QUANTITATIVE STUDIES OF IODINE METABOLISM IN THYROID DISEASE

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PREFACE

The thesis is based on an investigation reported in the Quarterly Journal of Medicine (Quantitative studies of iodine metabolism in thyroid disease. Alexander et al 1962, 31, 281), and on more recent studies. Much of the work will be included in a book written in conjunction with Professor E.J. Wayne and Dr. D.A. Koutras, entitled Clinical aspects of iodine metabolism, to be published shortly by Blackwell, Oxford.

By far the greater part of the studies reported here were made on outpatients who attended the Thyroid Clinic, Gardiner Institute, between 1959 and 1963. Since 1959 I have been Professor Wayne's deputy in effective charge of this Clinic, and the selection, study and assessment of the patients described in the investigations has been my personal responsibility*. I also have responsibility for the thyroid function studies carried out by the radioisotope department, and for supervision of the work of the chemical iodine laboratory where all the quantitative studies of iodine metabolism were undertaken. Without the painstaking and enthusiastic help of the technicians in these laboratories the work would not have been possible.

Throughout the studies I have had the advantage of much helpful discussion and advice from Professor Wayne. The section of the

* With the exception of 17 Icelandic patients.

work published in papers1 to 5 was planned, executed and analysed in collaboration with Dr. Koutras, that in paper 6 with Dr. Harden, and that in paper 7 with Dr. Harden and Dr. Harrison.

I am also grateful to the following:

Miss E.M. Macdonald and Mrs. S. Johnston for technical assistance with the radioiodine tests, and Dr. M. Richmond and Mr. T. Magee for carrying out the chemical estimations of iodine in serum and urine. Dr. Silvey, Dr. Robb, Dr. Robertson, Dr. Weir and Professor Bradt for advice on statistical aspects of the work. Mrs. Rae Ferguson for so kindly agreeing to type the thesis.

1. "Stable Iodine Metabolism in Non-Toxic Goitre". Lancet 2, 784, 1960.

2. "Stable Iodine Metabolism in Thyroid Dyshormonogenesis". Scottish Medical Journal 5, 331, 1960.

3. "Effect of D-Thyroxine on Thyrotoxicosis and on the Associated Exophthalmos". British Medical Journal 1, 1194, 1961.

4. "Studies of Stable Iodine Metabolism as a Guide to the Interpretation of Radio-iodine Tests". Acta Endocrinologica 37, 597, 1961.

5. "Quantitative Studies of Iodine Metabolism in Thyroid Disease". Quarterly Journal of Medicine N.S. 31, 281, 1962.

6. "Quantitative Aspects of Iodide Excretion in Human Thermal Sweat" Clinical Science (in press).

7. "Thyroid Function and Iodine Metabolism in Iodine Induced Hypothyroidism". Lancet 1, 1238, 1963.

QUANTITATIVE STUDIES OF IODINE METABOLISM IN THYROID DISEASE

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Chapter 4 (continued) Page

Abbreviations and terms used.

AIU Absolute iodine uptake of the thyroid (normal range 0.5 - 6.0 μg/hr)

DI* "Diagnostic index" for thyrotoxicosis
Normal range: Less than 11
Equivocal range: 11 to 19
Thyrotoxic range: 20+
(Crooks, Murray and Wayne 1959)

Diet* Dietary iodine estimated from diet history in μg/day

Dur.goi.* Duration of goitre in yr.

Dur.sym.* Duration of symptoms in yr.

IEI Intrathyroidal exchangeable iodine in mg.

Iodide This is used in the strict chemical sense to denote iodide ion or electrolytes containing the iodide ion.

Iodine Iodine is used to denote the element in either organic or inorganic form.

PBI Protein-bound iodine of serum (normal range 3.0 - 7.5 μg/100 ml).

PBI^{131} Protein-bound radioactivity in the plasma 48 hr after administration of the tracer dose in % dose/litre plasma.

PII Plasma inorganic iodine (normal range 0.08 - 0.60 μg/100 ml).

R.Cl. Renal clearance of iodide (normal range 15.0 - 55.0 ml/min).

T_3 3,5,3'-triiodothyronine

T_4 3,5,3',5'-tetraiodothyronine (thyroxine)

Th.Cl. Thyroid clearance of iodide (normal range 8.0 - 40.0 ml/min).

Th.Upt. Thyroid radioiodine uptake % dose

TPI^{131} Total radioactivity in the plasma 48 hr after administration of the tracer dose in % dose/litre plasma.

Thyroid hormone This term is used to mean the sum of all the biologically active substances produced by the thyroid (i.e. both T_3 and T_4)

24 hr Iur* Daily excretion of iodine in the urine in μg.

± Standard error of the mean, unless otherwise specified.

* These abbreviations are used only in Tables.

INTRODUCTION

'Valid quantitative deductions cannot be reached by throwing isotopes into physiological pools of unknown dimension'. This statement (Lancet 1960) is as true of radioactive iodine as of any other isotope, and summarises the limitations of tracer techniques when not combined with suitable chemical measurements. Isotopes are ideal for the measurement of the proportion of the body iodine which follows a particular metabolic pathway whereas chemical methods give information about the absolute quantities of iodine involved. It is only by combining the two techniques that a complete picture of iodine metabolism can be obtained (Riggs 1952). Although numerous papers have appeared dealing with radio-isotopic and chromatographic studies of thyroid physiology, comparatively little attention has been given to this type of quantitative study, possibly because of the technical difficulties of measuring the plasma inorganic iodine, since very small quantities are involved. In 1949, however, Stanley devised an indirect method for the estimation of the plasma inorganic iodine (PII) based on estimations of the amount of iodine in the urine. Although the practicability of this technique has been shown by several observers, normal and pathological ranges have not previously been fully defined, so that even figures such as the PII concentration in thyrotoxicosis are still

in doubt (Pochin 1960).

Even now most workers studying thyroid function rely solely on radio-isotopic measurements. Radio-iodine tests are of established value in the routine diagnosis of thyroid disease but, as shown in this thesis, a very poor correlation with thyroid function exists in cases in which the body stores of iodine are either abnormally low or high. There is thus a definite place for full quantitative studies of iodine metabolism, since they aid clinical diagnosis, especially when the clinician's impressions are not confirmed by the usual laboratory tests. Their wider use would certainly increase the accuracy of diagnosis in difficult cases of thyroid disorder. Their chief contribution, however, is to make more precise our knowledge of the nature of the abnormalities of iodine metabolism which occur in a number of diseases of the thyroid gland.

Chapter 1 - METHODS

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Iodine occupies a unique position in human physiology since its only known function is to form part of the thyroid hormone molecule. Iodine metabolism and thyroid physiology are therefore inextricably linked

THE IODINE CYCLE

Naturally occurring stable iodine I^{127} and the radioactive forms I^{131} and I^{132} follow exactly the same metabolic pathways.

When the diet is adequate an adult ingests about 160µg of iodine daily and excretes a similar quantity, so that he remains in iodine balance. Only that part of the ingested iodine which is in the form of iodide, or can be converted to iodide, is utilized for thyroid hormone synthesis. Absorption occurs largely in the small intestine, more rapidly in the fasting state, and following absorption iodide is distributed in the extra-cellular fluid. Most cell membranes are impermeable to iodide, notable exceptions being those of the red blood cells and of the renal tubules. Iodide is transported in the plasma, the concentration ranging from 0.08 to 0.60 µg/100 ml. Part of the plasma inorganic iodine is excreted by the kidney and part is trapped by the thyroid; the clearance rate of iodide by the kidney is relatively constant, but that of the thyroid is adjusted to the iodide

available in the plasma. In addition to the thyroid and kidney the salivary, gastric and mammary glands all maintain an increased concentration gradient of iodide with respect to the plasma. Losses of inorganic iodine in faeces, expired air and sweat are small.

The iodide trapped by the thyroid gland is there converted to free iodine under enzymatic control. The iodine replaces hydrogen on the benzene rings of tyrosyl residues present in peptide linkage in thyroglobulin, producing mono- and diiodotyrosine. Coupling of tyrosine nuclei to form the iodothyronines, thyroxine and 3 5 3'-tri-iodothyronine, also takes place. The structural formulae are shown in Fig 1.1. Other iodinated compounds (iodinated histidines and 3 3'5' triiodothyronine) have been found in thyroid tissue but are not known to have significant physiological function, and probably do not leave the gland under normal conditions.

The hormone is stored as thyroglobulin, a protein with a molecular weight of about 650,000, and is released from this protein only after hydrolysis by an enzyme system under TSH control. Most of the plasma thyroxine circulates in combination with a carrier protein, thyroxine-binding globulin, but some is attached to albumin, and perhaps to pre-albumin. Triiodothyronine is less firmly bound and is more rapidly removed from the circulation than thyroxine. Some recent studies suggest that iodotyrosines do indeed circulate, but it is generally believed that the iodinated amino-acids other than thyroxine

THYROID HORMONES AND PRECURSORS

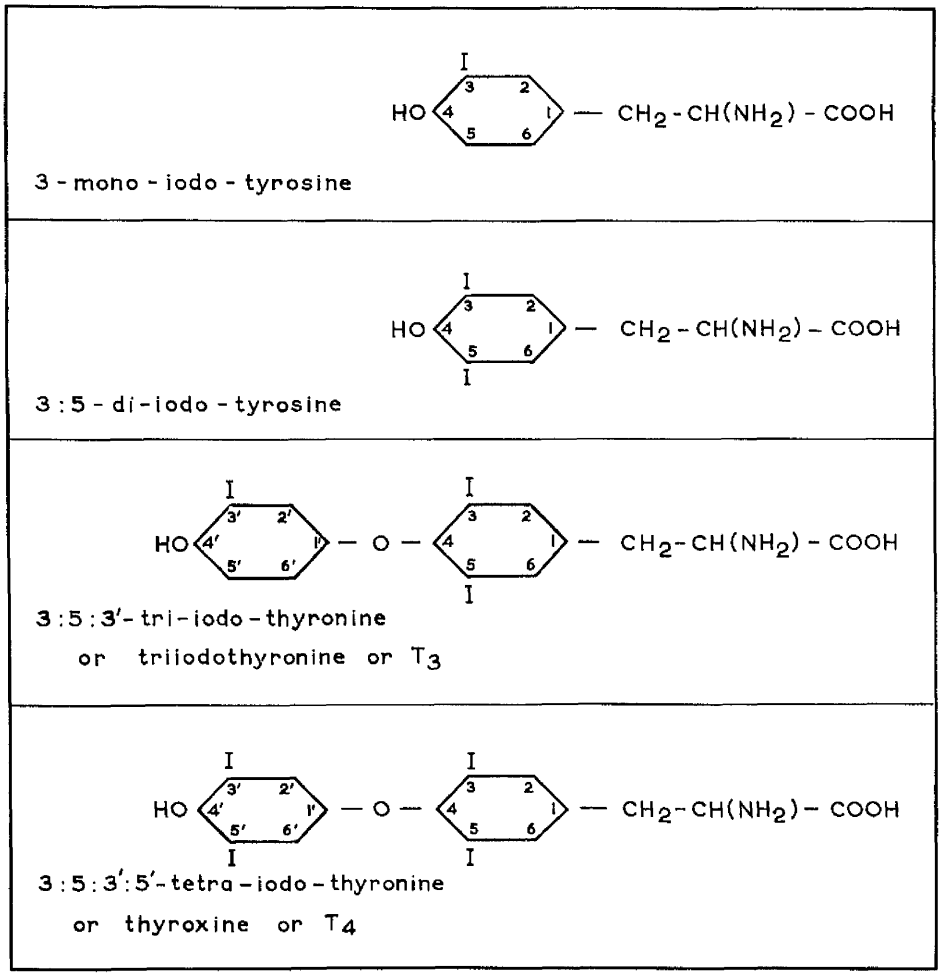

Figure 1.1

Thyroid hormones and precursors

and triiodothyronine are deiodinated within the gland. If iodotyrosines do in fact circulate, they may be a breakdown product of thyroxine metabolism. Thyroxine and triiodothyronine enter the cells at the periphery where in the course of exercising their metabolic effects iodide is liberated, and becomes again available for renal excretion or hormone synthesis (Fig 1.2).

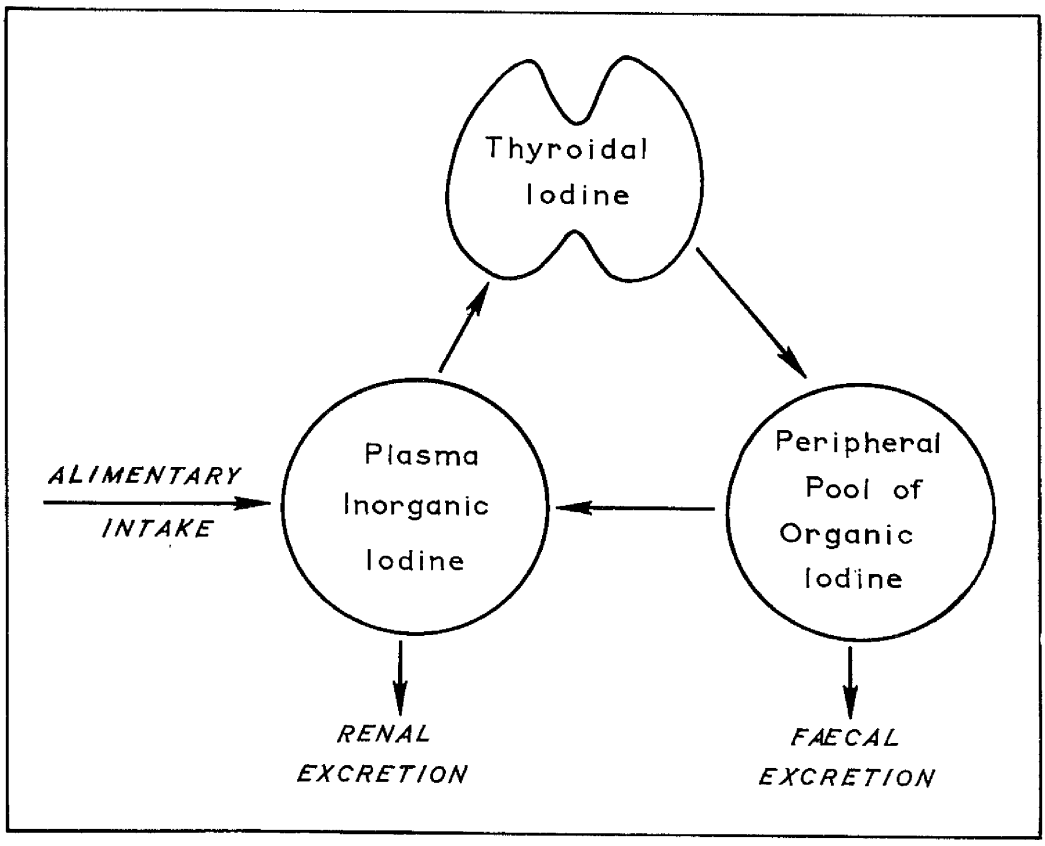

Figure 1.2

Outline of iodine metabolism

Iodine is absorbed from the alimentary tract into the plasma inorganic iodine pool. Some is excreted by the kidneys, and some is taken up by the thyroid and converted into thyroid hormone. Thyroid hormone is secreted from the thyroidal iodine pool into the peripheral pool of organic iodine. The latter is made up of thyroid hormone in the plasma and tissues. Part of the iodine leaves this pool in the faeces but most is deiodinated and re-enters the plasma inorganic iodine pool. The cycle is repeated.

THEORETICAL BASIS OF THE METHODS.

Since the thyroid cannot distinguish between radioactive and stable iodine atoms, the specific activity of the iodine (proportion of the radioactive to total iodine atoms) taken by the thyroid gland is the same as the specific activity of the inorganic iodine present in the plasma. If we express the absolute amount of iodine taken up by the thyroid as AIU, the uptake of radio-iodine during the same period of time as I^{132} uptake, the concentration of plasma inorganic iodine as PII, and the concentration of radioactive inorganic iodine as I^{132} plasma, we have the following equations:

$$\frac{I^{132}\ \text{uptake}}{AIU} = \frac{I^{132}\ \text{plasma}}{PII} \qquad (1)$$

From this equation it follows that:

$$I^{132}\ \text{uptake} = \frac{I^{132}\ \text{plasma} \times AIU}{PII}, \qquad (2)$$

and

$$AIU = \frac{PII \times I^{132}\ \text{uptake}}{I^{132}\ \text{plasma}}. \qquad (3)$$

It can be seen from equation (2) that for a given amount of chemical iodine entering the thyroid gland (and represented by the AIU) the radio-iodine uptake is inversely proportional to the plasma

inorganic iodine, that is, it rises when the PII falls, and decreases when the PII rises. That this actually happens is shown by the radio-iodine uptake measurements in cases with previous iodine administration, and in iodine-deficiency states.

