in circulating volume, which, in subjects intolerant of such a fall, gives rise to the systemic symptoms.

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THE DUMPING SYNDROME

II. CAUSE OF THE SYNDROME AND THE RATIONALE OF ITS TREATMENT

BY

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In the previous communication the role of a fall in plasma volume in the production of the dumping syndrome was described (Le Quesne *et al.*, 1960). It was shown that the fall in plasma volume following the ingestion of hypertonic glucose by patients who had undergone partial gastrectomy varies greatly from individual to individual, and in some with the passage of time. It was further shown that the development of symptoms depends not only upon the size of the fall in plasma volume but also upon the individual's response to a sudden reduction in circulating volume. In the course of these studies we noted that the coincident changes in blood-sugar concentration were far from constant. In the present paper we propose to examine the relation of the changes in blood-sugar concentration to those in plasma volume, and to describe further observations, made after the injection of insulin, which clarify this relationship. From these observations we have been able to devise means, by the use of insulin, of reducing the fall in plasma volume produced by hypertonic glucose or by meals, and thus of relieving the dumping syndrome.

Procedure and Material

Changes in plasma volume and blood-sugar concentration were estimated after the drinking of 175 ml. of 50% glucose. The test involved the taking of venous samples before and at 10 minutes after taking the glucose, and at varying intervals thereafter. Details of the conditions of the test have been given previously (Le Quesne *et al.*, 1960).

Observations were also made of the effects of the prior injection of insulin on the changes in plasma volume following (*a*) 175 ml. of 50% glucose by mouth, and (*b*) a carbohydrate meal.

The change in plasma volume was estimated by the use of Evans blue: details of the methods involved are given in our previous communication. The blood-sugar concentration was measured by the method of Haslewood and Strookman (1939), as described by Varley (1958).

Changes in plasma volume and blood-sugar concentration were estimated on 35 occasions in 28 patients, who fell into two groups. Group A consists of 13 patients admitted to the wards of the department for subtotal gastrectomy for benign peptic ulcer. These patients are the same as those in Series 1 in our previous paper, in which full details concerning them are given; Cases 4, 11, and 12 are omitted here, as blood-sugar estimations in them are not available. In the 13 patients post-operative studies were performed on 26 occasions; on seven of these the blood glucose was not estimated, leaving 19 for analysis here. Group B consists of 15 patients admitted for investigation of their dumping syndrome: in 14 this followed partial gastrectomy and in one a gastro-enterostomy. Of these 15 patients, seven form part of Series 2 in our previous communication; Cases 17, 20, 23, and 26 are omitted because again blood-sugar estimations are not available. Details of the remaining eight patients are given in Table I.

TABLE I.—*Details of the Eight Patients in Group B Additional to Those Described in Our Previous Communication*

Case No.	Age	Sex	Lesion	Operation	Time after Operation
28	53	F	G.U.	B.	7 months
29	73	M	D.U.	A.P.	26 ,,
30	47	M	Carc.	T.G.	5 years
31	54	M	G.U., D.U.	A.P.	5 ,,
32	71	F	D.U.	B.	3 ,,
33	43	M	D.U.	A.P.	2 ,,
34	55	F	Chol.	A.P.	8 months
35	77	M	D.U.	P. & V.	5 ,,

G.U. = Gastric ulcer. D.U. = Duodenal ulcer. Chol. = Recurrent cholangitis, from choledocho-duodenal fistula. B. = Billroth I gastrectomy. A.P. = Antecolic Polya gastrectomy. T.G. = Total gastrectomy. P.&V. = Pylorectomy and vagotomy.

The effect of the prior injection of insulin was observed in seven patients following the ingestion of 175 ml. of 50% glucose, and in three patients following a carbohydrate meal. Of these 10 patients, seven were drawn from those described in our previous paragraph. The remaining three (Cases 38, 43, and 44) were admitted for investigation of their dumping syndrome: in two (Cases 38 and 43) the fall in plasma volume was calculated from changes in the haematocrit (see previous paper) and not by direct measurement.

