Woods (1952) described the case of a man of 46 admitted to hospital with burns and shock following lightning. Ten weeks later he developed "pins-and-needles" in the fingertips, spasm of the forearm muscles, and weakness of both legs. A diagnosis of spinal atrophic paralysis resembling amyotrophic lateral sclerosis was made. He made an almost complete recovery in eight weeks.

Girard, Garde, and Jacquot (1954) described the case of a woman who was struck by lightning. She had momentary loss of sensation in her legs accompanied by pain, which soon passed off. Eight days later, however, progressive weakness of the legs began, making walking impossible. There was also marked weakness of the arms with pain in all four limbs. Considerable improvement took place later, though some weakness persisted.

Critchley (1934) described the pathological findings following death from injury by lightning. He found scattered petechiae throughout the brain, medulla, and spinal cord, especially around the anterior horn cells. Similar petechiae were found in the peripheral nerves and muscles.

Schallock (1952) described an incident where two juvenile football teams were struck by lightning, several players being thrown to the ground. One, a boy of 16 years, was killed. Post-mortem examination revealed no burns, but a minute wound in the web between the second and third toes of the right foot with minimal bleeding. The boot on this foot was torn open, but there were no burn marks on it. The metal nails and eyelets were blackened. Death was thought to be due to shock, the boy having been struck by lightning in the right foot.

Marriott (1951) recommended artificial respiration in suitable cases, prolonged for several hours if necessary, and the injection of nikethamide intravenously. Plasma transfusions would be required for extensive burns.

In this present series there was a wide variety of lesions, varying from mild paraesthesia and feathering burns of the skin to severe head injuries and full-thickness burns. It was interesting that a large number of minor burns occurred, but only one case of burns remained in hospital after 10 days. In this instance full recovery took place without grafting. There was also a wide variety of burns, several types sometimes being seen in the same patient. Finally, in no case was extensive deep necrosis present beneath the skin as is so often seen in electrical burns, despite the number of cases in which burns with small areas of full-thickness skin loss were found.

There were two fatalities, both due to cerebral damage, one case also having a fracture of the skull. The mechanism is uncertain. It is unlikely that these were caused by the patient falling to the ground; more likely they were due to the electrical discharge.

Summary

The circumstances and effects of a lightning storm at an Ascot race meeting are described.

More than 45 casualties occurred, with two fatalities, and the clinical features are analysed.

The literature on the history of lightning and its effects is reviewed.

We are indebted to Dr. G. S. Halley for his help in the preparation of this paper, and also to the late Sir John Bülteel for allowing us to revisit the site of the incident. Our thanks are also due to Mr. E. C. Glover, Mr. A. C. Maconie, and Dr. E. Sayle for the ophthalmological, otological, and pathological details. We are also indebted to the hospital photographers, Miss D. Bannister and Mr. P. Fiske, for the clinical photographic work.

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THE LOW TOXICITY OF CARBIMAZOLE

A SURVEY OF 1,046 PATIENTS

BY

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The search for an antithyroid drug free from toxicity at therapeutic levels has continued since the first use of thiourea and thiouracil for the control of thyrotoxicosis.^{3 48 49} The methyl and propyl derivatives of thiouracil were early found to be less toxic than the parent drugs and soon replaced them in clinical use. Subsequently other drugs have been introduced which appear to be less toxic, the three main ones being methimazole (2-mercapto-1-methylimidazole; "tapazole," "mercazole"), carbimazole (2-carbethoxythio-1-methylimidazole; "neo-mercazole"), and perchlorate.

Lawson *et al.*³⁷ first reported that carbimazole was a powerful antithyroid agent. Most of the preliminary clinical surveys of its use reported it to have low toxicity in the therapeutic dose range^{17 23 32 35 36 47 62} except that of Bartels,⁸ who encountered one case of agranulocytosis in 52 cases. Chemically, carbimazole is closely related to methimazole. A previous clinical comparison of

these two drugs²³ found them of approximately equal antithyroid potency, and carbimazole less toxic than methimazole. The present paper reports a more extensive analysis of the incidence of toxicity following the use of carbimazole in 1,046 patients at 12 hospitals.