From equation (3) it can be seen that for a given value of radio-iodine uptake the AIU is directly related to the PII. In other words, the radio-iodine uptake may give a very misleading indication of the amount of iodine actually going into the thyroid unless the PII is within the usual range. This is illustrated by the fact that a two-and-a-half-hour radio-iodine uptake of 25 per cent. (corresponding to a thyroid iodide clearance rate of about 30 ml per minute) is a perfectly normal value when the PII is at the usual level of 0.20 μg per 100 ml, in which case the AIU is 3.6 μg per hour. But the same value of 25 per cent. at two-and-a-half hours is suggestive of thyrotoxicosis when the PII is 2.00 μg (as may occur after iodine administration), in which case the AIU is 36.0 μg per hour, well within the thyrotoxic range.

As stated above, calculation of the AIU requires knowledge of, first, the volume of plasma cleared of its iodide content in unit time by the thyroid (the thyroid iodide clearance rate), and secondly, the concentration of iodide in this volume of plasma (the PII). The first of these values can be estimated by the method of Myant et al. (1949). The radio-iodine uptake per unit of time is divided by the plasma radioactivity at the same time, and the value obtained represents the thyroid clearance. The second value,

the PII, can be estimated when it is abnormally high (after iodine administration) as the difference between the total plasma (or serum) iodine and the protein-bound iodine. In normal circumstances, however, the PII is too small to be measured directly in this way. It can be calculated indirectly from measurements of the urinary iodine (Stanley, 1949), since after the administration of a tracer dose the specific activity of iodine is the same in both plasma and urine, as shown in the equations

$$\frac{I^{132}\ \text{plasma}}{\text{PII}} = \frac{I^{132}\ \text{urine}}{\text{urinary iodine}} \qquad (4)$$

$$\text{PII} = \frac{\text{urinary iodine} \times I^{132}\ \text{plasma}}{I^{132}\ \text{urine}} \qquad (5)$$

An alternative method of determining the PII is based on the specific activity of the salivary instead of the urinary iodine. Both these methods depend on the assumption that all the urinary or salivary iodine is derived from the PII and not from organic iodine compounds. It seems that this is not true of the salivary iodine (Cohen 1962; Weiss et al. 1962). Organic compounds or iodine in the urine, if present at all, are in low concentration except in the rare cases of de-iodinase deficiency or after administration of organic iodine compounds (p 113). With these exceptions the error introduced by assuming that the urinary iodine is entirely inorganic is negligible (Riggs 1952).

DESCRIPTION OF THE METHODS.

The following parameters of iodine metabolism were measured:

(1) The thyroid radioiodine uptake at 2½ hours (per cent. of dose)

(2) Thyroid clearance of radioiodine (ml of plasma/min)

(3) Plasma inorganic iodine (PII) (µg/100 ml)

(4) Absolute iodine uptake of the thyroid (AIU) (µg/hr)

(5) Serum protein-bound iodine (µg/100 ml)

(6) Renal clearance of iodide (ml/min).

The thyroid radioiodine uptake at 2½ hours was estimated after an oral tracer dose of 25 to 50 µc of I^{132} using a directional scintillation counter with a 1½ inch sodium iodide (thallium activated) crystal, connected to an auto scaler. The counter was set up vertically over the patients thyroid gland 29 cm from the surface of the skin. For each gland uptake measurement two counts were obtained. The first count gave the radioactivity in the thyroid and surrounding tissue but there was an appreciable contribution to this count from the rest of the body. For the second count a block of lead 4" x 4" x 2" was placed over the thyroid to cut out the radiation from the gland, leaving the background count. The difference between the two counts represented the radioactivity in

the gland. This was then expressed as a percentage of the counts obtained from a dose of radio-iodine similar to that given to the patient, measured at the same distance from the counter. The standard dose of radio-iodine was placed in a block of perspex 1½ inch thick.

The thyroid clearance of I^{132} was estimated by measuring the I^{132} uptake at one and at two-and-a-half hours, and the plasma radioactivity at the mid-point, according to the formula:

Thyroid clearance (ml/min) =

$$\frac{I^{132} \text{ uptake } 2\frac{1}{2}\text{-hr (\% dose)} - I^{132} \text{ 1-hour (\% dose)}}{I^{132} \text{ plasma (\% dose/ml)} \times \text{time between 2 uptakes in mins}}.$$

The plasma radioactivity at the mid-point between the two uptake measurements is assumed to be entirely due to inorganic iodine, since even in thyrotoxicosis significant amounts of protein-bound radio-iodine are not released during the first two hours following ingestion. Furthermore, this radioactivity is assumed to be the mean radioactivity of the plasma between the uptake measurements. This is not strictly correct, since the fall in plasma radioactivity is not linear but follows an exponential curve. A correction can be made by using the following formula.

$$B = \frac{B_1 - B_2}{\log_e B_1 - \log_e B_2},$$

where B represents the mean plasma concentration of radio-iodine during

a time period, B_1 the concentration at the beginning of the period, and B_2 at the end of the period (Keating et al. 1949). The difference in practice is small. If B_2 is 80 per cent. of B_1 the arithmetic mean is 90 per cent., the mean plasma concentration B is 89.6 per cent., and the concentration at the mid-point 89.4 per cent. The difference, therefore, between the mean plasma radioactivity (B) and the radioactivity at the mid-point is 0.2 per cent. of the initial radioactivity (B_1). If B_2 is 50 per cent. of B_1 the arithmetic mean is 75 per cent., the mean plasma radioactivity during that period is 72.1 per cent., the radioactivity at the mid-point 70.7 per cent., and the difference between these last values is 1.4 per cent. of the initial concentration. It can be seen that the fall in plasma radioactivity, if it does not exceed 50 per cent. of the initial concentration during the 90-minute period of the test, closely approximates to linearity. In practice this fall does not usually exceed 20 per cent. in euthyroid subjects or 50 per cent. in thyrotoxic patients, and we have therefore used the mid-point radioactivity in our calculations.

Extrathyroidal neck radioactivity. The thyroid uptake measurements used for the calculation of the thyroid clearance include a fraction due to extrathyroidal neck radioactivity. This fraction is of negligible importance when the radio-iodine uptake is normal or

elevated, especially since the calculation of the clearance is based on the difference between two uptake values, and the difference in net thyroid uptake* between one hour and two-and-a-half hours is much greater than the fall in extrathyroidal neck radioactivity during the same period. When, however, the thyroid clearance and uptake are diminished (as in hypothyroidism, or after iodide administration), the decrease of extrathyroidal neck radioactivity may be equal to, or even greater than, the rise in net thyroid uptake, in which case the difference between the thyroid uptake (net thyroid uptake + extrathyroidal neck radioactivity) measured at one hour and at two-and-a-half hours may be a negative one. Calculation based on these figures would indicate a 'negative' thyroid clearance (Hanbury et al. 1954), which is, of course, unacceptable.

This difficulty can be circumvented in the following way (Veall and Vetter, 1958). The tracer dose is given intravenously and the thyroid uptake measured two or three minutes thereafter (time 0). The value recorded is assumed to be entirely extrathyroidal neck radioactivity. A plasma sample is obtained simultaneously with

* Net thyroid uptake is the thyroid uptake as described above minus the extrathyroidal neck radioactivity included behind the lead block.

the uptake measurement, and the radioactivity estimated. The thyroid uptake is again measured at time (t), and another plasma sample is obtained. The extrathyroidal neck radioactivity at t time equals:

$$\frac{\text{Uptake (0 time) x plasma radioactivity (t time)}}{\text{Plasma radioactivity (0 time)}}.$$

The difference between the observed thyroid uptake and the extrathyroidal neck radioactivity at t time is the net thyroid uptake at t time, which can be used for calculation of the thyroid clearance. More simply, the extrathyroidal neck radioactivity at any time can be roughly calculated as equal to a half of the radioactivity of the thigh at the same time (Myant et al. 1949).

In our laboratory we use the following calculation of the extrathyroidal neck radioactivity in cases with a low thyroid uptake. After intravenous injection of the tracer dose the urine is collected between 0 and t time (2½ hours) and the radioactivity is measured. The extrathyroidal neck radioactivity (ENR) at t time is calculated as:

$$\text{E N R} = \frac{\text{Th.Upt. at 0 time x (100 - \% urinary radioiodine excretion)}}{100}$$

Our formula would be entirely correct if the urinary excretion represented all the radioiodine lost from the body iodide space, but the

error is negligible when the net thyroid uptake is less than 5% and we have used it only in such cases. Our formula is essentially a simplification of the formula of Berson et al. (1952) which can be used when greater accuracy is desired and which is applicable at any value of thyroid uptake. Using this formula the fall in extra-thyroidal neck radioactivity between 0 and t time is given by:

$$\frac{\text{Net uptake at t time + urinary iodine excretion (0 to t time)}}{\text{dose}} \times \text{Th. Upt. at 0 time.}$$

Since bromide is distributed in the body fluids in the same way as iodide, but is not trapped by the thyroid, it may be used as a measure of the extrathyroidal neck radioactivity: a method employing a mixture of Br^{82} and I^{131} has been used for this purpose (Dutreix and Buraggi 1962).

The plasma inorganic iodine (PII) was estimated simultaneously with the thyroid clearance by collecting the urine passed during the same period and measuring its radioactivity and chemical iodine content. The urine was not collected with a catheter, and this may have led to some error, but the fact that the tracer dose was given one hour before the urinary collection minimizes the effect of a small residue of urine remaining in the bladder. All patients received 100 ml. of water at the start of the period of urine

collection. The formula for the calculation of the PII is:

PII (μg/100 ml) =

$$\frac{\text{Chemical I urine } (\mu g/100 \text{ ml}) \times I^{132} \text{ plasma } (\% \text{ dose/ml})}{I^{132} \text{ urine } (\% \text{ dose/ml})}$$

The absolute iodine uptake (AIU) was calculated by the formula:

AIU (μg/hr) = PII (μg/100 ml) x thyroid clearance (ml/min) x 0.6.

The factor 0.6 is the result of $\frac{60}{100}$, 60 converting the ml per minute to ml per hour, and 100 converting μg per 100 ml to μg per ml.

The renal clearance of iodide was estimated at the same time as the thyroid clearance and the PII, using the same urine samples:

Renal clearance (ml/min) =

$$\frac{\text{Urine vol. (ml)} \times I^{132} \text{ urine } (\% \text{ dose/ml})}{I^{132} \text{ plasma } (\% \text{ dose/ml}) \times \text{time interval of urinary collection in minutes}}$$

Measurements of the parameters described above were routinely carried out while the patients were in the fasting state.

CHEMICAL MICRODETERMINATION OF IODINE IN BIOLOGICAL SAMPLES.

The procedure described is based on the methods of Zak and Boyle (1952) and O'Neal and Simms (1953), as modified by Farrell and Richmond (1961). Chloric acid digestion destroys organic material and oxidises iodine to iodate. Iodate in the digestion residue is reduced by arsenious acid and determined as iodide by its catalytic effect on the reduction of ceric sulphate by arsenious acid.

General procedure for all samples.

Materials and Solutions: Pyrex centrifuge tubes of 50 ml capacity (4" x 1"). A sand bath with accurate temperature control at 160°; alternatively an aluminium block heater containing holes drilled to fit the digestion tubes may be used. A photoelectric colorimeter with matching glass cuvettes. All water used is purified by distillation from a glass still followed by treatment in two columns of Amerlite MB - 3 ion exchange resin. Glassware is steeped in chromic acid and thoroughly rinsed with water before use. All solutions are prepared with the purest grade analytic chemicals.

Chloric acid with chromate: 500 g $KClO_3$ and 200 mg Na_2CrO_4 dissolved in 1,000 ml H_2O. Add 370 ml 72% perchloric acid to hot solution. Cool, stand for 8 hours, filter acid through Whatman 541 paper and store below 4°C.

Arsenious acid with sodium chloride: stock solution 12 g As_2O_3 + 8 g NaOH dissolved on 400 ml H_2O. Neutralise to phenol-

phthalein with 10% H_2SO_4, add 100 ml 50% H_2SO_4 + 30 g NaCl, cool, dilute to 1,000 ml with H_2O. Store below 4°C. Working solution prepared fresh for each analysis by 1 in 10 dilution of stock with H_2O.

Ceric sulphate: 50 g $Ce(SO_4)_2 \cdot H_2O$ in 1,000 ml 10% H_2SO_4.

Brucine sulphate: 5 g brucine sulphate in 1,000 ml 5% H_2SO_4.

Potassium iodate: stock solution 269.6 mg desiccated KIO_3 per 1,000 ml.

Dilution of 1 in 2,000 gives reference solution containing the equivalent of 8 µg I per 100 ml. Standards of 4, 8, 12 and 16 µg I per 100 ml are run with each batch of sera.

Technique: All samples are analysed in duplicate. To 0.2 - 1.0 g of sample in a centrifuge tube add 5 ml of chloric acid. The tube is then placed in the digestion apparatus and heated for 1½ - 2 hours at 160°C. Standards and a 0.5 ml water blank are treated in the same way as samples. At the completion of digestion approximately 0.5 ml of an amber-coloured solution remains in the tubes. On cooling the liquid becomes colourless and deposits red crystals of chromium trioxide. Care should be taken to avoid over-digestion and the consequent loss of iodine; this is indicated by the appearance of a green colour, due to Cr^{+++} ion, in the residue.

Add 15 ml of arsenious acid to the cooled tubes and mix thoroughly with the digestion residue by shaking. The tubes are then placed in a water bath at 37°C and the contents allowed to stabilize for

10-15 min. 1 ml of ceric sulphate is added to the tubes at 30 sec intervals. Each tube is carefully shaken to mix the contents. After a set time (20-40 min) 1 ml of brucine sulphate is added to terminate the catalysis. The tubes are removed from the water bath and allowed to attain room temperature.

Colorimeter readings are normally taken 10 min after brucine addition using a 420 mμ filter. A curve of iodine content is plotted against extinction both for the standards and blank. A fresh curve is constructed for each batch of samples analysed. The results of unknowns are read off from the calibration curve.

Serum protein-bound iodine (PBI).

Analyses are carried out on 0.5 ml aliquots. Treatment of serum in columns of Amberlite anion exchange resin provides a quick and efficient separation of inorganic iodide from PBI.

Resin Preparation: Amberlite IRA 400 (Cl) anion exchange resin (200 gm) is washed thoroughly with 10-15 litres H_2O under suction in a 21 cm Buchner funnel. It is necessary to dry the resin sufficiently to prevent hydration of the serum. Suction is left on for 1 hour for partial drying. The resin in 50 g aliquots is spread out on filter paper, dried at room temperature for 25-30 minutes and stored in air-tight polythene bottles.

Resin Treatment of Serum: Glass columns 3 mm x 120 mm plugged at the tips with cotton wool, are filled with resin to a depth of 10 cm and

2.5 ml serum is added from a Pasteur pipette without delay. The rate of flow of serum through the column is approximately 1 ml per min. One treatment is sufficient for each serum aliquot, the resin being discarded after use.

The recovery of added iodide in serum is by this method 99%.

Urinary iodine.

Urine aliquots of 0.2 - 0.1 ml are added directly to the digestion tubes. The mean recovery of added iodide is 98.5% with a S.D. of 2.9%. The effect of sample dilution on the results of urinary iodine estimations was studied by measuring the iodine concentrations in aliquots of 0.25, 0.5 and 0.75 ml from the same urine sample (Alexander et al. 1962). A linear relation was found; the mean residual error was 0.3 µg/100 ml, and the coefficient of variation 6.6%.

All the iodine present in the urine was assumed to be entirely inorganic for the purpose of PII estimations. However a screening procedure was used to detect organic iodine compounds when present in significant amounts (Richmond 1962). This was done by passing a 2.5 ml sample through the resin column prepared as described for serum PBI analyses. Recovery experiments using MIT, DIT, T_3 and T_4, showed that in addition to iodide a small proportion of these compounds was also retained in the column, but this was usually less than 10%. Thus although the method does not give accurate quantitative results it can be used successfully as a screening

procedure to detect urine samples with an increased content of organic iodine compounds. Such urine samples should not be used for estimation of the PII.