Observations on Blood Sugar and Plasma Volume

After ingestion of the test dose of 175 ml. of 50% dextrose it was noted that the greater the fall in plasma volume the more rapid and pronounced was the rise in blood sugar. Typical blood-sugar curves associated with a large and small fall in plasma volume are shown in Fig. 1.

The data on blood sugar and plasma volume for all the patients were analysed in various ways in an attempt to discover any correlation between the two. No correlation could be found between, on the one hand, either the greatest height to which the blood sugar rose or the time taken to return to its resting level, and, on the other, the fall in plasma volume. There is, however, a clear correlation between the fall in plasma volume

and the rate at which the blood-sugar concentration rises shortly after drinking the hypertonic glucose. An index of this rate is provided by expressing the blood-sugar concentration 10 minutes after the ingestion of glucose as a percentage of the concentration at zero time. If this figure is plotted against the maximum percentage fall in plasma volume (Fig. 2) a direct linear correlation is found (correlation coefficient +0.863 : $P<0.000000001$).

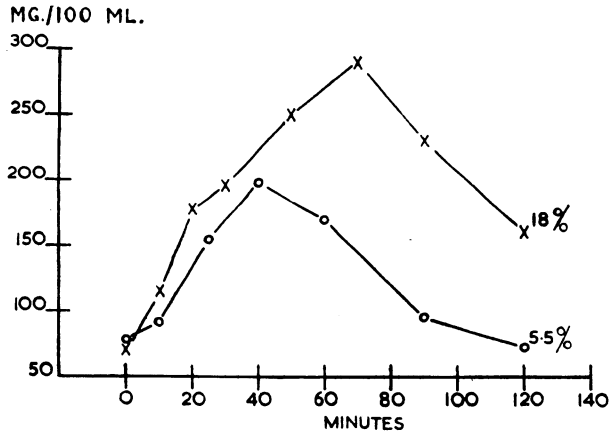

FIG. 1.—Blood-sugar curves from two patients following the ingestion of 175 ml. of 50% glucose. In one (Case 2) the fall in plasma volume was large (18%), while in the other (Case 6) it was small (5.5%).

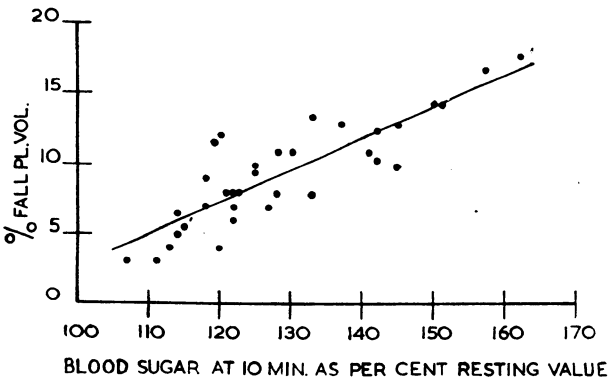

FIG. 2.—Graph showing the relationship between the maximum percentage fall in plasma volume following the ingestion of 175 ml. of 50% glucose and the rate of rise of the blood-sugar concentration, measured by expressing the concentration at 10 minutes as a percentage of that at zero time (resting value). Each point represents a single test, and the results from every test are included. The line drawn satisfies the following regression equation: $y=0.23x-20.3$, where x = the blood-sugar concentration at 10 minutes as a percentage of that at zero time, and y = the maximum percentage fall in plasma volume.