The mode of antithyroid action exerted by methimazole and carbimazole is similar to that of thiouracil and its derivatives. They block or in smaller dosage impair the thyroid's production of thyroxine by interference with the organic binding of iodide into tyrosine. Normally this iodine-binding probably occurs by an enzymic oxidation of iodide to free iodine in the proximity of tyrosine,⁶³ into which it is then bound. Antithyroid drugs such as thiouracil and carbimazole probably inhibit this action by interfering with the oxidation of iodide to iodine. They are all reducing agents which can bind free iodine.⁶⁰ It is possible that some of these antithyroid drugs, especially the least toxic ones, achieve this effect mainly by inactivating the oxidative enzymes concerned.²² In contradistinction, perchlorate, like thiocyanate, has a different mode of antithyroid action, acting only by inhibiting the preliminary concentration of iodide into the thyroid gland.^{1 75 83} The antithyroid action of perchlorate therefore will have the serious clinical disadvantage of being suppressible by even a few milligrams of iodide intake.

The toxic effects of antithyroid drugs may conveniently be divided into minor and major categories. The former group comprises mainly rashes, but can also usefully include the various disabilities which have been dubiously attributed to the drug—for example, nausea, headache, jaundice, gastric distress, etc. Major toxic effects are of two main types: (1) serious depression of some blood-forming tissue usually causing agranulocytosis and very occasionally thrombocytopenia; and (2) a drug-fever reaction—that is, fever either uncomplicated or associated with glandular enlargement and/or arthritis-like manifestations. When major reactions occur with the thiouracils, the agranulocytosis syndrome is the more common, whereas with methimazole and carbimazole they usually consist of the drug-fever syndrome.

Goitrogenesis occurring during the administration of an antithyroid drug should not be regarded as a toxic effect, but merely as a sign of overdosage²¹; it is to be expected whenever such drugs lower thyroid hormone secretion below the normal range.

Method of Survey

A large random sample of patients receiving carbimazole was sought by approaching various colleagues for permission to supplement our own series by abstracting details from their clinical notes. From each hospital have been included all the traceable records of patients who had been treated with the drug. Some colleagues kindly supplied the data already abstracted for us. Almost all these patients were being treated for thyrotoxicosis; some received the carbimazole in preparation for operation or radio-iodine therapy, some for prolonged antithyroid treatment. The daily dosage and its duration were recorded, both as the initial and as the mean maintenance dosage; the former being usually given unaltered for one to two months, and the latter being recorded as the subsequent mean of what was often a varied dosage (total drug given divided by the number of days administered). Details of all toxic reactions were abstracted; any doubtful syndromes were included, unless the clinician concerned agreed that these were not attributable to the drug.

Results

The survey covers 1,046 patients, treated for a mean duration of 9.2 months. They included three main hospital groups and a series of smaller groups from nine hospitals. The age and sex constitution of the whole group is shown in Table I.

TABLE I.—Age and Sex Distribution of 1,046 Cases Surveyed

Age Group	Male	Female
0-10 years	1	2
11-20 "	2	36
21-30 "	23 (1)	185 (2)
31-40 "	27 (1)	225 (8)
41-50 "	39	224 (4)
51-60 "	26	135 (5)
61-70 "	18	74
71 and over	3	21
Unclassified	1	4
Total	140 (2)	906 (19)

Figures in parentheses refer to those with toxic responses.

Of the 721 patients who continued the carbimazole beyond two months, the mean total duration was for 12.3 months, varying from 2 to 51 months, and 297 patients continued this drug therapy for more than nine months (Table II). The dosages used therefore covered all the ranges likely to be used therapeutically; the physicians were satisfied that adequate antithyroid action was being achieved.

All the toxic reactions occurred within the first two months. The incidence of toxicity has therefore been shown in Table III against the initial dosage in relation to its dura-

TABLE II.—Duration of Dosage of Carbimazole in Cases Surveyed

Daily (Maintenance*) Dosage	Duration			Totals
	Up to 2 Months	2-9 Months	Over 9 Months	
Over 30 mg. ..	24	28	3	55
20-30 mg. ..	242	177	30	449
Under 20 mg. ..	59	219	264	542
Total ..	325	424	297	1,046

* Those receiving the drug for under two months have been classified here according to their initial (or only) dosage.