A more elegant application of ion-exchange resins (Galton and Pitt-Rivers 1959a) permits quantitative separation of iodide, iodotyrosines and iodothyronines in body fluids.

PRECISION OF THE METHODS

The practicability of the quantitative measurements of iodine metabolism described by Stanley (1949) has been confirmed by several other workers (Perry and Hughes, 1952; Burrows et al., 1953; Shipley and Chudzik, 1957; Reilly et al. 1958; Fauvert et al. 1958; Feinberg et al. 1959). However, no study of the precision which can be expected had been reported. We therefore investigated the accuracy and reproducibility of the various parameters by performing repeated estimations on the same individual, allowing the shortest practicable time interval between successive estimates.

The thyroid clearance was measured in duplicate in 10 patients in the following way. The thyroid uptake was measured at one, one-and-a-half, two-and-a-half, and three hours after the tracer dose. The thyroid clearance was estimated between one and two-and-a-half hours, and between one-and-a-half and three hours, the two plasma samples being drawn at the mid-point of each of these two time periods. The results varied between 4.8 and 78.7 ml per minute (Table 1.1). The arithmetic difference between duplicates ranged from 0.7 ml to 12.3 ml; mean 4.3 ml. When the data were pooled, the standard error of a single measurement (or mean residual error) was 3.5 ml per minute. This standard error gives an estimate of the reproducibility of the thyroid clearance, but is valid only for the range of values tested, and

Table 1.1

Thyroid radioiodine clearance in ml/min: duplicate measurements in the same individual

Patient	1st measurement (th.cl. measured 60 to 150 min)	2nd measurement (th.cl. measured 90 to 180 min)
1	32.5	20.2
2	51.5	50.8
3	21.2	22.5
4	77.0	78.7
5	4.8	8.2
6	48.7	44.4
7	24.9	14.9
8	17.0	14.0
9	13.7	12.0
10	11.2	20.0

In every case plasma radioactivity was measured in each of two plasma samples, obtained at the mid-point of each of the two time periods.

probably would be greater in the higher values of clearance found in thyrotoxicosis.

The plasma inorganic iodine (PII) was estimated repeatedly by the use of collections of urine passed between one and three, three and five, five and seven, seven and nine, nine and 11, and 11 and 13 hours after a tracer dose of I^{131}. In this way six separate estimates were obtained within 12 hours in each of three patients. The mean and standard deviation for the three patients were respectively 0.16 $\pm$ 0.02, 0.22 $\pm$ 0.02, and 0.11 $\pm$ 0.02 µg per 100 ml (Figs. 1.3 and 1.4). It must be pointed out that these fluctuations in the PII are due both to technical errors in the measurement and to biological variations, since the patients took normal meals (not, however, containing fish or iodized salt) during the period of the test. The standard error of a single measurement was 0.02 µg per 100 ml.

A comparison between simultaneous direct and indirect estimations of the PII was made in 17 cases after previous iodine administration (Fig. 1.5). In this way the PII was large enough to be estimated directly as the difference between the total serum iodine and the protein-bound iodine. There is a very close linear correlation ($r = 0.95$). The direct estimation gave systematically slightly smaller values, the regression equation being $y = 0.02 + 1.3x$ where x = direct result and y = indirect result.

The renal clearance was estimated six times within 12 hours

Figures 1.3 and 1.4

Reproducibility of measurements

Repeated measurements of renal iodide clearance, plasma inorganic iodine, and urinary iodine excretion during a 12-hour period, in two patients.

G.L.

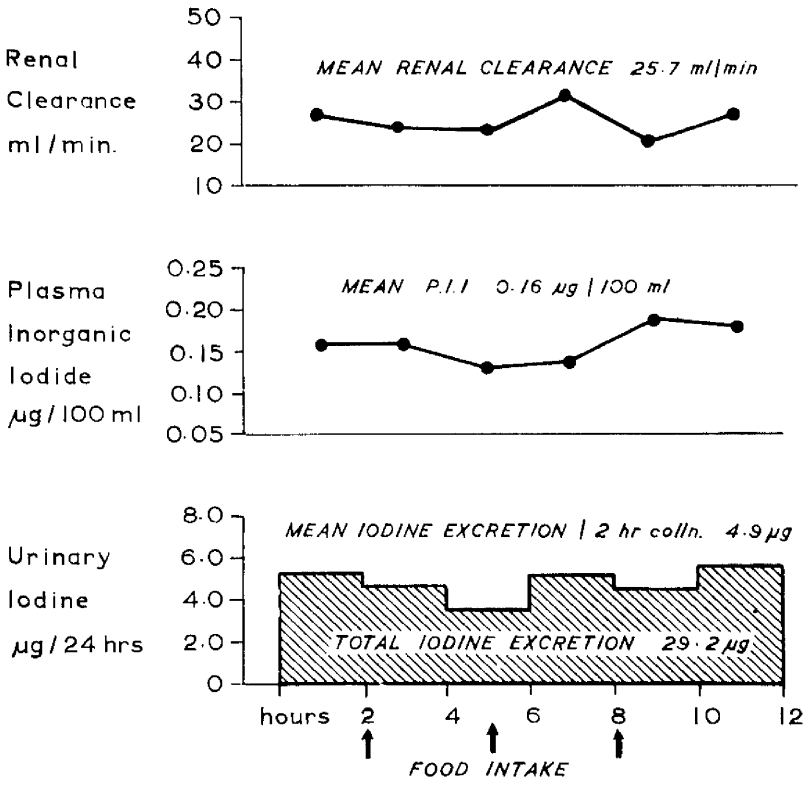
Renal
Clearance
ml/min.
50
40
30
20
10
MEAN RENAL CLEARANCE 25.7 ml/min
Plasma
Inorganic
Iodide
µg/100 ml
0.25
0.20
0.15
0.10
0.05
MEAN P.I.I 0.16 µg/100 ml
Urinary
Iodine
µg/24 hrs
8.0
6.0
4.0
2.0
0
MEAN IODINE EXCRETION / 2 hr colln. 4.9 µg
TOTAL IODINE EXCRETION 29.2 µg
hours
2
4
6
8
10
12
FOOD INTAKE

Figure 1.3

V.P.

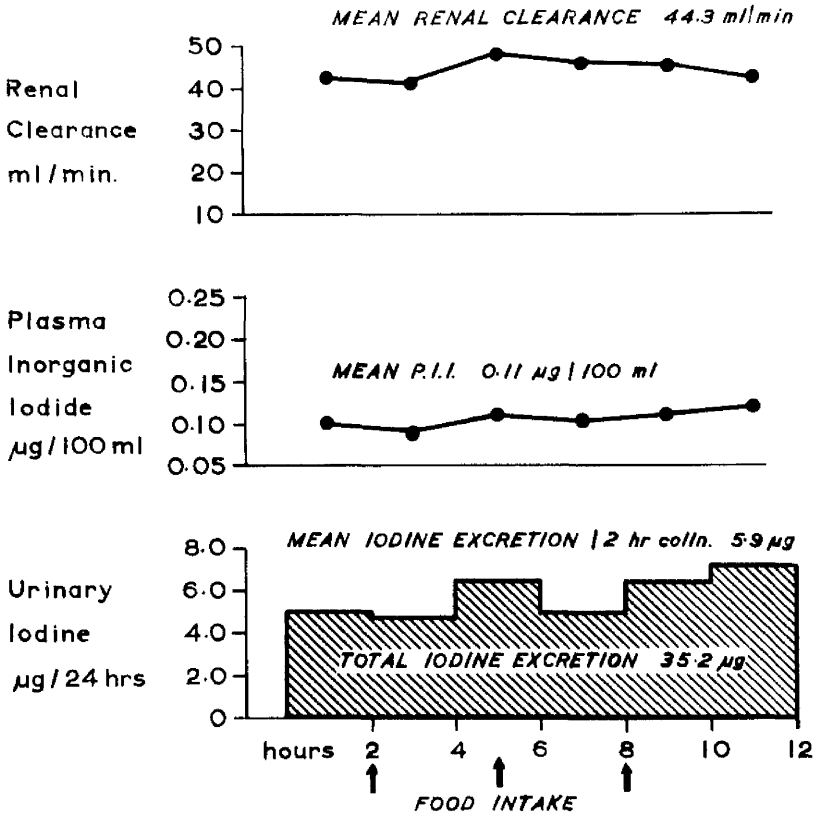
MEAN RENAL CLEARANCE 44.3 ml/min
Renal Clearance ml/min.
50
40
30
20
10
Plasma Inorganic Iodide µg/100 ml
0.25
0.20
0.15
0.10
0.05
MEAN P.I.I. 0.11 µg/100 ml
Urinary Iodine µg/24 hrs
8.0
6.0
4.0
2.0
0
MEAN IODINE EXCRETION 12 hr colln. 5.9 µg
TOTAL IODINE EXCRETION 35.2 µg
hours 2 4 6 8 10 12
FOOD INTAKE

Figure 1.4

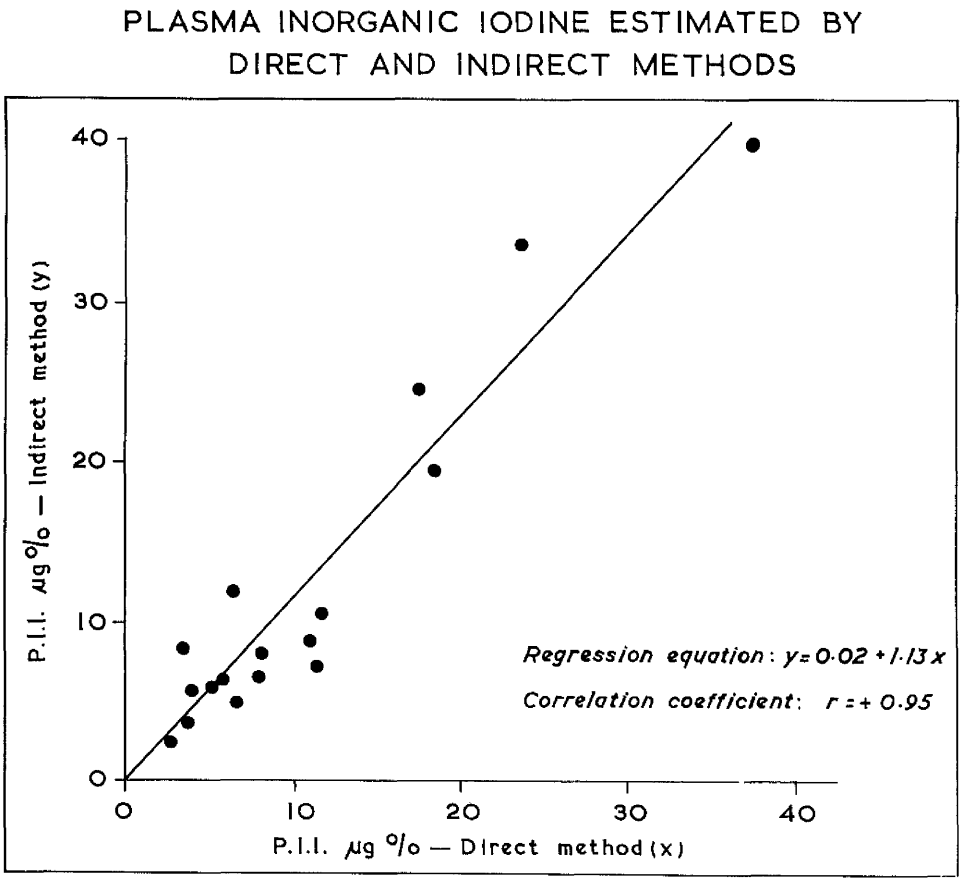

Figure 1.5

Plasma inorganic iodine estimated by direct and indirect methods

There is a good correlation between estimates made on the same serum sample : $r = +0.95$, $p < 0.001$.

in each of the same three patients as were used for studying the PII. The mean value and the standard deviation for each patient were respectively 25.7 ± 3.5, 18.0 ± 2.1, and 44.3 ± 2.4 ml per minute. The standard error of a single measurement was 2.9 ml per minute.

The influence of fish intake on the PII was examined by repeating the estimations on two successive mornings in five patients*, and giving 150 g of haddock (corresponding, according to our own measurements, to approximately 1,200 µg of iodine) with the evening meal immediately preceding the second test (Table 1.2). The PII rose from a mean control value of 0.16 µg per 100 ml to 0.23 µg per 100 ml on the day after the fish meal. The rise varied from 0.01 to 0.13, with a mean of 0.07 µg per 100 ml.

* In this study, and in others of a physiological nature, the patients were volunteers, and had agreed to take part after the nature and purpose of the investigation had been explained to them.

Table 1.2

Influence of fish intake on the plasma inorganic iodine (µg/100 ml)

Patient	1st measurement (0 hours)	(+ 10 hours)	2nd measurement (+ 24 hours)
1	0.16	Haddock 150 g	0.22
2	0.18		0.23
3	0.14		0.35
4	0.14		0.22
5	0.18		0.31

150 g haddock is approximately equal to 1200 µg iodine.

Time is measured from the start of the first PII estimation.

OTHER MEASUREMENTS

In certain cases estimates were made of the dietary intake of iodine (p140), the 24 hour urinary excretion of iodine, and the intrathyroidal exchangeable iodine (Nodine et al 1957). Standard radioiodine tests using I^{131}, with measurement of the 4 and 48 hr thyroid radioiodine uptake and 48 hr PBI^{131} (Wayne 1954) were also carried out in a proportion of patients, for comparison with the I^{132} tests.

Intrathyroidal exchangeable iodine

The patient was given 75 µc I^{131} by mouth. After allowing 9 days for equilibration of the dose the thyroid radioiodine uptake, PBI and PBI^{131} were measured. Immediately thereafter an intramuscular injection of 10 units of TSH was given, and 24 hours later measurements of the PBI and PBI^{131} were repeated. The rise in PBI and PBI^{131} observed enabled the specific activity of the newly released hormone to be calculated. Using this value, and the thyroid radioiodine uptake before the TSH injection, the intrathyroidal exchangeable iodine (IEI) was calculated:

$$IEI = \frac{\text{rise in PBI} \times \text{Th. Upt. } I^{131}}{\text{rise in PBI}^{131}}$$

In 9 patients, clinically euthyroid and without goitres, values of 0.9 to 15.7 mg were obtained (p252). Nodinçet al (1957) found values of 1.3 to 18.1 mg in euthyroid subjects. The estimate of the intrathyroidal iodine obtained in this way refers only to the quantities of iodine with which the tracer dose has equilibrated in nine days. If one could wait for a sufficiently long time the estimate would closely approximate to the total quantity of iodine present in the thyroid.

Chapter 2 - IODINE METABOLISM IN HEALTH

Chapter 2 - IODINE METABOLISM IN HEALTH

AIMS OF THE STUDY

The object of the investigation was to make a comprehensive study of the normal behaviour and variations of the plasma inorganic iodine concentration (PII), the thyroid radioiodine clearance, the absolute uptake of iodine by the thyroid gland (AIU), the level of circulating thyroid hormone (PBI), and the renal excretion of iodine.

The various groups studied included 98 patients, all with clinically normal thyroid function. This haspermitted definition of the normal ranges, essential for the proper interpretation of the alterations observed in patients with thyroid disease (p156). Detailed analysis of the relations between the PII, AIU and PBI in a normal group has been carried out in an attempt to answer the questions:

(1) In individuals with a high-normal PII concentration, is more iodine taken up (AIU) by the thyroid gland than in the average case?

(2) If more iodine is taken up by the thyroid gland than average (high-normal AIU), is more thyroid hormone (PBI) produced?

These same questions have been examined from another point of view. Serial studies of stable iodine metabolism were made on 22 persons with normal thyroid function who received iodine supplements for three months. The aim was to find the effect of small iodine supplements (of the order found in a meal containing fish or in iodised salt) on iodine uptake (AIU) and hormone production (PBI)

by the thyroid gland. Lastly, iodine metabolism in Iceland has been studied. In that country the PII is on average 2½ times higher than in Glasgow, due to the high level of consumption of fish and fish products. The influence of the life-long high-normal dietary intake of iodine on iodine uptake (AIU) and hormone production (PBI) has been examined.

A knowledge of the normal plasma concentration and renal excretion of iodide has made possible a new assessment of the iodine requirements in man.