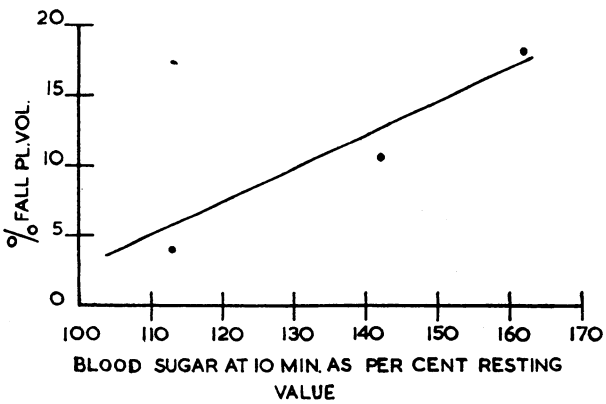

FIG. 3.—Graph showing the relationship between the maximum percentage fall in plasma volume and the rate of rise of the blood-sugar concentration for each of the three tests performed in Case 2. The oblique line is the regression line from the previous figure.

The relationship between these two factors is even more clearly shown by the results in Case 2. In the early days after her gastrectomy this patient had severe dumping symptoms, which spontaneously cleared up in the ensuing six months. Plasma volume studies were performed on this patient shortly after operation and three months and six months later. Fig. 3 shows the points obtained by plotting the maximum percentage fall in plasma volume against the rate of rise of the blood-sugar concentration for each of these three studies.

Effects of Insulin Administration

Experiments were performed to see whether lowering of the blood-sugar concentration by the prior injection of insulin affected the fall in plasma volume following the drinking of hypertonic glucose. In six patients the fall in plasma volume was measured after 175 ml. of 50% dextrose, and in one patient after 125 ml. This observation was then repeated after a subcutaneous injection of soluble insulin which was intended to lower the blood-sugar concentration to about 50 mg./100 ml.

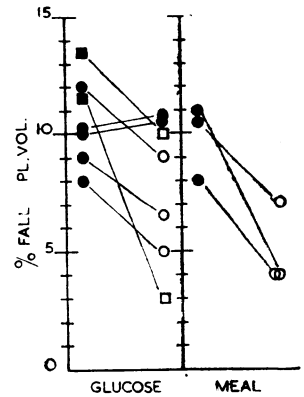

FIG. 4.—Graph showing the effect of the prior injection of insulin on the maximum percentage fall in plasma volume following ingestion of 175 ml. of 50% dextrose or of a carbohydrate meal. The pair of observations on each patient are linked by a straight line, the left-hand point representing the study without insulin and that on the right the study with insulin. Blocked symbols indicate that the test produced dumping symptoms, while clear ones indicate a lessening or absence of symptoms. Square symbols indicate that the change in plasma volume was calculated from the change in haematocrit, while in those with circles it was measured by Evans blue.

The dosage and timing of the insulin injection, based on the results of a previous subcutaneous insulin tolerance test, are given in Table II, together with the blood-sugar level achieved, and the fall in plasma volume on each of the two tests. In five patients the prior injection of insulin lessened the fall in plasma volume and in two the fall was unchanged (Fig. 4).

TABLE II.—*Details of the Insulin Studies*

Case No.	Stimulus: Type	Stimulus: CHO Content (g.)	% Fall in Plasma Volume: How Measured	% Fall in Plasma Volume: Without Insulin	% Fall in Plasma Volume: With Insulin	Insulin: Dosage: Units, Soluble	Insulin: Time before Stimulus (min.)	Insulin: Blood Sugar Reduced to (mg. 100 ml.)
5	Gl	87·5	E.B.	12	9	15	75	61
23	Gl	87·5	E.B.	10	10·5	12·5	60	58
24	Gl	87·5	E.B.	10	10·5	15	65	59
33	Gl	87·5	E.B.	8	5	10	50	72
34	Gl	62·5	E.B.	9	6·5	10	80	45
38	Gl	87·5	Ht.	13·5	10	10	60	58
43	Gl	87·5	Ht.	11·5	3	10	80	45
20	M	75	E.B.	11	4	25	55	60
26	M	55	E.B.	8	4	10	50	—
44	M	89	E.B.	11	7	15	60	53

Gl = 175 ml. of 50% dextrose. M = Carbohydrate-rich meal. E.B. = Evans blue. Ht. = Haematocrit.