TABLE III.—Incidence of Toxicity in Relation to Duration and Level of Initial Dose

Initial Daily Dosage	Incidence of Toxicity = $\frac{\text{Major} + (\text{Minor}) \text{ Toxicity}}{\text{Number Treated}}$			
	Up to 1 Month	Up to 2 Months	After 2 Months	Total
Over 30 mg. ..	$\frac{0+(1)}{151}$	$\frac{1+(0)}{80}$	$\frac{0+(0)}{34}$	$\frac{1+(1)}{151}$
20-30 " ..	$\frac{4+(13)}{786}$	$\frac{0+(2)}{506}$	$\frac{0+(0)}{244}$	$\frac{4+(15)}{786}$
Under 20 " ..	$\frac{0+(0)}{109}$	$\frac{0+(0)}{87}$	$\frac{0+(0)}{51}$	$\frac{0+(0)}{109}$
Total ..	$\frac{4+(14)}{1,046}$	$\frac{1+(2)}{673}$	$\frac{0+(0)}{329}$	$\frac{5+(16)}{1,046}$

Figures on Table, e.g. $\frac{4+(14)}{1,046}$, signify 4 major and 14 minor reactions out of 1,046 patients treated at this dosage.

tion. During the first two months of administration there was an overall incidence of 2.01% toxic reactions (1.53% minor and 0.48% major) in the 1,046 patients studied, while among the 109 who had received initial daily dosages under 20 mg. a day there were no toxic reactions.

Table V gives details of the syndromes of the patients who had toxic reactions. Of the five instances of a major toxic effect, one was agranulocytosis and four were drug fever with rash and arthritic features. Three of these five gave a history of previous allergic illness, and 3 of the 16 with minor toxic reactions had similarly had a previous allergic illness.†

Discussion

As shown in Table IV, our survey confirms and amplifies the previous preliminary findings that the toxicity of carbimazole is as low as, if not lower than, that of any available antithyroid drug (references given under Table IV). A

TABLE IV.—Toxic Reactions to Antithyroid Drugs

Drugs	No. of Cases Surveyed	Toxic Reactions (%)		Total
		Major	Minor	
Thiouracil ^{4 7 9 11 18 19 20 24 26 27 28 29 30 39 41 46 52 53 55 57 58 59 63 64 65 69 71 76 77 78 79 80}	8,709	5.4%	7.4%	12.8% (10-17%)
Methylthiouracil ^{6 7 33 40 43 51 52 54 56 73}	1,300	9.2%	3.8%	13% (9-13%)
Propylthiouracil ^{2 5 7 13 15 26 27 31 32 42 45 50 52 66 67 72 80 81 82}	2,774	0.9%	2.2%	3.1% (0.8-10%)
Methimazole ^{7 10 12 14 16 23 31 32 34 44 61 70 74}	1,933	1.45%	4.5%	5.95% (4.8-7.5%)
Perchlorate ^{25 56}	132	0.7%	2.3%	3%
Carbimazole ^{8 17 23 32 35 35 62}	319	0.6%	1.25%	1.85%
Already published*	..	0.48%	1.53%	2.01%
Present series ..	1,046			

This table was compounded by adding together published reports and classifying the toxic reactions into major and minor according to the following criteria: major = agranulocytosis, fever, fever and arthralgia, or purpura; minor = the rest, including those doubtfully attributable. The percentages given are those derived from all the series added together; those in parentheses give the range among individual series of over 100 cases.

* Cases reported in references¹⁷ and²³ have been included in the present series.

† None of these were fatal. Since the completion of this survey we have encountered one fatal case of bone-marrow aplasia during carbimazole therapy. This patient succumbed to a cerebral haemorrhage (see article by C. D. Burrell at page 1456).

previous study²³ has compared carbimazole with the least toxic of the other similar antithyroid drugs—methimazole. The antithyroid potency of carbimazole was found to be at least as high as that of methimazole when given in equivalent (milligram) dosage, and on small groups given high dosages (60 mg. a day) the toxicity of carbimazole was less.