Application of the specific activity method to human thermal sweat has permitted precise measurement of the quantity and rate of iodide loss in the sweat.

PATIENTS STUDIED

Ninety-eight patients without goitre or other clinical evidence of thyroid disease, were studied. No patients with renal failure were included since this may result in abnormal renal excretion of iodine (p122). The patients were attending the wards or out-patient clinics of the Department of Medicine at the Western Infirmary. About one half were receiving treatment as in-patients, and one half as out-patients. All were taking a normal diet, and acutely ill patients on light or otherwise abnormal diets were not included in the study. Care was taken that none of the patients received phenindione, butazolidine, salicylate, or other drugs known to influence tests of thyroid function.

The 98 patients were divided into four groups:

Group 1: Measurements of the plasma inorganic iodine, thyroid clearance of radioiodine, absolute iodine uptake, PBI and renal iodide clearance were made on 48 patients - 24 males and 24 females. The methods have been described in detail (p 12). The results are presented in Table 2.1 which includes details of sex, age, and clinical diagnosis. These results are analysed and discussed in the light of previous studies in the subsequent sections of this Chapter.

Group 2: Serial studies of the same parameters before and during the administration of iodide supplements were made in 22 out-patients, over a period of twelve weeks (Table 2.6, and see p 77).

Group 3: Seventeen patients - all females - attending the State Hospital, Reykjavik, were studied in exactly the same way as group 1 (Tables 2.7-2.9, and see p. 88).

Group 4: Studies of the concentration of iodine in thermal sweat, the sweat iodide clearance, and the ratio of sweat iodide/plasma iodide content were made on 11 ward patients (Tables 2.14-2.17, and see p 124).

No.	Name	yr.	upt.%	ml/min	µg%	µg/hr	ml/min	µg%	µg	Diagnosis
1	A.M.	40	29.2	31.7	.14	1.9		3.1		Aortic stenosis
2	D.C.	33	23.4	18.6	.14	1.9	25.1	5.6		Aortic stenosis
3	J.P.	53	19.7	13.5	.25	2.0	53.8	5.6	75	Hypoparathyroidism
4	J.R.	27	23.7	38.0	.34	8.2	31.3	6.1	99	Hypercalcaemia
5	D.D.	67	17.6	13.8	.35	2.9	29.1	4.5	61	Diabetes mellitus
6	S.C.	54	19.4	15.4	.04	0.3	37.3	3.4		Myocardial infarction
7	E.M.	34		11.6	.39	2.7	61.8	5.8	171	Obesity
8	A.S.	60	19.2	24.6	.12	1.8	21.0	4.9		Myocardial infarction
9	J.M.	48	19.3	22.1	.14	1.9	17.9	5.5		Myocardial infarction
10	W.F.	61	33.5	36.0	.04	0.8	30.8	6.4		Myocardial infarction
11	A.C.	48	14.2	31.8	.27	5.2	39.7	5.3		Ischaemic heart disease
12	D.M.	47	19.4	13.6	.09	0.7	44.6	5.4		Myocardial infarction
13	C.D.	25	9.5	44.4	.11	2.9	32.9	3.3	40	-
14	D.C.	25	14.7	14.9	.25	2.2	34.0	5.0	151	Hodgkins disease
15	M.C.	62	20.5	26.8	.16	2.5	27.7	6.5	46	Bronchiectasis
16	T.F.	38	21.4	24.0	.18	2.6	40.6	6.8	97	Syphilitic aortitis
17	J.F.	18	22.4	23.0	.14	2.0	27.0	5.6	51	Delayed puberty
18	J.O.	51	10.9	17.7	.14	1.5	32.8	5.9	33	Myocardial infarction
19	M.S.	33	11.4	9.7	.32	1.9	46.8	6.9		Mitral stenosis
20	S.C.	43	11.0	38.5	.18	4.3	31.2	4.1	59	Angina pectoris
21	W.F.	54	20.8	30.5	.36	6.7	42.8	6.4		Constipation (functional)
22	J.H.	22	24.0	57.8	.08	2.2	42.1	5.7		-
23	M.A.	38	23.5	28.7	.26	4.5	49.6	6.4		Myocardial infarction
24	J.H.	54	8.9	2.9	.08	0.1	48.7	5.2		Myocardial ischaemia

(For abbreviations used see p vi)

No.	Name	Age yr.	2½ hr. upt.%	Th.Cl. ml./min.	Iodine Studies PII µg%	Iodine Studies AIU µg/hr.	R.Cl. ml./min.	PBI µg%	24 hr. Iur µg	Diagnosis
1	J.S.	29	43.0	29.3	.15	2.5	-	4.2		Mitral stenosis
2	G.P.	16	16.2	31.5	.10	1.9	32.7	3.3		Iron-deficiency anaemia
3	J.M.	48	23.7	8.6	.20	1.0	36.3	5.2		Epilepsy
4	A.C.	71	36.3	38.6	.14	3.1	38.5	5.3		Pagets disease
5	R.F.	35	39.7	27.2	.12	1.9	41.3	5.5		Ventricular septal defect
6	M.S.	61	28.8	27.6	.14	2.3	20.4	5.2	44	Cerebral arteriosclerosis
7	S.M.	45	24.5	14.1	.26	2.2	32.2	5.2		Enlarged L. pupil
8	S.L.	42	24.1	26.7	.08	1.2	25.4			Pruritus (functional)
9	M.M.	55	28.2	10.7	.23	1.5	18.5	5.7		Hypercholesterolaemia
10	I.N.	39	15.3	23.1	.18	2.5	24.6	4.2		Iron-deficiency anaemia
11	G.L.	58	19.8	21.3	.16	2.1	27.3	5.6		Myasthenia gravis
12	K.S.	36	19.3	20.8	.27	3.4	18.3	3.9		Rheumatic heart disease
13	J.B.	64	11.9	5.4	.16	0.5	19.3	5.2	87	Peptic ulcer
14	A.H.	63	16.0	15.7	.33	3.0	11.7	5.8		Myocardial infarction
15	C.W.	79	9.7	6.6	.57	2.3	13.4	3.7	104	Haematemesis
16	C.G.	31	24.3	38.2	.04	0.9		4.1		Obesity
17	D.B.	12	22.6	40.9	.06	1.4	30.2	4.4		Obesity
18	M.H.	44	13.0	7.9	.14	0.6	27.5	5.2		Angina
19	J.T.	67	17.5	16.7	.16	1.6	16.6	4.3		Rheumatoid arthritis
20	M.M.	20	11.5	19.7	.19	2.2	15.7	8.2		Amenorrhoea
21	S.S.	56	12.0	5.7	.19	0.6	19.0	3.6		Tiredness (functional)
22	A.S.	46	22.2	37.6	.07	1.6	37.4	5.1		Essential hypertension
23	B.M.	48	13.6	12.7	.14	1.1	27.1	6.7		Coronary artery disease
24	M.H.	54	14.2	11.1	.13	0.9	33.3	6.9		Anxiety state

THE PLASMA INORGANIC IODINE.

Many aspects of iodine metabolism and of thyroid function in health and disease can only be fully understood if the concentration of inorganic iodine in the plasma (PII) is known. Unfortunately the quantity is usually very small and cannot be measured directly by the methods of assay at present available, although this has been attempted (Klein 1954; Numberger et al. 1961). If, however, the concentration is unusually high it can be directly determined either as the iodine concentration of the supernatant fluid after protein precipitation, or by deducting the protein-bound iodine from the total plasma iodine.

Activation analysis of iodine (Bowen 1959; Wagner et al. 1961; Kollershohn et al. 1961) can now be used for determination of the protein-bound iodine, and it is possible that further development may permit direct estimation of the PII. However, this is not possible at present, partly because chloride is simultaneously activated and interferes with the analysis. On the other hand, the method has been successfully used for the measurement of urinary iodine (Wagner et al. 1961).

When the normal PII concentration is too low to be measured directly, the isotope dilution principle can be used (p 17). The specific activity of the urinary iodide after a tracer dose of radioiodine is identical with that of the plasma iodide.

Thus $\frac{I^{132}\ \text{plasma}}{\text{PII}} = \frac{I^{132}\ \text{urine}}{\text{urinary iodide}}$

and from this equation the PII can be calculated as

$$\text{PII} = \frac{\text{urinary iodide} \times I^{132}\ \text{plasma}}{I^{132}\ \text{urine}}$$

This indirect method of measuring the PII was first described by Stanley (1949) and since then has been used by several other workers (Perry and Hughes 1952; Burrows et al. 1953; Shipley and Chudzik 1957; Reilly et al. 1958; Feinberg et al. 1959; Wagner et al. 1961) including our own group (Koutras et al. 1960a, and b, 1961; Alexander et al. 1961, 1962; Buchanan et al. 1961). We have shown that at high PII values, where the PII can be measured both directly and by the specific activity method, the results of the two methods show good agreement (Fig. 1.5).

Since the distribution of PII values from a population does not form a normal distribution curve, the standard deviation cannot be used to define the normal range. We have therefore adopted the suggestion of Wootton et al. (1951) and have recorded in Table 2.2 the standard error of the mean together with the observed range. More useful figures for the normal PII range give the best separation between the normal cases and patients with iodine-deficiency goitre on one side, and normal cases and those receiving pharmacological doses of exogenous iodine on the other (Alexander

et al 1962). On this basis our normal range is 0.03 to 0.60 μg/100 ml.

Table 2.2 presents the normal PII values (shown individually in Table 2.1) grouped according to age and sex. The mean PII for each sex is similar. In the females, however, a positive correlation was found with increasing age ($r = 0.510$) and this was statistically significant ($p < 0.02$). Such a correlation was not apparent in males. The lower PII values found in younger females may be due to loss of iodine from the body in menstruation, pregnancy and lactation and may afford a partial explanation of the special predilection of this group to develop iodine-deficiency goitre. Part of the iodine loss during pregnancy is mediated by increased renal iodide clearance (p207).

Four of the 48 normal cases shown in Table 2.1 had PII values below the lower limit of the normal range, thus three had 0.04 and the fourth 0.06 μg/100 ml. A year later one of the first three cases was seen again, this time with a diffuse goitre of about 75 gm. It appears therefore that although low PII values may be found occasionally in persons without thyroid enlargement some of them may later develop an iodine-deficiency goitre.

Our normal PII range is not very different from the values previously reported (Table 2.3) except those of Stanley (1949), which have been thought on theoretical grounds to be unduly high (Riggs 1952), and of Shipley and Chudzik (1957) who also found normal values around

Table 2.2

Normal plasma inorganic iodine values (PII) in µg/100 ml grouped according to age and sex.

Age Yr	Males (24 cases) Mean ± S.E.	Observed range	Females (24 cases) Mean ± S.E.	Observed range	Total (48 cases) Mean ± S.E.	Observed range
0-19	0.14		0.08	(0.06 - 0.10)	0.10±0.023	(0.06 - 0.14)
20-39	0.23±0.037	(0.08 - 0.34)	0.16±0.030	(0.04 - 0.27)	0.20±0.020	(0.04 - 0.34)
40-59	0.17±0.030	(0.04 - 0.36)	0.16±0.019	(0.07 - 0.26)	0.16±0.017	(0.04 - 0.36)
60-	0.17	(0.04 - 0.35)	0.25±0.071	(0.14 - 0.57)	0.22±0.047	(0.04 - 0.57)
Total	0.19±0.021	(0.04 - 0.36)	0.18±0.022	(0.04 - 0.57)	0.18±0.015	(0.04 - 0.57)

The individual values are shown in Table 2.1.

Table 2.3

Normal values of the plasma inorganic iodine (PII) in µg/100 ml.

	Mean	Range	S.D.	S.E.
Feinberg et al. 1959	0.28	0.10 - 0.43		
Perry and Hughes 1952	0.17			0.005
Reilly et al. 1958	0.55			0.06
Wagner et al. 1961	0.50		0.30	
Zing and Perry 1953	0.23			0.06
Bockers 1962	0.26		0.09	0.028
Author's study	0.18	0.04 - 0.57	0.10	0.015

1.0 µg/100 ml: neither give precise ranges. The somewhat higher values recorded in the U.S.A. are probably due to the widespread use of iodised salt in North America. The extremely high PII values obtained by direct chemical estimation (Numberger et al 1961) are out of keeping with all other published data. Their method has not been satisfactorily validated, and it seems likely that direct chemical measurement of the normal PII is impossible without further refinement of the techniques involved. When the PII is high following iodide administration, reaching levels of the same order as the PBI, direct measurements may properly be used.

The wide limits of the normal PII suggest that there is no homeostatic mechanism. In the case of certain other ions, for instance sodium and chloride, the kidneys adjust their clearance with respect to the dietary intake, and so keep the plasma concentration relatively constant. The renal clearance exerts no such regulatory effect in the case of iodide (see page 151 and page 152).

Theoretically one would expect the PII level to be directly proportional to dietary iodine intake minus faecal excretion, and inversely related to the value of the renal clearance.

The first of these expectations is confirmed by finding the PII to be abnormally low when iodine intakeis low and abnormally high after iodine administration, the second by finding high PII levels in patients with renal disease and decreased renal iodide

clearance rates (Perry and Hughes 1952). However, in our full series of control cases we could not find an overall relation between the PII and the renal clearance ($r = -0.016$). We interpret this as meaning that the effect of variations in renal clearance are overshadowed by the much greater variations in iodine intake. However, if only female cases are considered, a significant inverse relation between the PII and the renal clearance can be shown ($r = -0.563$, $p<0.01$).

Our estimates of the PII have been carried out in the fasting state using urine samples collected over 90 minutes. We have carried out serial estimations on the same day in 3 patients receiving normal meals excluding fish and iodised salt (p 26 and Figs. 1.3, 1.4). The values did not fluctuate more than 0.03 µg/100 ml from the mean value of each case, except for one measurement in one case which was 0.04 µg/100 ml higher than the mean PII value. It is clear, therefore, that the hour to hour variation in PII is relatively small unless the diet contains much iodine. When fish was given, however, a constant elevation of PII was observed the following morning (p 31). If a 24 hour urine collection is used instead of the 90 minute one which we have adopted, the mean daily PII can be calculated (Riggs 1952; Beckers 1962).

It is possible that the PII may also be influenced by factors interfering with either iodine absorption or iodine

excretion. Renal excretion of iodine is discussed on p112; losses in the sweat are usually unimportant (p135). Florsheim and Volcoff (1962) have found that 2,4-dichlorophenoxyacetic acid decreases the PII, without offering any explanation of the mechanism responsible.

THE IODIDE TRAPPING MECHANISM.

The thyroid, and also the salivary, gastric and mammary glands are able to concentrate iodide from the plasma. This step is not easily demonstrated in the normal thyroid gland since the iodide taken up is almost immediately bound in organic form, but after the administration of such drugs such as methylthiouracil a concentration gradient of about 40 to 1 can be demonstrated. The magnitude of this gradient appears to depend both on TSH and on the quantity of stored iodine within the gland (Halmi 1954; Vanderlaan and Caplan 1954). This "trapping mechanism" is not fully understood but it seems that the maintenance of a concentration gradient depends on the active transport of iodide ions across the cellular membrane by an energy-requiring process. Slingerland (1955) studying iodide trapping in sheep thyroid slices found that aerobic conditions were necessary for iodide concentration. Extremes of temperature and pH diminished iodide trapping, as did many compounds reacting with sulphydryl groups. All substances depressing respiration of the slices also depressed iodide concentrating power, but the reverse was not true. Freinkel and Ingbar (1955) also found that iodide concentration required energy which was channelled through high-energy phosphate bonds. The trapping mechanism shows some similarities in all the glands which are able to accumulate iodide. Thus in a goitrous cretin with a congenital inability of the thyroid to trap iodide, the salivary and gastric glands

were similarly affected (Stanbury and Chapman 1960).

Thyroidal and plasma inorganic iodine are exchangeable, but equilibration of a radioiodine tracer dose may take an appreciable time when the ratio of the iodide concentration in the thyroid to that in the serum (T/S ratio) is large, as is usual. This equilibrium was reached more rapidly in rats than in mice (Wollman and Reed 1962).

The "iodide space of the thyroid" is defined as that volume which would contain the free thyroidal iodide at the same concentration as that of the iodide in the plasma. Ingbar (1955) found this space to be 1.0 ± 0.05 litres in controls and 6.1 ± 1.0 litres in thyrotoxic patients. Recent work (Halmi and Pitt Rivers 1962) suggests that the situation may be more complex. These authors have shown in rats that there are two thyroidal iodide pools, the first one in equilibrium with the PII. The second pool, larger than the first, is formed from iodide liberated by deiodination of iodotyrosines: it is not dischargeable by perchlorate, and has a longer turnover time.