In three other patients similar observations were carried out after the stimulus of a breakfast type meal rich in carbohydrate, instead of the hypertonic glucose. In each instance the size of the meal was such as had been found by previous observation to be the largest the patient would take. In all three patients the insulin lessened the fall in plasma volume (Table II ; Fig. 4).

All 10 patients on whom this insulin test was performed were suffering from the dumping syndrome, and in each the hypertonic glucose or carbohydrate meal reproduced their symptoms. In all those patients in whom the insulin caused a lessening of the fall in plasma volume the symptoms were distinctly less: in all three cases after the meal and in two cases (Nos. 33 and 34) after the glucose the symptoms were completely prevented by the insulin.

No correlation could be found between the level to which the blood-sugar concentration had been lowered by the insulin and the extent to which the fall in plasma volume was affected. But it was found that in those cases in which the fall in plasma volume was distinctly less the blood-sugar curve was much lower throughout the 2½-hour period of observation. One such pair of curves is shown in Fig. 5.

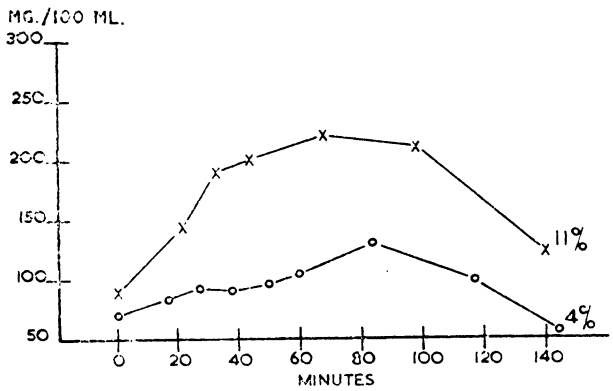

FIG. 5.—Blood-sugar curves from Case 20, following the ingestion of a meal containing 75 g. of carbohydrate, with and without the prior injection of 25 units of soluble insulin. Without insulin (×——×) the meal produced marked dumping symptoms and a fall in plasma volume of 11%; after insulin (O——O) there were no symptoms and a fall of only 4%.

In Case 26 the prior subcutaneous injection of insulin permitted the patient to eat a carbohydrate meal without symptoms, and reduced the fall in plasma volume from 8% to 4%. However, when 5 units (0.1 unit/kg. body weight) were injected intravenously five minutes before starting an exactly similar meal the onset of severe dumping symptoms prevented her finishing the meal.

Discussion

It is well established that after partial gastrectomy many patients have an abnormal response to a glucose-tolerance test, the blood-sugar curve showing a rapid rise, an abnormally high maximum level, and often a subsequent fall to abnormally low levels (Adlersberg and Hammerschlag, 1947 ; Gilbert and Dunlop, 1947). This type of curve is often called the lag curve. It is also known that after partial gastrectomy the ingestion of hypertonic glucose causes a variable fall in plasma volume as the result of an osmotic transfer of fluid into the intestine. The results reported here show that there is a close correlation between these two phenomena, and that the larger falls in plasma volume occur in those patients showing a lag type of blood-sugar curve. Further, there is a direct relation between the size of the fall in the plasma volume and the initial rate of rise of the blood-sugar curve. Any explanation of the abnormal glucose-tolerance curve must therefore also be capable of explaining why it is associated with a large fall in plasma volume.

The usual explanation of this abnormal glucose-tolerance curve is that, in those subjects in whom it occurs, there is excessively rapid emptying of the gastric remnant: this results in a very rapid presentation of glucose to the small intestine, a rapid absorption, and hence a rapid increase in blood-sugar concentration. This explanation could obviously account for the close correlation between the initial rate of rise of the blood-sugar concentration and the extent of the fall in plasma volume, in that the more rapid the gastric emptying the greater must be the osmotic force exerted in the small intestine. In other words, this explanation postulates that the basic difference between those patients who do and do not have a large fall in plasma volume is the rate at which the gastric remnant empties. No immediate reason is apparent why in some patients the gastric remnant should empty faster than in others.