As with many other drugs, the toxic effects have emerged especially among those patients with a predisposition to allergic manifestations, 6 of our 21 toxic reactions having occurred in individuals who had previously had allergic illnesses (Table V). Thus when a patient gives a history of such illness the physician's attention can be alerted to the risks of developing toxicity. Further, this varying susceptibility emphasizes the need to survey a large group of patients when assessing the toxicity of any antithyroid drug. Even then, however, comparison between antithyroid drugs is often hampered by uncertainty over whether an equivalently therapeutic range of dosage has been used with each drug. For example, propylthiouracil was initially popularized at a dosage which was less antithyroid than the dosage of the other drugs in common use. Hence the toxicity shown in Table IV for this drug probably relates to its minimal therapeutic dosage. It is likely that in truly equivalent dosage its toxicity is similar to that of methylthiouracil. However, the use of surveys based upon large numbers of patients should ensure at least that any comparisons involve dosages which are within the therapeutic range.

The initial dosage of carbimazole required for antithyroid treatment is usually 30 mg., and ranges from 15 to 45 or 60 mg. a day, rising with size of the goitre and the severity of the hyperthyroidism. After the hyperthyroidism has been brought under control the maintenance dosage required usually ranges downwards from 15 mg. a day. Thus after two months' treatment, the dosage will usually be below that which is potentially toxic (Table II)—though 238 of our patients were maintained beyond the second month at dosages of over 20 mg. a day.

Certain special features of the toxicity of carbimazole that are of practical importance have emerged from this survey. Among the major serious toxic effects agranulocytosis is a rarity, whereas this has been the commonest major toxic result with the thiouracil series of drugs. The usual major toxic effect from carbimazole is a drug fever complicating the rash and also often associated with arthritis, features suggesting rheumatic fever. As a protective measure, therefore, regular white blood counts would be of

little value with this drug—as indeed they are with most antithyroid drugs—because of the usually sudden onset of agranulocytosis. So far only four cases of agranulocytosis following carbimazole have been reported from the U.K. and the U.S.A.; and at least several thousand patients must have received this drug. It is also of practical importance that all the toxic syndromes with carbimazole in this series have developed within two months of the commencement of administration; that they occurred only with dosages of over 20 mg. a day; and that the major toxic syndrome usually includes a rash which the patient is likely to report.

In the clinical use of carbimazole it is probably sufficient precaution to warn patients that, since fever or skin rash or a sore throat may be evidence of a toxic reaction, these must be reported at once.⁴² It is also desirable that the physician should see the patient at least monthly for the first two months. When any serious toxic features are encountered the drug can be stopped and the blood count checked—usually sufficient action to ensure recovery. As with other drugs, when agranulocytosis is encountered antibiotic cover must also be given until the marrow production recovers. When minor toxic features occur with carbimazole, the common one being a rash, such toxic effects can often be eliminated merely by either the additional prescription of antihistamines (done in six of our patients) or by reducing the dosage. If the drug has to be stopped, we have found it possible to continue antithyroid drug treatment with perchlorate. We have found that patients sensitized to either methimazole or carbimazole are usually sensitive to both.

Summary and Conclusions

By surveying 1,046 patients treated with carbimazole for a mean duration of 9.2 months, it was found that 0.5% developed major and 1.5% minor toxic reactions.

All these reactions occurred within the first two months of administration; and none occurred on dosages of less than 20 mg. a day. Six of the 21 affected patients gave a history of previous allergic disease.

Comparison is made with the incidence of toxicity reported with other antithyroid drugs, and in this series the toxicity of carbimazole is definitely lower than that of other antithyroid drugs (major toxic reactions: methylthiouracil, 9.2%; thiouracil, 5.4%; methimazole, 1.45%; propylthiouracil, 0.9%).