Organic binding of iodine can not only be abolished by drugs but may also be defective in disease. When binding is blocked, serial thyroid radioiodine uptake measurements show a rapid initial uptake and a rapid decline due to loss of iodine from the thyroid. In fact in such cases the radioiodine uptake curve parallels plasma radioactivity closely, since iodide trapped by the thyroid is readily exchangeable with that in the plasma. Even in the normal gland some release of iodide from the thyroidal iodide space into the plasma must occur continuously, but this is overshadowed by the much greater

number of iodide ions moving in the opposite direction, that is from the plasma to the thyroid. When drugs which abolish iodide trapping, such as perchlorate and thiocyanate, are given to a patient who has previously received a tracer dose of radioiodine, accumulation in the gland ceases. Moreover, if a patient's thyroid happens to contain a large quantity of iodide not bound in organic form, as may happen for example in one type of dyshormonogenesis, this unbound iodide is released after perchlorate administration.

The thyroid/serum (T/S) iodide ratio is a useful measure of the iodide trapping capacity of the thyroid per unit mass, but this estimate cannot be readily obtained in humans. Work in animals suggests that this ratio may be affected by differences in strain and in diet. Some strains of rats and mice possess thyroid glands more efficient in trapping iodide than others (Silverstein and Lee 1961; Silverstein et al. 1960). A lower T/S ratio is found in rats fed a high fat diet, and also in younger rats as compared with older ones (Silverstein et al. 1962).

THYROID CLEARANCE OF IODIDE.

The accumulation of iodide by the thyroid can be measured and expressed in several ways. It is usual, in clinical practice, to measure the thyroid radioiodine uptake, that is to say the percentage of a tracer dose of radioiodine which is present in the thyroid at a specified time after its administration, usually 2, 4, 6, 24 or 48 hours. This is a simple procedure, useful for the routine diagnosis of thyroid disease (p240). However, for several reasons the radioiodine uptake is not suitable when accurate quantitative information about thyroid function is required. Thus although it measures the quantity of radioiodine present in the thyroid at a specific time, it does not take into consideration the radioiodine already discharged as hormonal iodine, which may be significant after some hours. It is, moreover, influenced by the renal clearance of iodide and, since the thyroid and the kidney compete to clear iodide from the plasma, it bears a complex and logarithmic relation to the true iodide concentrating power of the thyroid.

When quantitative studies of thyroid function are required the radioiodine uptake should be replaced by the thyroid clearance of iodide, that is the volume of plasma completely cleared of its iodide content by the thyroid per unit of time (p13). In the present work the thyroid clearance is expressed in ml/min.

The relation of the thyroidal radioiodine uptake and clearance has been studied by Myant et al. (1949). These workers have calculated that the fraction of the tracer dose taken up by the thyroid (Th. Upt.) at any time t depends on the thyroid clearance (Th. Cl.), the renal iodide clearance (R.Cl.)* and the iodide space of the body (V):

$$\text{Th. Upt.} = \frac{\text{Th. Cl.}}{\text{Th. Cl.} + \text{R. Cl.}} \times 1 - e^{-\frac{\text{Th. Cl.} + \text{R. Cl.}}{V} t}$$

If one waits long enough for all the radioiodine to be taken up by the thyroid or excreted by the kidneys, and assuming that all the radioiodine taken up by the thyroid is retained within the gland, the radioiodine uptake is:

$$\text{Th. Upt.} = \frac{\text{Th. Cl.}}{\text{Th. Cl.} + \text{R. Cl.}}$$

Fig.2.1 shows the theoretical relation between the 2½ hour and 24 hour radioiodine uptake and the thyroid clearance in an individual with a body iodide space of 25 litres. The values of the 2½ hour radioiodine uptake corresponding to values of thyroid clearance above 100 ml/min are shown in Fig. 2.2 for values of renal clearance of

* It is assumed that all the iodide leaving the plasma is either taken up by the thyroid or excreted by the kidneys, and that the iodide trapped by the thyroid is retained in the gland. The small losses of iodine in the sweat etc. are not taken into account.

RELATION BETWEEN THYROID RADIOIODINE UPTAKE AND CLEARANCE

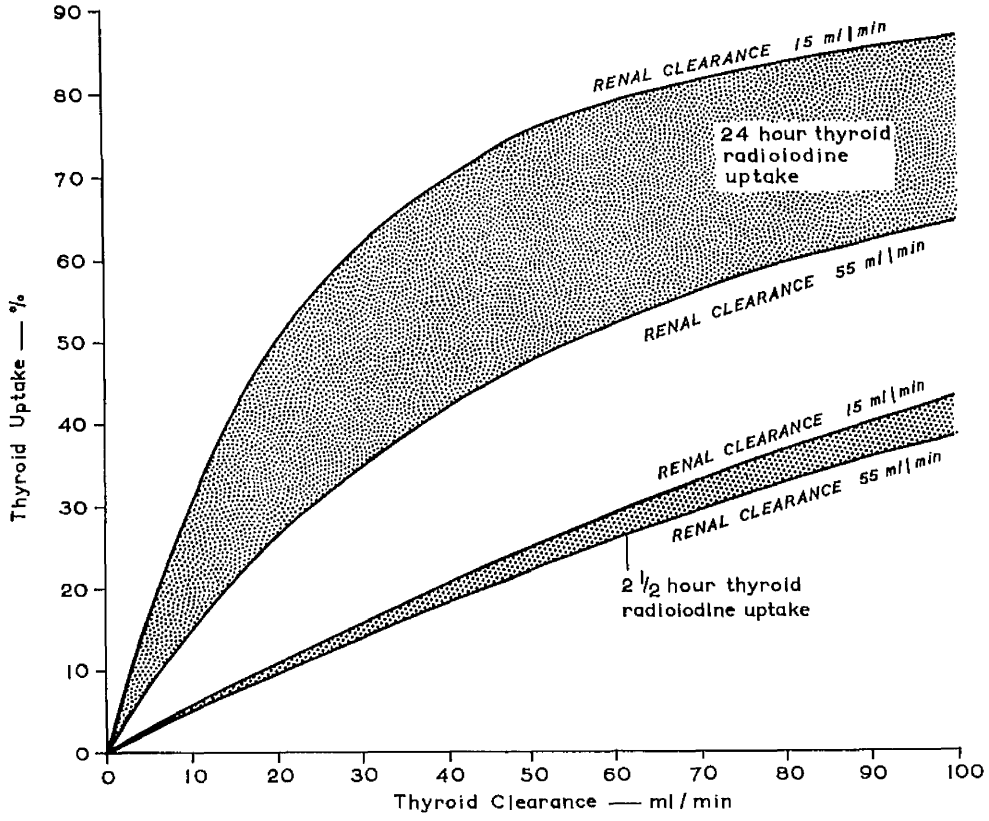

Figure 2.1

Relation between thyroid radioiodine uptake and clearance

The values have been calculated using the formula of Myant et al (1949) assuming a body iodide space of 25 litres. The upper border of the shaded areas corresponds to a renal iodide clearance of 15.0 ml/min, the lower to 55.0 ml/min. The 2½ hour uptake shows a better straight line relation with the thyroid clearance, and the influence of the renal iodide clearance is less marked.

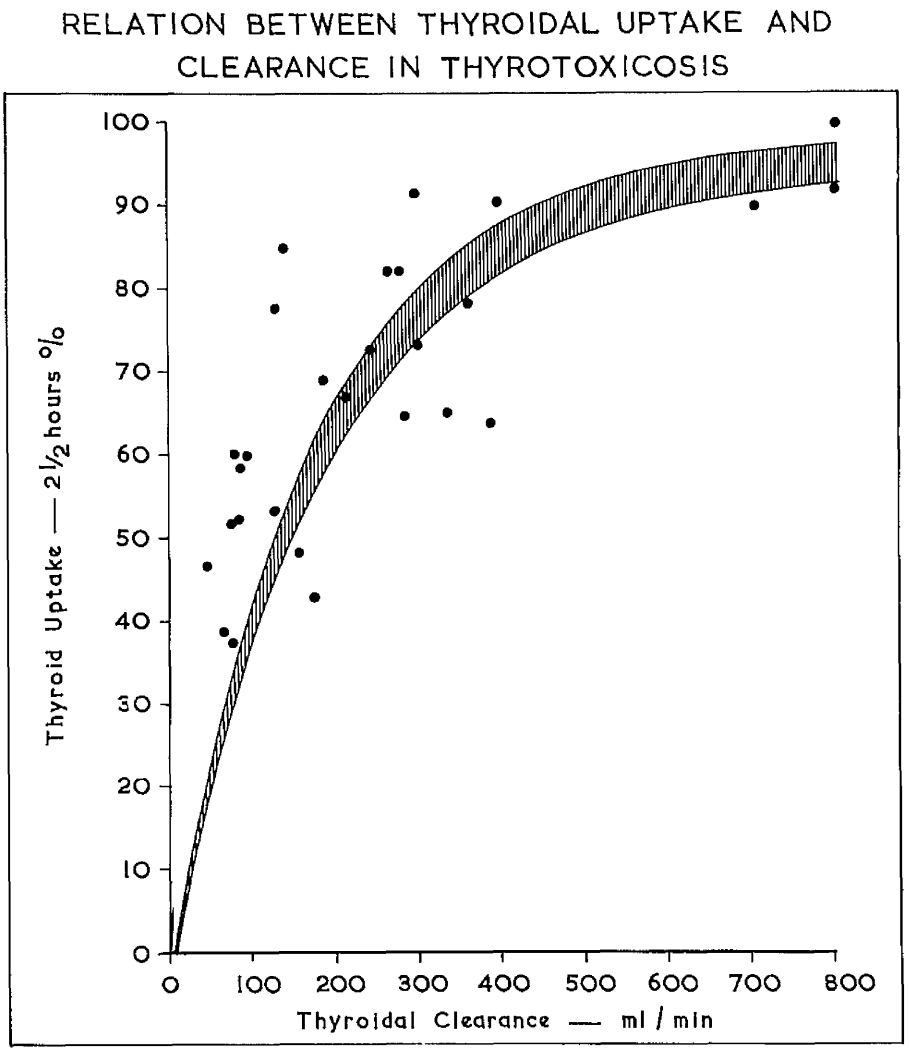

Figure 2.2

Relation between the thyroid radioiodine uptake and clearance in thyrotoxicosis.

The shaded area is constructed as in Figure 3. The values obtained in 28 thyrotoxic patients are shown.

iodide between 15 and 55 ml/min. These figures show that the relation between the Thyroid uptake and the thyroid clearance is not a linear one, although it approaches linearity at low uptake values. Fig.2.1shows that the 24 hour uptake is much more influenced by the renal clearance of iodide than the 2½ hour uptake. At a thyroid clearance of 50 ml/min the 24 hour uptake is 47.5% when the renal clearance is 55 ml/min, but 75.2% when the latter is only 15 ml/min. The difference is considerable, but is not usually taken into consideration when interpreting radioiodine uptake tests. The graphs of Fig.2.1 and2.2 can be used for deriving uptake values when the corresponding thyroid and renal clearance are known. One must take into consideration, however, that the 24-hour uptake may be lower than the theoretical value shown in these figures, because by that time some of the radioiodine taken up has already left the gland as thyroid hormone; this is of importance chiefly in thyrotoxicosis or in other conditions with a rapid intrathyroidal turnover of iodine.

Table2.4presents our measurements of thyroid clearance in 24 normal male and 24 normal female subjects (individual values shown in Table2.1) grouped according to age and sex. Males on the whole had a higher thyroid clearancethan females, but the difference was not statistically significant ($p < 0.2$). In female patients there was an inverse correlation with age ($r = -0.455$, $p < 0.05$), but not in males. The relatively higher thyroid clearance rates of younger

Table 2.4

Normal thyroid clearance of iodide in ml/min grouped according to age and sex.

Age yr	Males (24 cases) mean ± S.E.	Females (24 cases) mean ± S.E.	Total (48 cases) mean ± S.E.
0 - 19	23.0	36.2 (31.5 - 40.9)	31.8 (23.0 - 40.9)
20 -39	27.5 ± 5.44 (9.7 - 57.8)	26.4 ± 2.83 (19.7 - 38.2)	27.1 ± 3.37 (9.7 - 57.8)
40 - 59	21.8 ± 3.49 (2.9 - 38.5)	15.6 ± 3.16 (5.7 - 37.6)	18.7 ± 2.35 (2.9 - 38.5)
60 -	25.3 ± 4.54 (13.0 - 36.0)	18.3 ± 5.25 (5.4 - 38.6)	21.1 ± 3.62 (5.4 - 38.6)
Total	24.6 ± 1.47 (2.9 - 57.8)	20.7 ± 2.27 (5.4 - 40.9)	22.6 ± 1.72 (2.9 - 57.8)

The observed range is shown in brackets below the mean ± S.E.

The individual values are shown in Table 2.1.

females is presumably a compensatory process for the relatively lower plasma inorganic iodine values found in that age group.

Factors affecting the thyroid uptake and clearance.

There are many studies of the effect of age and sex on the iodide trapping mechanism of the thyroid, more often using the thyroid uptake than the thyroid clearance. Quimby et al. (1950) carried out an extensive study of the thyroid uptake in apparently euthyroid subjects. However, the ratio of one male to 2.3 females makes it improbable that these were random observations.* These authors found that season had no effect. However, the thyroid uptake decreased with age; women of all age groups had higher values than males. The differences were statistically significant but too small to be of clinical importance. It is interesting that when the thyroid uptake is used women have a higher value than men, whereas our own measurements of thyroid clearance (which reflects more accurately the level of thyroid activity) show the reverse trend. This difference is due to the fact that males have a higher renal

* Commonly the normal range is established not by carrying out measurements in healthy persons or in hospital controls but on persons referred because of suspected thyroid disease and subsequently classified as euthyroid. It is obvious that this is not an entirely satisfactory way and data so obtained must be viewed with some reservation. In our studies, we have avoided these defects as much as possible.

clearance of iodide than women and this tends to lower their thyroid uptake relative to their thyroid clearance.

McGregor and Wagner (1958) obtained indirect estimates of the thyroid uptake by measuring the urinary iodide excretion and reported substantially similar results to those of Quimby et al. (1950). Oddie et al. (1960) also found thyroid uptake decreasing with age both in males and females, but in the latter the decrease was not evident till the age of 45 yr and after. On the other hand Oliner et al. (1957) did not find any difference in the uptake values of children aged 3 months to 18 years, and West et al. (1961) did not find any difference between men aged 25 to 40 and 60 to 96 years.

The 20 minute thyroid radioiodine uptake was found to be lower in males than in females (Bürner 1961); there was a negative correlation with age but in females this was apparent only after the age of 45 yr. The radioiodine uptake and thyroid clearance (the latter expressed as a fraction of the iodide space) were increased in neonates, with maximum values at 48 hr after birth (Fischer et al.1962).

An important study has recently been made by Gaffney et al. (1962) on 131 euthyroid men aged 41 to 94 yr. The thyroid clearance decreased with age whereas the 24 hr radioiodine uptake remained practically unchanged. This discrepancy may have been due to a decrease of both renal and thyroid iodide clearance with age.

For quantitative studies the thyroid clearance is preferable

to the radioiodine uptake, but an even better correlation might be obtained if the thyroidal clearance was related to body size (e.g. surface area or lean body mass). Taken as a whole however, the above results suggest that the effect of age and sex on iodide trapping by the thyroid is a small one.

The thyroid uptake and clearance are increased after TSH injection, in thyrotoxicosis, iodine deficiency, and dyshormonogenesis, and decreased in hypothyroidism and after the administration of iodine or other antithyroid compounds. The cortisone group depress thyroid function and uptake (Hill et al. 1950; Berson and Yalow 1952; Sherer and Stofring 1956; Wikholm and Einhorn 1963). ACTH, which increases the output of cortisol, has the same effect. In adrenalectomised subjects, however, ACTH increases thyroid uptake: this is interpreted by Notter (1962) as a specific effect of the hormone, but the possibility of contamination with TSH cannot be entirely excluded.

The application of the radioiodine uptake and clearance to clinical diagnosis is discussed on p240and summarized in Table 5.4. Extensive reviews of diseases and drugs affecting the radioiodine uptake have been made by Magalotti et al. (1959) and Greyson (1960).