There is, however, an alternative explanation. Following the oral administration of glucose, even after gastrectomy, the shape of the blood-sugar curve must depend upon the balance between the rate of absorption of glucose from the intestine and the rate of removal of glucose from the blood-stream. It may be that in patients with the lag type of curve the rapid rise of the blood-sugar curve is due to slow removal of glucose from the blood-stream, and that the resultant high blood-sugar concentration results in a slowing of absorption due to interference with diffusion processes. This slowing of the absorption of glucose will result in a considerable osmotic shift of fluid into the intestine, so increasing the fall in plasma volume, and, as a result of the increase of fluid in the gut, stimulating intestinal peristalsis. This in turn will increase the rate of emptying of the gastric remnant, so increasing the osmotic load in the intestine and setting up a vicious circle. This alternative hypothesis postulates that the basic difference between those who do and those who do not have a large fall in plasma volume lies in their ability to metabolize absorbed glucose, and that the difference in gastric emptying is a secondary phenomenon.

This latter hypothesis depends upon the assumption that after gastrectomy the emptying rate of the gastric remnant depends not upon its own intrinsic muscular activity but upon jejunal or duodenal peristalsis, and further, that intestinal peristalsis is increased in those with the dumping syndrome. It is difficult to find direct evidence upon the first of these points, but on the basis of their observations Vitkin (1940), Bruusgaard (1946), and Porter and Claman (1949) all suggest that jejunal contraction is a factor of major importance in gastric emptying after partial gastrectomy. As regards the second point, it is well established that in patients with the dumping syndrome there is increased intestinal peristalsis (Glazebrook and Welbourn, 1952).

Either of the two hypotheses outlined above demands that the emptying rate of the gastric remnant is faster in those patients with the dumping syndrome. That this is true has been shown with meals by Abbott *et al.* (1958) and with hypertonic glucose by Amdrup *et al.*

(1958). At present it does not seem possible to decide whether this is a primary or a secondary phenomenon. However, the following considerations support the second hypothesis—namely, that glucose metabolism is the factor of major importance.

1. The dumping syndrome affects many patients in the early weeks after partial gastrectomy, but in the majority it disappears spontaneously. This recovery must represent an adaptation to the altered gastro-intestinal conditions. As it is the distal portion of the stomach, the part which controls the emptying rate of the intact organ (Thomas, 1957), that has been removed, it is difficult to believe that this adaptation depends solely upon an alteration in the rate at which the gastric remnant empties itself.

2. Lundh (1958) has shown that while, in general, glucose absorption is within normal limits after partial gastrectomy, it is impaired in those cases in which the intestinal transit is extremely rapid. Lundh did not correlate the rate of glucose absorption with the presence or absence of dumping symptoms, but an exceptionally rapid intestinal transit is a known feature of the dumping syndrome (Amdrup *et al.*, 1958). Further, as shown above, the dumping syndrome is associated with a rapidly climbing glucose-tolerance curve, which is therefore occurring in the presence of impaired absorption.

3. As our insulin studies show, the fall in plasma volume after the ingestion of hypertonic glucose, and hence presumably the osmotic transfer of fluid into the intestine, can be diminished by accelerating carbohydrate metabolism. The effect of the insulin must be due to an increase in rate of glucose absorption, probably as the result of facilitating diffusion processes. From an examination of the blood-sugar curves after giving insulin it is clear that this is not due to an alteration in intestinal membrane permeability, as the insulin produces a lower blood-sugar curve. Probably the effect is due to an increased rate of removal of glucose from the blood-stream. Whatever the exact mechanism by which it works, the clinical significance of the effect of insulin lies in the fact that by altering carbohydrate metabolism the fall in plasma volume occurring after hypertonic glucose can be modified.

