. daily to be judged, as toxic signs appeared and treatment was stopped. In general these findings agree with those of Stanley and Astwood (1948).

In Cases 5 and 14 the drug was stopped owing to possible toxic reactions, and in Case 16 it was decided to remove a very large goitre. The remaining 12 patients were adequately controlled on maintenance doses for periods of 5 to $11\frac{1}{2}$ months.

It is unlikely that the rash which appeared within two days of treatment in Case 4 was due to the drug, as she was sweating profusely, and it was irritative and confined to the forearms. Further, it disappeared with the continuance of treatment. The change of rhythm from auricular fibrillation to flutter is a doubtful toxic manifestation and is not mentioned in the literature.

It is interesting that the two probable toxic reactions were neurotoxic. Frawley and Koepf (1950) discuss the neurotoxic manifestations described in the literature in relation to thiouracil, methyl thiouracil, propyl thiouracil, and cyclopropyl thiouracil, although, according to Bartels (1948), they constitute only an almost negligible fraction (1.8%) of the total toxic reactions. Confusional states, aural and visual hallucinations, and even toxic psychoses have been seen after thiouracil; numbness of the extremities, vertigo, paraesthesia, and loss of taste after methyl thiouracil; and tingling in the tip of the tongue, numbness of the lips, a burning sensation in the throat, pain in the jaws and facial muscles, and emotional disturbances after propyl thiouracil.

Frawley and Koepf postulate that as thiouracil derivatives depress the peroxidase enzyme system of the thyroid, they may well interfere with other enzyme systems necessary for function of the nervous structures. These authors state that the neurotoxic manifestations may be the first, the sole, or the most pronounced evidence of intoxication with these drugs.

Although a confident clinical diagnosis of polyarteritis nodosa was made in Case 5, it was not proved by muscle biopsy. Astwood (1949—personal communication) had heard of another possible case in his series, then enlarged to 50 cases, treated with 2-mercaptoimidazole, but that case was not under his immediate supervision at the time.

Although the incidence of two cases (13%) showing neurotoxic signs is relatively high, this series is far too small for an assessment to be made, and the true perspective is probably to be obtained from Bartels's (1948) statement that the incidence is really extremely low—1.8% of all toxic reactions. Because of its high activity/toxicity ratio in animals, and this confirmation of Astwood's data, 2-mercaptoimidazole merits extended clinical use in thyrotoxicosis.

Summary

2-Mercaptoimidazole was used for treatment of 15 unselected cases of thyrotoxicosis during periods of 5 to $11\frac{1}{2}$ months.

A dose of 60 mg. daily was found adequate to control the condition in 66.6%. In three other subjects control was achieved by 80 mg. daily. A fourth patient required 100 mg. daily, and the remaining case was not treated.

One patient developed polyarteritis nodosa after 47 days' treatment, otherwise toxic reactions were few and of fleeting and mild nature.

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INTRAVENOUS IRON IN TREATMENT OF HYPOCHROMIC ANAEMIA ASSOCIATED WITH RHEUMATOID ARTHRITIS

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In a previous communication (Sinclair and Duthie, 1949) we reported the results following the administration of intravenous iron in 23 cases of rheumatoid arthritis with hypochromic anaemia. These cases have now been followed up for periods varying from 7 to 23 months. A further 28 cases have been studied in respect of the haemoglobin response and changes in the erythrocyte sedimentation rate (E.S.R.) following 1 g. of intravenous iron. Iron absorption has been measured in seven cases. In four cases large doses of ascorbic acid have been given in order to assess its effect on the utilization of iron.

Haemoglobin percentages were estimated by a photoelectric colorimeter graduated to register 14.8 g. Hb per 100 ml. as 100%. Westergren tubes were used to measure the E.S.R. Wintrobe's dry mixture of ammonium and potassium oxalate served as an anticoagulant. No correction for anaemia was made, as no reliable method is available. Davis (1946) states that correction for anaemia is usually unnecessary if the Westergren method is used, and that such correction may lead to fallacious results. The moderate degree of anaemia present in most cases of rheumatoid arthritis would be unlikely to influence the E.S.R. to any significant extent.

Results

Follow-up of First Series.—Of the original 23 cases 16 responded to intravenous iron ("ferrivenin"), and seven remained refractory. Of the 16 cases that showed a satisfactory rise in haemoglobin percentage 13 have maintained this level without further iron for periods varying from 7 to 23 months. In the remaining three cases the initial response was not maintained; but all three responded to a second course. Details are given in Table I. Of the seven refractory cases, three received a second course without effect.

Results in Second Series.—Twenty-eight new cases have been given courses of intravenous iron. All were subjected to the same basic regime as the original cases and showed no significant response to oral iron for one month. In 14 cases the preparation used was ferrivenin. A test dose of

TABLE I.—Follow-up of 16 Cases with Good Haemoglobin Response to Intravenous Iron

Case No.	Haemoglobin %			
	After 1 Month on Iron by Mouth	Response to Ferrivenin 1.05 g. Intravenously		
		1 Month After Injection	Final Level	Time in Months
1	79	83	96	13
2*	66	87	90	13
3	72	92	92	9
4	68	80	100	23
5	71	90	90	11
6	74	96	96	14
7*		65	84	12
8	76	88	96	17
9	65	78	82	9
10	70	82	93	7
11*	63	83	93	10
12		76	86	13
13	82	97	96	9
14	75	90	96	16
15		75	84	7
16	80	92	100	15

* Required second course.

50 mg. was followed by 200 mg. daily for five days. In the remaining 14 cases "iviron" was used. A test dose of 200 mg. was followed by 400 mg. daily for two days. Mild toxic symptoms were encountered occasionally with both preparations. These have become very much less frequent since all-glass syringes were adopted in place of glass and metal syringes. In 22 cases a good haematological response was obtained. The average haemoglobin percentage in these cases on admission to hospital was 70. After one month on oral iron it was 71.8. One month after 1 g. of intravenous iron the average figure was 84.3. At three months the average figure was 87.1. In the remaining six cases in this group the response was poor or absent.

Iron Absorption.—To ascertain whether faulty absorption of iron from the gut might explain the failure of these patients to respond to iron by mouth, serum iron values were measured after the administration of 18 gr. (1.2 g.) of ferrous sulphate in seven cases. The method used was that described by Dahl (1948). The results are shown in Table II. In all seven cases serum iron values and absorp-

TABLE II.—Serum Iron Absorption (7 Cases)

Time	Serum Iron Levels μ g. per 100 ml.						
10 a.m. (before oral iron) ..	90*	83	66	89	90	75	94
12 noon (after 18 gr. oral iron)	200	126	—	166	150	83	146
2 p.m. " " " "	210	250	200	116	150	110	155
4 p.m. " " " "	160	83	56	106	80	96	103

* In spite of good absorption curve there was no appreciable rise in haemoglobin level following two courses of intravenous iron.

tion curves fell within the normal range. In six cases the response following the administration of 1 g. of iron intravenously was satisfactory. In one case no rise in the haemoglobin level followed the administration of a total of 2 g.

Erythrocyte Sedimentation Rate.—A fall in E.S.R. was noted in cases responding to intravenous iron in the first series of cases studied. This point has now been investigated in more detail. In 10 cases the E.S.R. was measured daily during the course of injections. The results are given in Table III. It will be noted that in six cases showing a good response the E.S.R. fell sharply, while in the four refractory cases there was no significant alteration in rate. Five cases were selected in which haemoglobin values were 80% or over but in which the E.S.R. was markedly raised. After 1 g. of intravenous iron the rate fell and the haemoglobin percentage rose in all five (Table IV). In Case 5 the