ABSOLUTE IODINE UPTAKE.

The best estimate of the amount of iodide trapped and retained by the thyroid is given by measurements of the absolute iodine uptake (AIU), that is the absolute quantity of iodide (in μg) retained by the thyroid in unit time. The AIU has sometimes been called "stable iodide uptake" or "I^{127} uptake". We prefer the term AIU since what is measured is the total amount of iodide retained, irrespective of whether it is stable or radioactive, and also because the term AIU emphasises the main difference between this estimate and the thyroid radioiodine uptake; the latter is not an absolute quantity but a proportion of a given tracer dose expressed as a percentage of the dose.

The absolute iodine uptake (AIU) can be calculated as the product of the thyroid clearance and the plasma inorganic iodine (PII) that is

$$AIU = Th.\ Cl. \times PII$$

In the present work the thyroid clearance is expressed in ml/min, the PII in μg/100 ml, and the AIU in μg/hr. The above formula must, therefore, be adjusted for the different units, and becomes

$$AIU = Th.\ Cl. \times PII \times 0.6$$

The AIU can also be calculated without knowledge of the PII; since the thyroid clearance is the thyroid uptake (per unit of time) divided by the plasma radioactivity (shown as I^{132} plasma) and

the PII is

$$PII = \frac{I \text{ urine} \times I^{132} \text{ plasma}}{I^{132} \text{ urine}}$$

the AIU can be calculated as

$$AIU = \frac{\text{Th. Upt.} \times I \text{ urine} \times I^{132} \text{ plasma}}{I^{132} \text{ plasma} \times I^{132} \text{ urine}}$$

$$AIU = \frac{\text{Th. Upt.} \times I \text{ urine}}{I^{132} \text{ urine}}$$

This last formula can be transposed:

$$\frac{\text{Th. Upt.}}{AIU} = \frac{I^{132} \text{ urine}}{I \text{ urine}}$$

that is the specific activity of the iodine retained by the thyroid is the same as the specific activity of the urinary iodine: this is reasonable since both are derived from the PII. From these considerations it is also clear that the technical error in measuring the AIU is the same whether the PII is measured or not, because the additional estimate involved (the I^{132} plasma) is self cancelling in the final formula

$$AIU = \text{Th. Cl.} \times PII$$

The theoretical relation between the radioiodine uptake (Th. Upt.) and the AIU is given by the formula

$$\frac{\text{Th. Upt.}}{AIU} = \frac{I^{132} \text{ plasma}}{PII}$$

$$\text{Th. Upt.} = \frac{AIU \times I^{132} \text{ plasma}}{PII}$$

$$AIU = \frac{\text{Th. Upt.} \times PII}{I^{132}\ \text{plasma}}$$

It follows that for any given thyroid uptake value the AIU is proportional to the PII, rising when the PII rises and falling when the PII level decreases. On the other hand if the AIU remains constant, the thyroid uptake is inversely proportional to the PII, rising when the PII falls and falling when the PII rises.

Table 2.5 shows the AIU measurements grouped according to age and sex in 48 normal subjects (individual values shown in Table 2.1). Males had, on the whole, a higher AIU ($p < 0.05$), probably because of their larger body size. There was no consistent age effect, but patients aged 20-39 years had a higher AIU than those aged 40-59; this was significant for the female patients ($p < 0.05$).

The normal AIU range can be defined as lying between 0.5 and 6.0 μg/hr. This gives the best separation between normal cases and patients suffering from hypo- and hyper-thyroidism. Our normal AIU values are in keeping with those previously recorded (Zingg and Perry 1953; Reilly et al. 1958; Fauvert et al. 1958; Dowling et al. 1960; Wagner et al. 1961). Perry and Hughes (1952) found slightly lower values (1.1 ± 0.23 μg/hr) and Stanley (1949) and Semprebone et al. (1959) higher. Our values are consistent with the amounts of thyroid hormone produced (Nodine et al. 1957)

Table 2.5

Normal absolute iodine uptake values (AIU) in μg/hr grouped according to age and sex.

Age yr	Males (24 cases) Mean ± S.E.	Females (24 cases) Mean ± S.E.	Total (48 cases) Mean ± S.E.
0 - 19	2.0	1.6 (1.4 - 1.9)	1.8 (1.4 - 2.0)
20 - 30	3.2 ± 0.67 (1.9 - 8.2)	2.2 ± 0.34 (0.9 - 3.4)	2.8 ± 0.43 (0.9 - 8.2)
40 - 50	2.5 ± 0.70 (0.1 - 6.7)	1.3 ± 0.18 (0.6 - 2.2)	1.9 ± 0.37 (0.1 - 6.7)
60 -	2.0 ± 0.46 (0.8 - 2.9)	2.1 ± 0.40 (0.5 - 3.1)	2.1 ± 0.28 (0.5 - 3.1)
Total	2.7 ± 0.37 (0.1 - 8.2)	1.8 ± 0.17 (0.5 - 3.4)	2.2 ± 0.22 (0.1 - 8.2)

The individual values are shown in Table 2.1.

suggesting that most of the iodide taken up is actually converted to thyroid hormone. However, in rats Nadler and Leblond (1955) found that 55% of the iodide taken up was bound organically and the rest discharged as iodide. In man the degree of utilization seems normally to be greater, but it may be low in pathological states e.g. in dyshormonogenesis.

Relation between plasma inorganic iodine and absolute iodine uptake.

The relation between the AIU and the PII is one of the most interesting problems in thyroid physiology. The mathematical relation is given by the formula

$$AIU = Th.\ Cl. \times PII$$

It follows that when the PII fluctuates, one of three possibilities exists; either the thyroid clearance adjusts to the PII and so keeps the AIU constant, or it does not adjust, in which case the AIU follows the PII fluctuations closely, or both mechanisms may operate simultaneously, that is the clearance may adjust only partially. It is important to know which of these three theoretical possibilities actually occurs in man, since if the thyroid clearance does not adjust to the PII there would be a direct relation between AIU and PII, and the implication would be that persons with a high dietary iodine intake and so a high PII would have a higher AIU, and perhaps produce more thyroid hormone.

The evidence on this point is incomplete but on balance it favours the view that in the long run the thyroid clearance adjusts to the PII level and so keeps the AIU relatively constant. Thus there are substantial differences between our PII values (Table 2.3) obtained in Scotland, and those recorded in several parts of the U.S.A. (Reilly et al. 1958; Wagner et al. 1961), whereas the AIU values obtained in all these areas were not very different. The different behaviour of these two parameters is not likely to be due to technical factors, since error in the chemical estimation of the urinary iodide would affect both PII and AIU proportionately. It seems therefore that in Scotland the average PII is lower than in these parts of the U.S.A., but this is compensated by higher thyroid clearance values in Scotland. These observations explain why the average thyroid radioiodine uptake varies from locality to locality even when the most meticulous standardisation of the uptake measurement is ensured. Further support for the view that the thyroid clearance adjusts to the PII is the fact that persons who have received iodide loads have a low thyroid uptake, though few quantitative studies have been made on this point.

On the other hand Levy et al. (1959) found no consistent relationship between day to day changes in thyroid uptake and changes in the urinary iodine excretion on two consecutive days, suggesting that the AIU was varying from day to day. Since they

did not present individual results of this aspect of their work one cannot tell how much of the variation found by those authors was due to technical error and how much to real alterations in thyroid uptake and ATU. More careful studies have been made in animals by Simon and Morel (1960) who found that rats with a high iodide intake produced more thyroid hormone than rats on a low iodide intake (p77).

Quantitative studies of iodine metabolism can be used to test which of the three theoretical possibilities previously outlined actually occurs in man. Two techniques are available: one can correlate the individual values of these parameters in normal subjects, or one can give iodine supplements and study the effects. Studies of the first type are described below, and those of the second type in the subsequent section.

We have first correlated the thyroid clearance and the PII (individual values shown in Table 2.1) in our normal subjects (Fig. 2.3) and we have found that there is a significant inverse relation, i.e. normal persons with a high-normal PII have on average a low-normal thyroid clearance and vice versa. The correlation coefficient between thyroid clearance and PII (Fig. 2.3) is $r = -0.376$ ($p < 0.01$) and the correlation coefficient between thyroid clearance and $\frac{1}{PII}$ is $r = 0.389$ ($p < 0.01$). However, this adjustment is not a complete one. The variations in thyroid clearance are not sufficiently large to compensate fully and there is therefore

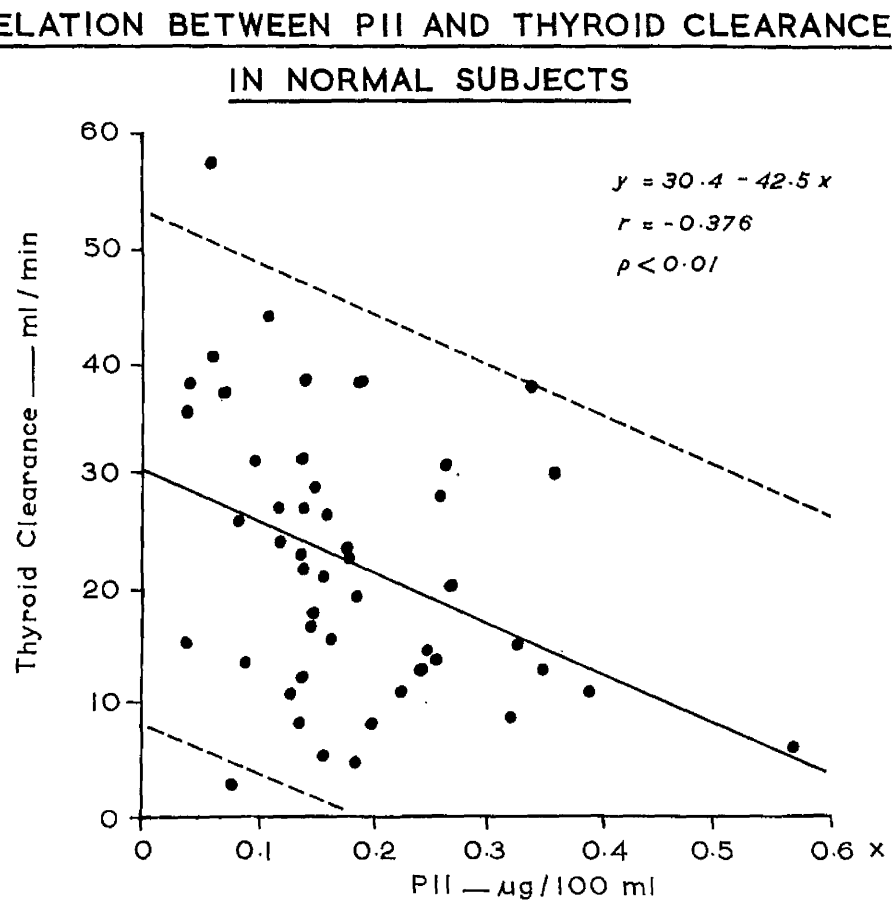

Figure 2.3

Relation between plasma inorganic iodine and thyroid radioiodine clearance in normal subjects.

The regression line ± 2 SD is shown.

a correlation between PII and AIU shown in Fig.2.4 ($r = 0.535$, $p < 0.001$). To sum up, in normal subjects when the PII is relatively high the thyroid clearance is relatively low, but the adjustment is incomplete. Hence relatively high PII levels are associated both with a low thyroid clearance and a raised AIU.

A second problem is whether in euthyroid persons there is a clear relation between the amount of iodine taken up by the thyroid (AIU) and the amount of hormone produced. The amount of thyroid hormone produced is difficult to measure but the PBI (p 98) is a useful index, although perhaps not a very sensitive one (Sturnick and Losses 1959). If euthyroid, thyrotoxic and hypothyroid persons are examined as one group a clear relation between AIU and PBI does exist since in thyrotoxicosis both the AIU and PBI are high whereas in hypothyroidism the opposite picture is seen. However, within our euthyroid group we could not establish a significant correlation between the AIU and the PBI. Thus persons with a high-normal AIU did not on average have a high-normal PBI too. Two mechanisms are possible. Either there is a varying utilization of the iodide taken up by the thyroid, or alternatively hormone synthesis and release, obviously quantitatively equal in the long run, are not so over a short time period. This latter is possible since the thyroid gland has considerable stores of thyroid hormone and so may maintain a steady rate of secretion from day to day in spite of wide fluctuations in both AIU and amount of thyroid

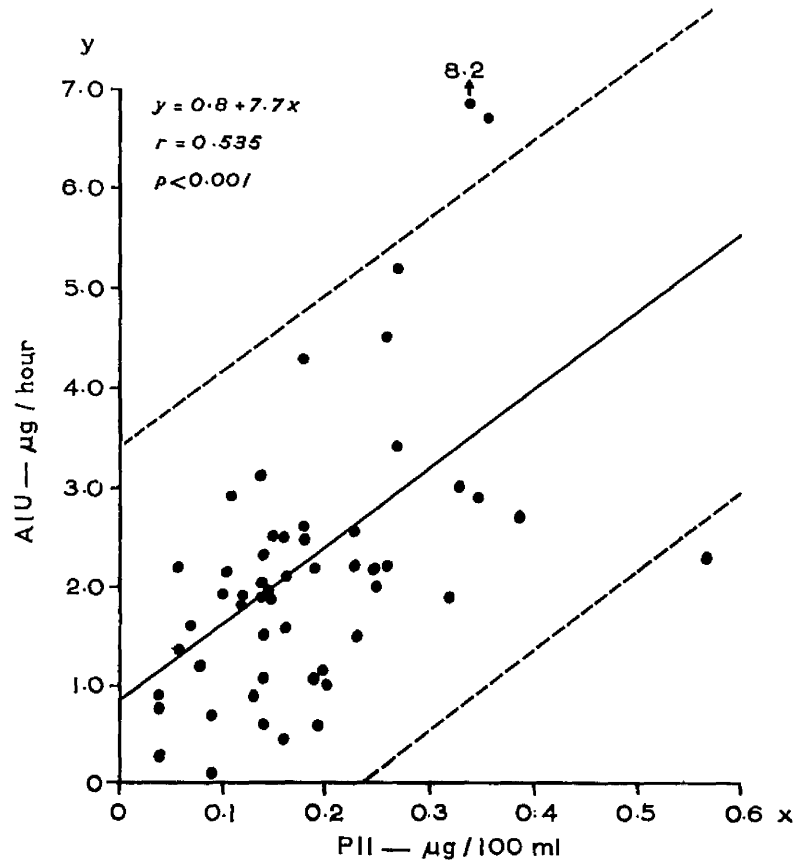

Figure 2.4

Relation between plasma inorganic iodine and absolute iodine uptake in normal subjects

The regression line ± 2 SD is shown.

hormone synthesis. In other words the amount of thyroid hormone released may be proportional to the average amount synthesised over the last months rather than the amount synthesised on any particular day.

Most probably both the mechanisms mentioned above may be operating. A varying utilisation of iodine is suggested by the work of Perry and Hughes (1952) who observed high PII values in patients with renal disease; and although the thyroid clearance was diminished, the AIU was still higher than in their normal controls, without any increase in PBI or clinical evidence of thyrotoxicosis. This suggests that when the PII increases beyond a limit the AIU also increases, but decreased utilization of the iodide taken up maintains a euthyroid state. On the other hand, the normal AIU and PBI values found in iodine deficiency (p197) means that normally, provided the PII remains within a certain range there is no great variability in iodide utilization. This is consistent with the view that normally almost all the iodide trapped by the human thyroid becomes organically bound (Berson and Yalow 1955), although Ingbar and Freinkel (1956) suggest that in rats thyroidal organic-binding reactions proceed at a limited rate, and may play a rate-limiting role in hormone synthesis.

It seems that there is a sex difference in the adjustment to the PII level. Females, as a group, readily adjusted their thyroid clearance to the PII level, and consequently the AIU

fluctuates less than in males. The difference in the correlation coefficients r between males and females after z transformation was found to be statistically significant ($p < 0.04$). Fig 2.5 shows the PII and thyroid clearance in the 24 normal female persons whose individual values are shown in Table 2.1. There is a close inverse relation:

$$\text{Th. Cl.} = 8.7 + \frac{1.55}{\text{PII}},\ r = 0.688,\ p < 0.001$$

The area enclosed between the lines in Fig 2.5 represents $\pm$ 2 S.D. of the regression equation: it should contain 95% of the points, and in fact contains 23 of the 24. It is not clear why females show a closer adjustment of their thyroid clearance to the PII level, but conceivably this has some bearing on the greater prevalence of iodine-deficiency goitre in females.