Two further points concerning the insulin studies require comment. First, the observation that insulin given intravenously immediately before a meal has no effect as opposed to an equivalent subcutaneous dose given some time previously shows that the insulin must work not by its mere presence in the blood-stream but by an indirect effect, presumably on carbohydrate metabolism, which takes time to develop. Secondly, in general, insulin was more effective, both in lowering the fall in plasma volume and in preventing symptoms, when given before a meal than when given before hypertonic glucose. This is probably due to two factors: (*a*) except in one case, the carbohydrate content of the meal was lower than that of the hypertonic glucose; and (*b*) whereas the glucose was drunk in less than one minute, the meal took five to seven minutes to consume, and, further, some of the carbohydrate in the meal was in the form of starch, which requires a little time for its digestion into osmotically active glucose. As a result of both these factors the meal imposes a less severe strain upon the absorptive capacity of the patient.

In our previous communication we produced evidence that the dumping syndrome is caused, in patients sensitive to a sudden fall in circulating volume, by an osmotic shift of fluid from the circulation into the lumen of the intestine. On the basis of the observations reported here we suggest that the essential factor in the production of the osmotic shift is a defect in carbohydrate metabolism. Following partial gastrectomy, glucose is presented to the intestine more rapidly than usual. Most patients react to this by an adaptation of glucose metabolism by which the glucose-tolerance curve remains normal, absorption proceeds rapidly, and there is only a small osmotic transfer of fluid into the intestine. In some patients this adaptation does not occur. In these patients the glucose-tolerance curve is of the lag type, glucose absorption is relatively slow, and a large osmotic shift of fluid occurs, which, by increasing the rate of gastric emptying, increases the osmotic load: thus a vicious circle is set up.

The observation that the administration of insulin can diminish the fall in plasma volume and modify the symptoms of the dumping syndrome has obvious therapeutic implications. A small number of patients are being treated by subcutaneous insulin, either once or twice a day before meals. It is as yet too early to reach firm conclusions, but preliminary results are encouraging, many of the patients showing not only subjective benefit, with lessening of distension and exhaustion, but also objective improvement as shown by cessation of diarrhoea and a gain in weight. Full results will be reported later.

Summary and Conclusions

Observations were made of (*a*) the changes in blood-sugar concentration, and (*b*) alterations in plasma volume following the oral administration of 175 ml. of 50% glucose to 26 patients who had undergone gastrectomy, and to one patient who had had a gastro-enterostomy. In these 27 patients the test was performed 34 times.

In patients with a large fall in plasma volume following the ingestion of hypertonic glucose, the rise in blood sugar was more pronounced and prolonged than in those with a small fall.

A direct linear correlation was found between the maximum fall in plasma volume caused by the hypertonic glucose and the rate at which the blood-sugar concentration rose in the first 10 minutes after the ingestion of the glucose.

In patients in whom the hypertonic glucose caused a large fall (>8%) in plasma volume, the administration of insulin so as to lower the blood-sugar concentration at the time of the ingestion of the glucose diminished this fall and also lessened or abolished the associated dumping symptoms.

Insulin was also shown to have a similar effect in diminishing the fall in plasma volume and abolishing dumping symptoms following a meal rich in carbohydrate.

The hypothesis is put forward that the essential factor in the production of the dumping syndrome is a defect of carbohydrate metabolism, as a result of which the glucose-tolerance curve is of the lag type and glucose absorption is relatively slow. This results in an increased osmotic transfer of fluid into the intestine, causing a large fall in plasma volume which, in those patients sensitive to such a fall, gives rise to the dumping syndrome.