TABLE V.—Cases Showing Toxic Reactions

Case No	Sex and Age	At Time of Onset		Toxic Category	Syndrome	Previous Allergic Illness	Treatment Other than Cessation of Carbimazole Therapy
		Daily Drug Dosage	Days on Therapy				
N.1	M 34	30 mg.	4	Minor	Depression—swelling of lips, etc.	Nil	—
R.1	M 28	20 "	4	"	Generalized rash	Severe urticaria on and off for years and with all previous drugs	—
R.2	F 51	30 "	6	"	Rash	Previous rashes with several other drugs	—
R.3	F 50	30 "	7	"	Patient said she had sore throat with goitre swelling (dubious)	Nil	—
H.1	F 32	30 "	7	Major	Rash at 7 days. Some joint pains at 21 days. All gone at 28 days	"	Reduced dosage plus antihistamines
R.4	F 31	20 "	10	Minor	Sore throat and tongue	"	—
R.5	F 34	30 "	10	Major	Polyarthritis with E.S.R.=36 for 1 month	Urticaria spontaneously and after sulphonamides and penicillin	Antihistamines given
R.6	F 35	40 "	10	Minor	Rash	Nil	—
R.7	F 33	33 "	13	Major	Rash, pyrexia, and multiple joint pains	"	—
N.2	F 48	30 "	14	Minor	Depression with slight rash	"	—
X.1	F 50	30 "	16	"	Urticaria	"	Antihistamines given
H.2	F 38	30 "	17	"	Rash—very slight sore throat	"	Resumed with antihistamines
R.8	F 51	30 "	21	"	Rash	Rash and leucopenia on thiouracil	Reduced dosage plus antihistamines
N.3	F 43	30 "	24	"	"	Nil	—
R.9	F 32	30 "	28	Major	Rash and vague joint pains	Urticaria all life and after several drugs	Antihistamines given
X.2	F 50	20 "	28	Minor	Rash	Nil	—
X.3	F 52	20 "	28	"	Headache and vomiting	"	—
X.4	F 56	20 "	28	"	Urticarial rash	"	—
H.3	F 31	60 "	30	Major	Agranulocytosis and sore throat	Fever, rash, and joint pains with mercazole and methylthiouracil	—
N.4	F 28	30 "	35	Minor	Rash	Nil	Continued
N.5	F 28	30 "	38	"	"	"	Stopped

The toxic effects of carbimazole can usually be readily recognized and controlled, and after serious toxic effects drug therapy can be continued where necessary with perchlorate. It is probably better to reserve perchlorate for this role on account of its potentially less smooth antithyroid control.

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FATAL MARROW APLASIA AFTER TREATMENT WITH CARBIMAZOLE

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The incidence of severe toxic reactions—that is, serious depression of haemopoietic tissue—after carbimazole is low; in the series of 1,046 cases reported by Burrell *et al.* (1956) only one case of agranulocytosis (non-fatal) occurred. Among many cases treated since this survey the following fatal case of marrow aplasia was encountered; this is the seventh published case of serious marrow depression following carbimazole (two fatal) (Table I).

TABLE I.—Severe Haematological Reactions to Carbimazole

Author	Type of Reaction	Days on Carbimazole	Daily Dosage
Greene and Morgan (1956)	Pure red-cell anaemia	1	30 mg.
Bartels (1953)	Agranulocytosis	24	40 "
Batty Shaw (1955)	"	30	30 mg. for first 16 days, thereafter 15 mg.
Fraser <i>et al.</i> (1954)*	"	30	60 mg.
Harrison (1954) ..	"	39	15 mg. for first 9 days, thereafter 30 mg.
Richardson <i>et al.</i> (1954)	Bone marrow aplasia (fatal)	54	30 mg.
Present case ..	" "	165	30 "

* Also reported in Burrell *et al.* (1956).

Case Report

Between 1943 and 1951 this patient had several periods of antithyroid drug treatment with which she never persisted carefully, and often lapsed (three months on thiouracil in 1943, two months on methylthiouracil in 1946, and twenty-one months on methylthiouracil in 1949–51). During the last period (1950) she developed dermatitis, treated with antihistamines, but had no other sign of toxic reactions.

At Hammersmith Hospital out-patient department, on August 8, 1955, this married woman of 47 started carbimazole in preparation for thyroidectomy for a clinically obvious recurrence of thyrotoxicosis. She had lost over a stone (6.4 kg.) in weight, and her thyroid was avid for radioiodine (48-hour urine excretion 14.8%, "T" = 55). The initial drug dosage was carbimazole, 30 mg. a day, sodium L-thyroxine, 0.1 mg. a day, and phenobarbitone, 30 mg. twice a day. Owing to an unfortunate oversight this was continued beyond her two and a half months' visit, when she was judged euthyroid and ready for operation.