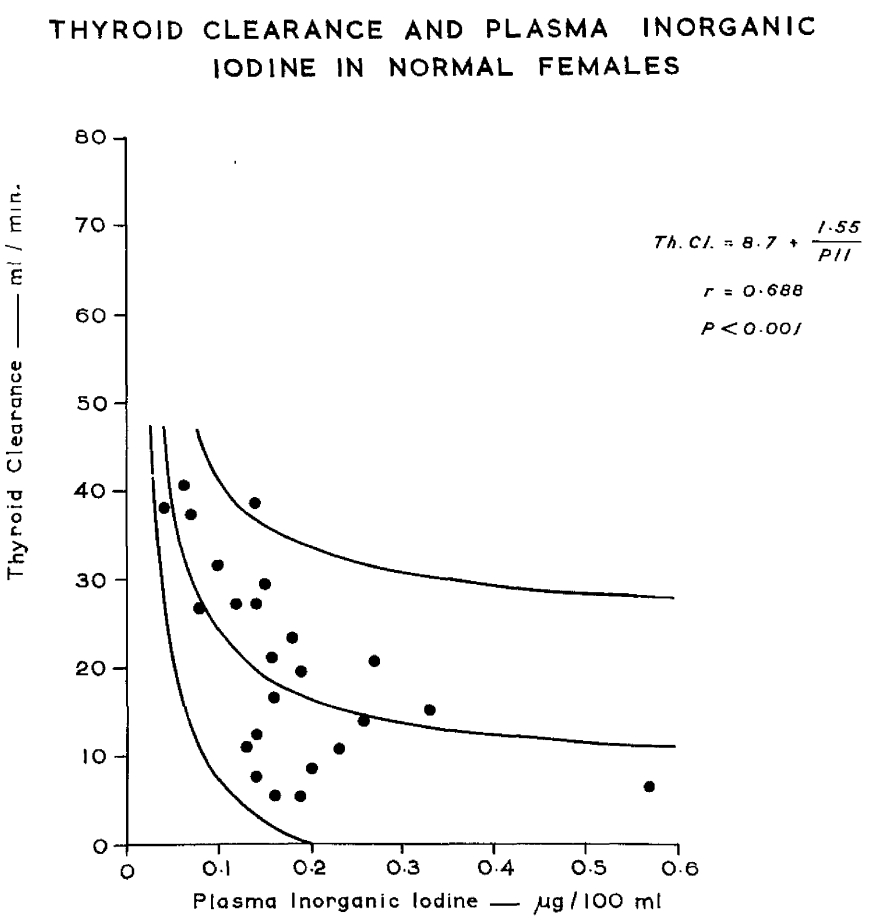

Figure 2.5

Relation between plasma inorganic iodine and thyroid clearance in normal females only

The correlation is better if the thyroid clearance is plotted against $\frac{1}{PII}$ rather than PII. The regression line ± 2 SD is shown.

EFFECT OF IODINE SUPPLEMENTS IN NORMAL SUBJECTS

When considering the effect of iodine administration on thyroid function it is necessary to distinguish between large doses of iodine with a pharmacological action, and small doses of the same order as may exist in the diet. Furthermore the duration of iodine administration is also of great importance since some effects are apparent only after several weeks' administration.

Large doses of iodide.

It is well established that prolonged administration of large doses of iodine to normal people results in a marked reduction in the thyroid clearance of radioiodine. In most instances this is not associated with any clinical effect but rarely iodide goitre and hypothyroidism may occur (p225).

Systematic studies have been mainly of the immediate results of the administration of large doses of iodine. Apart from any biological action the addition of iodine to a tracer dose will reduce the uptake of radioiodine by the thyroid in proportion to the amount of added iodine. This is a simple "specific activity" effect and must be taken into account whenever the intake of iodine increases significantly. The mechanism is similar to, but the reverse of that shown in iodine deficiency (Fig 5.2 p245). The absolute iodine uptake (AIU) is the only satisfactory index of thyroid trapping when additional iodine is administered either in single doses or over a period of time. Stanley (1949) found that a rise in plasma inorganic iodine (PII) after iodide administration was accompanied by a proportional

increase in absolute iodine uptake (AIU). Stanley's results have been confirmed by Reinwein and Klein (1960), who noted however, that when there was a marked rise in the PII (more than 6.1µg/100 ml) this relationship did not hold, but on the contrary further increase in PII was accompanied by a decrease in AIU. The same authors (Reinwein and Klein 1962) found that cases of non-toxic goitre showed less response to the iodide ion, and the radioiodine uptake was suppressed only when the PII rose above 100 µg/100 ml.

The effects of iodides on the biosynthesis of thyroid hormone has been studied in rats by Wolff and Chaikoff (1948a,b) who observed that when the PII level rose to more than 20.00-35.00µg/100 ml organic binding of the newly accumulated iodine in the thyroid was blocked, although the gland was still able to concentrate iodide.

Secretion of hormone is also affected. Mercer et al (1960) showed that iodide in a dose of 65 mg 8-hourly slowed the rate of secretion of I^{131} from the thyroid glands of euthyroid people receiving carbimazole. The complication however, introduced by using this anti-thyroid drug together with possible changes in the specific activity of the iodine during their experiments make interpretation of their results difficult, but it is possible that iodides produce an effect on the secretion rate by inhibiting the thyroid proteolytic enzymes. An inhibitory effect of iodide loads on thyroidal radioiodine release in rats (Yamada et al 1963) appeared to be dependent not only on the dose of iodide used, but also on that of propyl-thiouracil, which was given simultaneously.

The studies mentioned above are of pharmacological rather than physiological importance, since they are mostly concerned with large doses of iodine. They have, however, important physiological implications as well. They show that in acute experiments a rise in PII, unless extremely large, is not accompanied by a reduction in the thyroid clearance, so that the AIU rises in proportion to the PII.

Results of more prolonged administration of iodine have been described by Burrell and Fraser (1957). These authors gave 10 mg of potassium iodide daily for two weeks followed by an interval without iodide lasting for four weeks. Before iodide administration and again four weeks after stopping it they studied the thyroid uptake by an indirect method which uses urinary radio-iodine measurements. The thyroid uptake decreased in normal persons, in euthyroid patients with non-toxic goitre, and in patients presumed cured of thyrotoxicosis after the prolonged administration of antithyroid drugs. Thyrotoxic patients on the other hand continued to maintain a high radioiodine uptake.

Small doses of iodide.

From the physiological point of view, the effect of long continued administration of small doses of iodine is more important, and I have made a detailed study of this problem (Alexander et al, to be published).

In normal persons taking their normal diet there is a relation between the plasma inorganic iodine (PII) concentration and the

absolute amount of iodine taken up by the thyroid gland in unit time(AIU), that is to say, the higher the PII the more iodide is taken up by the thyroid (p69). This correlation has important implications, suggesting that persons with a high dietary intake of iodine might retain more iodine in their thyroids and might make more thyroid hormone. This seems actually to happen in rats, and evidence that increased iodine intake results in increased thyroid hormone production in those animals has been obtained using the isotopic equilibrium method (Simon and Morel 1960).

We have given supplements of iodine of the same order as those obtainable from iodised salt, or a meal containing fish, in an attempt to answer the question: What is the influence of an increase in dietary iodine on the uptake of stable iodine by the thyroid (AIU) and on thyroid hormone production (PBI) in man? We administered daily supplements of potassium iodide of 0.1 mg, 0.2 mg, and 0.3 mg respectively to three groups of normal persons during a 12-week period, and have followed the resulting changes in iodine metabolism. Another approach to this same problem is to study the AIU in countries where there is normally a high dietary intake of iodine, and thus a high PII, and I have initiated such studies in Iceland (p 88).

MATERIALS AND METHODS

The thyroid radio-iodine clearance, PII, AIU, renal iodide

clearance and PBI were measured as described in Chapter 1 in 22 patients. All the persons investigated* were euthyroid without a goitre or other evidence of thyroid disease. Throughout the study they remained outpatients, and continued to take their normal diet. Three dose levels of potassium iodide were employed, and in all cases control measurements were followed by administration of iodide supplements for 12 weeks.

The first group of 9 persons, 5 males and 4 females, aged 44 to 69 years, received 0.1 mg potassium iodide (equivalent to 77 µg iodine) daily. At one, two, four, eight and twelve weeks after starting the iodide tablets measurements of all parameters were repeated.

The second group consisted of 6 persons, 3 males and 3 females, aged 37 to 70 years. They were studied in exactly the same way as the first group, and at the same time intervals, the only difference being that they received 0.2 mg potassium iodide daily, divided into two doses.

The third group consisted of 7 persons, 3 males and 4 females, aged 50 to 62 years. These patients received one 0.4 mg potassium iodide tablet twice daily, but otherwise they were studied in the same way as the previous groups.

In the majority of the 22 patients studied all the parameters of iodine metabolism were measured twice before starting administration of potassium iodide, and the mean was taken as the control value. However, for 7 patients in group 1, and for 1 patient in group 3 a single control

* The majority of these patients suffered from coronary artery disease or from peptic ulcer dyspepsia.

measurement was obtained.

RESULTS

The control values before starting iodide supplements are shown in Figs 2.6, 2.7 and 2.8. They were within the normal range, and for each parameter studied there was no significant difference between the means in the three treatment groups.

The changes in plasma inorganic iodine, absolute iodine uptake, thyroid clearance and PBI are shown in Table 2.6 and Figs 2.6, 2.7 and 2.8. The renal iodide clearance did not show any significant change and does not merit further comment.

Effect of 0.1 mg Potassium Iodide Daily

As shown in Table 2.6 and Fig 2.6, the PII rose following the administration of the tablets, but the increase was statistically significant only at 1, 2 and 8 weeks ($p = 0.02$ at 1 week, $p < 0.01$ at 2 and 8 weeks). There was no statistically significant change in the thyroidal iodide clearance, and the AIU rose significantly only at 2 weeks ($p<0.001$). Nevertheless the AIU was increased at all times during iodide administration and a t test on all values during this period shows that the rise is a significant one.

The average quantity of additional iodine taken by the thyroid gland is proportional to the area under the AIU curve in Fig 2.6, and

Table 2.6

Change in plasma inorganic iodine, thyroid radioiodine clearance, absolute iodine uptake and PBI during administration of iodine supplements

Week	PII μg/100ml (mean ± SE)	Th.Cl. ml/min (mean ± SE)	AIU μg/hr. (mean ± SE)	PBI μg/100ml (mean ± SE)	Dose of Pot.Iodide
1	+0.10±0.034	+5.2±6.43	+1.9±1.26	+0.4±0.60	
2	+0.16±0.040	+5.0±3.48	+2.6±0.79	+1.8±0.43	0.1 mg
4	+0.07±0.043	+0.5±2.19	+0.9±0.71	+0.9±1.14	per
8	+0.29±0.084	+2.5±5.05	+5.6±3.27	+0.6±0.75	day
12	+0.23±0.138	+2.7±4.84	+4.5±2.34	+0.5±0.61	
1	+0.38±0.102	-1.4±1.90	+3.3±1.48	-0.5±0.46	
2	+0.20±0.060	-4.6±1.77	+1.5±0.99	-0.6±0.45	0.2 mg
4	+0.35±0.066	-7.5±0.55	+1.5±0.58	0 ±0.48	per
8	+0.64±0.143	-12.3±1.97	+1.4±0.67	+0.6±0.57	day
12	+0.44±0.155	-10.3±4.88	+1.5±0.67	-0.6±0.54	
1	+1.06±0.268	-12.0±3.56	+3.1±1.09	-0.7±0.51	
2	+1.46±0.274	-11.8±2.91	+6.0±2.44	-0.3±1.12	0.3 mg
4	+1.22±0.197	-12.9±3.80	+3.4±1.70	-0.5±1.30	per
8	+1.12±0.114	-13.5±2.52	+0.8±1.01	-0.9±2.25	day
12	+1.58±0.309	-12.6±3.72	+6.9±1.10	-0.7±1.79	

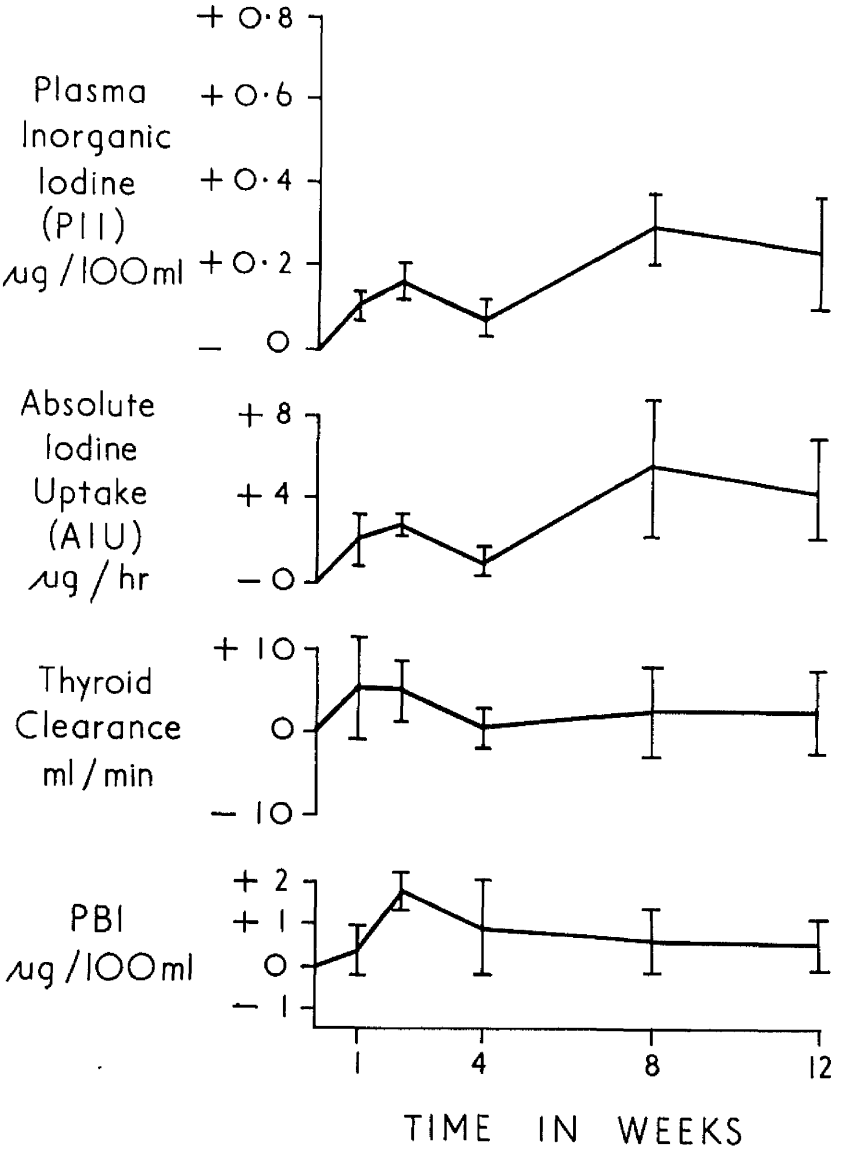

Figure 2.6

Effect of iodine supplements

Changes in plasma inorganic iodine, absolute iodine uptake, thyroid clearance and protein-bound iodine (mean ± SE) during oral administration of 0.1 mg potassium iodide for 12 weeks.