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EFFECT OF PRETREATMENT WITH METHYLTHIOURACIL ON RESULTS OF ^{131}I THERAPY

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Little is known about the fundamental biological changes produced in thyroid cells when they are irradiated by radioactive iodine, and still less about factors which modify these changes. It might be expected that thyroid tissue would become more sensitive to ionizing radiations after treatment with antithyroid drugs which increase both the vascularity of the gland (Thomas, 1945) and the number of mitoses in thyroid cells (Řeřábek and Řeřábek, 1947). Indeed, Williams *et al.* (1949) in an uncontrolled trial had the impression that patients pretreated with propylthiouracil required a lower dose of ^{131}I than untreated cases. Furthermore, Fraser *et al.* (1954) devised a procedure which involved pretreatment by methylthiouracil and thyroxine and which was said to give more consistent results than the standard methods of ^{131}I administration. On the other hand, Chapman and Maloof (1955) and Blomfield *et al.* (1959) observed no consistent difference in the response of those which had received no pretreatment. Werner (1955), however, states that methylthiouracil produces a radioresistant gland.

Since ^{131}I produces its effects relatively slowly it is sometimes necessary to control thyrotoxicosis with antithyroid drugs before treatment with the radioisotope. Moreover, many patients are referred for this form of treatment who have previously received courses of antithyroid drugs. We decided, therefore, to carry out a trial to see whether pretreatment with methylthiouracil influenced the results of ^{131}I therapy.

We decided to use a simple clinical method for the assessment of the dose of ^{131}I which we would use. This is similar to that described by Macgregor (1957), and we report our experience using this procedure. Our results confirm and extend his conclusions.

Material and Methods

One hundred and fifty patients in whom the diagnosis of thyrotoxicosis had been confirmed by the clinical index, described by Crooks *et al.* (1959), and by ^{131}I studies were considered on the criteria laid down by Blomfield *et al.* (1955) to be suitable for ^{131}I therapy.

Since the method of assessment of dosage is subjective and the prescribing physician might have altered his criteria during the three and a half years over which the observations were spread, certain precautions were taken in the design of the investigation. The doses of ^{131}I given to the different groups of patients were prescribed by the same physician (J. C.), and the observations on pretreated cases were controlled by those on untreated cases over the same time intervals. Four groups were studied.

Group 1 consisted of 28 patients who had received methylthiouracil for periods ranging from three months to one year. Administration of the drug ceased one week before treatment with ^{131}I. At this time all the subjects were either euthyroid or minimally thyrotoxic.

Group 2 consisted of 45 patients who had been treated with ^{131}I over the same period as Group 1, and who had never received an antithyroid drug.

When it became clear that methylthiouracil conferred some degree of radioresistance on the thyroid gland two further groups were studied.

Group 3 consisted of 21 patients previously treated with methylthiouracil in the same way as those in group 1 but in whom the dose estimated in the standard manner was arbitrarily increased by 25%.

Group 4 acted as the control to group 3. It included 56 patients who were not pretreated and whose dose was determined in the same way as that of patients in groups 1 and 2. They differed from group 2 only in the fact that they were treated contemporaneously with group 3.

All cases, with the exception of a few who were treated early in the course of the investigation, were given tracer doses of ^{131}I during the week before treatment in order to determine the 48-hour gland uptake of ^{131}I. In patients who had been receiving methylthiouracil the drug was stopped 48 hours before the tracer dose was administered.

Method of Dose Estimation

The basic principle of dose estimation used was that small doses were prescribed for patients with small glands and large doses for patients with large glands. It was decided from a review of the results of other workers that patients with impalpable glands would be given doses of 4–5 mc., those with minimal but definite diffuse enlargement of the gland 6–7 mc., and patients with larger glands doses from 7–25 mc. according to the size of the goitre. Many other factors besides gland size influenced the dose prescribed; for example, post-thyroidectomized patients were given 5–6 mc., unless the gland remnant was exceptionally large. Relatively high doses were given to patients with nodular glands, cardiac