The control values before starting the supplements were:

PII 0.16 ± 0.02 µg/100 ml
AIU 1.8 ± 0.50 µg/hr
Th.Cl. 20.1 ± 3.4 ml/min
PBI 5.7 ± 0.22 µg/100 ml

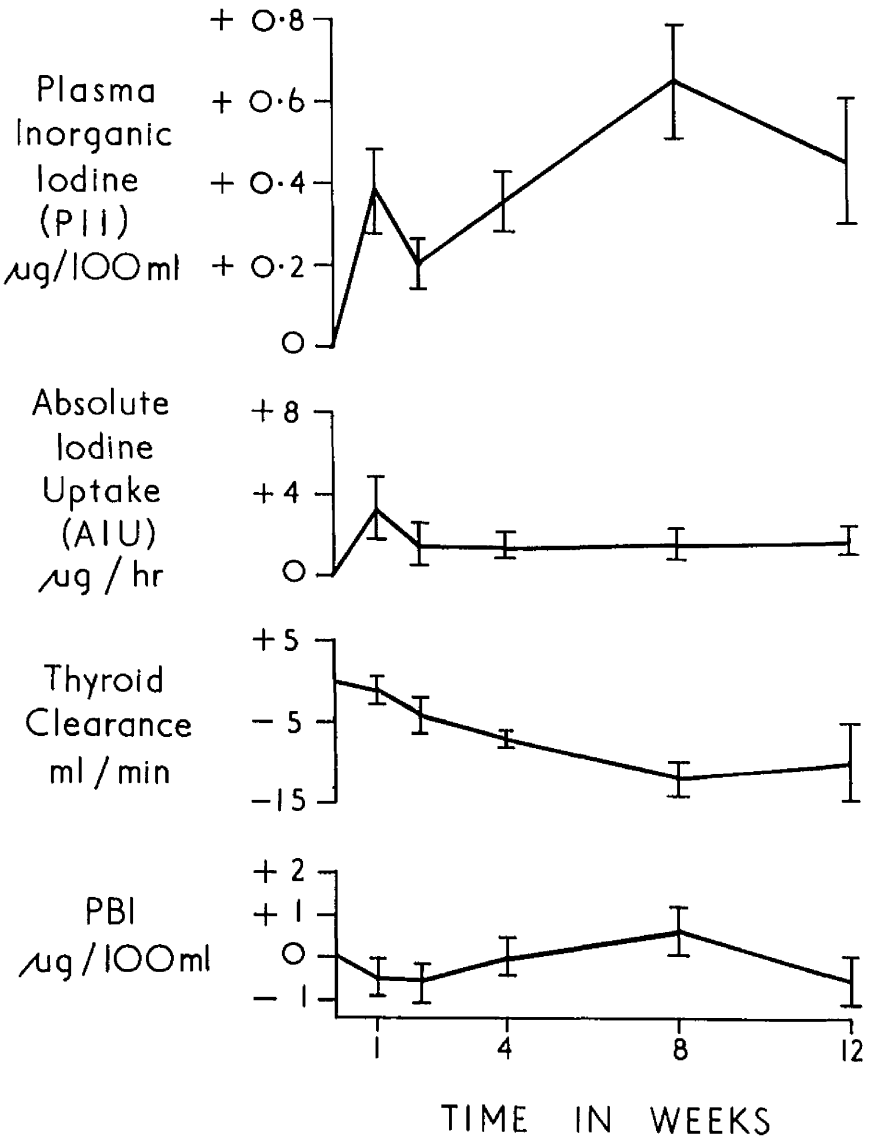

Figure 2.7

Effect of iodine supplements

Changes in plasma inorganic iodine, absolute iodine uptake, thyroid clearance, and protein-bound iodine (mean ± SE) during oral administration of 0.2 mg potassium iodide for 12 weeks.

The control values before starting the supplements were:

PII	0.27 ± 0.06 µg/100 ml
AIU	2.6 ± 0.65 µg/hr
Th.Cl.	16.6 ± 1.8 ml/min
PBI	5.7 ± 0.25 µg/100 ml

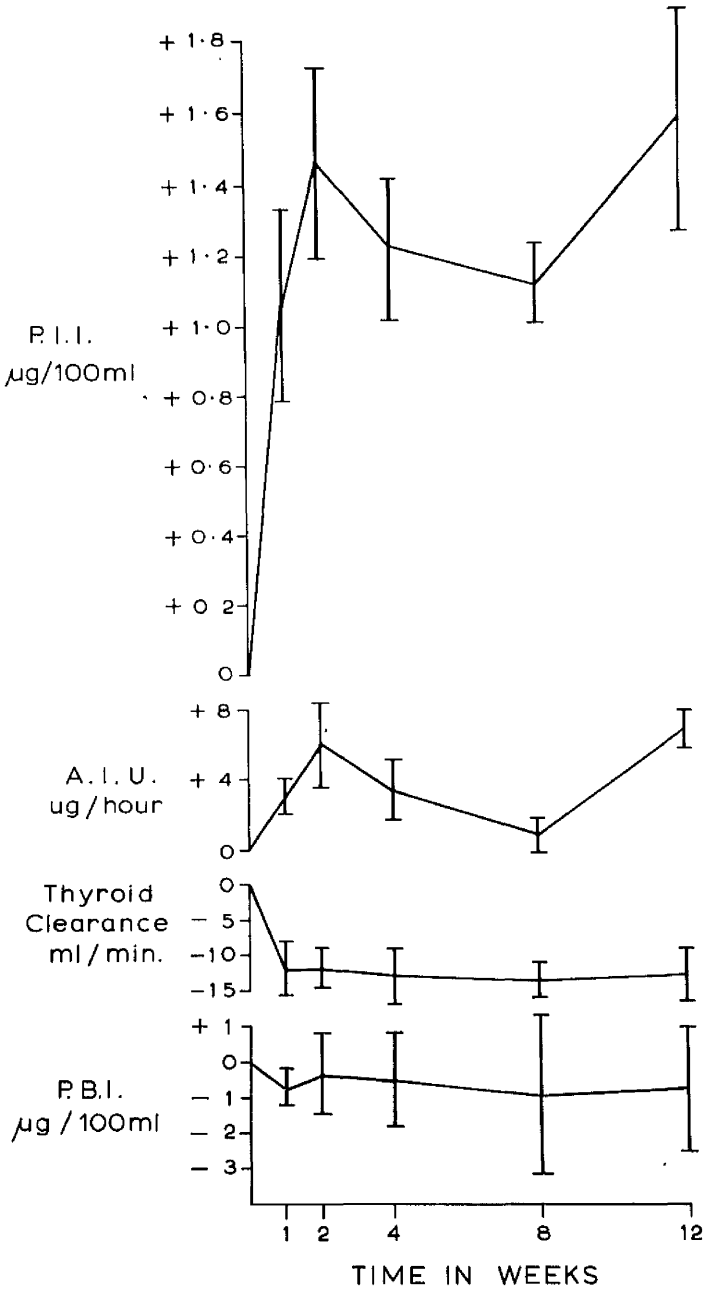

Figure 2.8

Effect of iodine supplements

Changes in plasma inorganic iodine, absolute iodine uptake, thyroid clearance and protein-bound iodine (mean ± SE) during oral administration of 0.8 mg potassium iodide for 12 weeks.

The control values before starting the iodide supplements were:

PII	0.20 ± 0.04 µg/100 ml
AIU	1.9 ± 0.35 µg/hr
Th. Cl.	19.5 ± 3.0 ml/min
PBI	5.4 ± 0.38 µg/100 ml.

measurement shows that the thyroid took up 7.0 mg of additional iodine throughout the 12 week period of the study. To sum up, an increase in PII was accompanied by a small rise in the AIU, and the PBI also showed a slight increase.

Effect of 0.2 mg of Potassium Iodide Daily.

The PII showed a statistically significant increase at all times during iodide administration (Table 2.6, Fig. 2.7). This was accompanied by a progressive decrease in the thyroidal radioiodine clearance, reaching a maximum fall at 8 weeks. The decrease was statistically significant at 2, 4 and 8 weeks but not at 1 and 12 weeks. At the latter time, however, the lack of significance was due to the large S.E. The fall in the thyroid clearance almost, but not quite, compensated for the rise in PII and the AIU rose slightly. This resulted in the thyroid taking up 6.0 mg of additional iodine during the 12 week period of study. To sum up, a rise in the PII was accompanied by a progressive decrease in the thyroid radioiodine clearance; the AIU rose slightly but did not exceed the normal range. There was no consistent alteration in PBI.

Effect of 0.8 mg Potassium Iodide Daily.

The PII showed a marked and significant increase at all times after supplements were started (Table 2.6, Fig. 2.8). This was

accompanied by a significant decrease in the thyroid clearance, which remained relatively constant from the first week until the end of the study. This decrease in thyroid clearance was not sufficient to compensate completely for the rise in PII and so the AIU increased. Thus the thyroid took up 6.4 mg of additional iodine throughout the study. At no time was a significant change in the PBI noted, but the mean remained below the control value at all five time intervals during administration of supplements. In summary, following 0.8 mg potassium iodide daily the thyroid clearance decreased, but not enough to compensate for the rise in PII. Therefore the AIU increased, but there was no concomitant increase in PBI.

DISCUSSION

Many workers have noticed a fall in the thyroidal radioiodine uptake after iodide administration, but their results have rarely been quantitative, giving no indication whether the decrease in the thyroid radioiodine uptake was associated with a high, normal, or low absolute uptake of iodine by the thyroid (AIU). Quantitative measurements are particularly desirable since there is often a very poor correlation between radioactive and stable iodine uptake by the thyroid when the iodine stores of the body are increased or decreased, and in these circumstances radio-isotopic measurements alone give a very limited, and

sometimes frankly misleading, impression of thyroid activity (p253).

Using larger supplements of iodine than in our study Wagner et al (1961) gave an initial dose of 1.2 mg potassium iodide daily and progressively increased the dosage to 10 mg/day over a 37 day period. They noticed that the radioiodine uptake decreased, but the AIU increased and even at the end of the 37 day period of the study it exceeded the control values. However, these authors did not continue the same dosage for a sufficient time interval to study its ultimate effects, and the quantities of iodine administered were completely outwith the physiological range.

In the present investigation we administered small doses of iodide for longer periods, and each group received a constant dose throughout the study. With 0.1 and 0.2 mg daily, the PII increased, but still remained in or near the normal range of 0.08 to 0.60 µg/ 100 ml. With the latter dose a progressive decrease of the thyroidal iodide clearance occurred, reaching its maximum only after 8 weeks of continuous administration. We have noticed this delayed adjustment of thyroid clearance not only in normal persons, but also in some patients with iodine deficiency states, confirming the observations of Stanbury et al. (1954).

Within the dose range studied we have found that on average when the PII rises the thyroid clearance falls, but not sufficiently to keep the AIU constant. The amount of additional iodine taken up by the thyroid gland during the twelve-week study showed a mean value of 6.0 mg to 7.0 mg. A higher PII is therefore usually accompanied by both

a reduced thyroid clearance and an increased AIU. There was no relation between the amount of iodine taken up by the thyroid (AIU) and the amount of hormone produced (PBI).

It is uncertain whether the AIU would have returned towards the control value if the study had been continued for a longer time. It might do so, but it seems possible that with even a moderate increase in iodine intake of 0.8 mg/day, there is faulty utilization of iodine, i.e. the thyroid traps more iodine than it converts into thyroid hormone. Studies of the AIU in countries where there is normally a high dietary intake of iodine might help to resolve this question, and have been initiated by me for this purpose. Preliminary results are reported in the next section.

STUDIES OF IODINE METABOLISM IN ICELAND

In the previous section I described the influence of a high dietary iodine intake lasting 12 weeks on the uptake of stable iodine by the thyroid (AIU) and on hormone production (PBI). In this section I describe the influence of a life-long high dietary intake of iodine on these parameters.

Previous work has shown that in some parts of the U.S.A. the average PII was substantially higher than in Glasgow, but the AIU values obtained were not very different (Reilly et al. 1958; Wagner et al. 1961), suggesting that the higher PII was compensated by a lower thyroid clearance. The data are insufficient to permit consideration of the question whether or not compensation was complete (i.e. whether the AIU was the same in all areas), due to uncertainties about the comparability of the methods used in the various departments, and to discrepancies in some of the published results.

What is required are studies in areas where the dietary iodine intake is normally low and high, using identical techniques, and preferably with the chemical measurements made in the same laboratory. The visit of Dr. M. Bluhm to Iceland provided an opportunity for a study of this type. The aim was to investigate the relation between the PII, AIU, and PBI in individuals with normal thyroid function in Reykjavik, and to compare them with similar studies in Glasgow (p 69). Great care

was taken to see that the results obtained in the two centres were comparable.

Since it was known that fish-cake was extensively used to feed livestock in Iceland (Gudmundsson 1962, personal communication) milk samples sent by air were analysed for iodine content in Glasgow.

Methods

The thyroid radioiodine uptake and clearance, PII, AIU, PBI, and renal iodide clearance were measured as described in Chapter 1. Neck uptake measurements, and counting of radioactivity in plasma and urine samples was undertaken at the Landspitalinn Reykjavik, under Dr. Bluim's supervision. To suit local conditions the tracer dose consisted of 25 μc I^{131}. Samples were immediately flown to Renfrew air-port, and chemical analyses of urinary iodine and serum protein-bound iodine were undertaken in the Gardiner Institute.

The subjects studied were 17 females, aged 20 to 56 years, who were attending either as out-patients or in-patients at the State Hospital, Reykjavik, and who volunteered to take part in the investigation. One subject was a staff-member. None suffered from overt thyroid or renal disease.

The iodine content of the milk samples was estimated as described by Richmond (1962).

Results

The results in individual Icelandic subjects are shown in Table 2.7, and Table 2.8 summarises the values obtained in normal females in Glasgow and in Reykjavik.

The PII was on average 2½ times higher in Iceland (0.45 ± 0.067 µg/100 ml). This was accompanied by a significantly lower thyroid radioiodine clearance (10.7 ± 1.1 ml/min), but not sufficient to compensate completely for the elevated PII, and so the AIU (2.6 ± 0.31) was higher than in Glasgow. The mean PBI was the same in both centres.

Results of the milk analyses are shown in Table 2.9, and compared with those reported by Richmond (1962) on milk obtained in Glasgow.

Discussion

The consumption of fish and fish products in Iceland is high (Sigurjonsson 1961). Fish cake is widely used to feed livestock, and this results in a high iodine content of milk, butter, eggs and cheese. Thus the average iodine content of milk in Reykjavik is more than 3 times greater than that in Glasgow (Table 2.9). It is therefore not surprising to find that the PII was 2½ times higher in Reykjavik.

The results obtained can be regarded as representing the

No.	Name	Age yr.	2½ hr. upt. % dose	Th.Cl. ml/min	PII µg/100 ml	AIU µg/hr.	R.Cl. ml/min	PBI µg/100 ml
1	Hjordis Thordarsdottir	29	10.9	10.0	0.65	3.9	31.0	
2	Sigridur Arnadottir	56	9.4	6.2	0.46	1.7	29.5	4.8
3	Ingibjorg Olasdottir	21	10.3	10.6	0.58	3.7	17.3	7.4
4	Anna Thordardottir	22	7.0	10.0	0.95	5.7	29.5	5.8
5	Thorlaug Brynolfsdottir		12.3	16.1	0.27	2.6	34.2	4.0
6	Nanna Jonsdottir	20	17.3	18.7	0.17	1.9	24.1	6.2
7	Sesselja Magnusdottir	48	12.5	9.9	0.25	1.5	25.4	4.0
8	Magdalena Buadottir	25	14.0	14.8	0.22	2.0	36.3	3.6
9	Elsa Sigurdardottir	42	22.5	21.3	0.22	2.8	25.0	5.9
10	Sigurhelga Palsdottir	27	9.3	9.0	0.23	1.2	21.9	5.0
11	Magnea Tomasdottir	28	6.5	7.0	0.75	3.2	19.3	3.6
12	Valgerour Bjarnadottir	55	5.4	6.7	0.45	1.8	30.5	4.5
13	Sigriour Vigfusdottir	49	11.2	9.6	0.52	3.0	30.2	4.2
14	Gudbjorg Gudjonsdottir	22	11.6	6.5	0.37	1.4	24.6	5.6
15	Valgerdur Bjornsdottir		6.1	8.4	0.17	0.9	47.5	4.6
16	Rosa Steingrinsdottir	33	8.2	6.8	1.08	4.4	38.3	4.3
17	Arndis Stingrims	30	9.8	10.5	0.31	2.0	38.9	2.4

Patients and staff of the Landspitalinn, Reykjavik. None showed any clinical features of thyroid or renal disease.

Table 2.8

Summary of results in normal females in Glasgow and in Iceland

	Normal females (Glasgow)	Normal females (Iceland)	Statistical analysis
Number of patients	24	17	
Thyroid radioiodine clearance ml/min	20.7±2.27 (5.4-40.9)	10.7±1.1 (6.2-21.3)	$p < .001$
Plasma inorganic iodine µg/100 ml	0.18±0.022 (0.04-0.57)	0.45±0.067 (0.17-1.08)	$p < .001$
Absolute iodine uptake µg/hr	1.8±0.17 (0.5-3.4)	2.6±0.31 (0.9-5.7)	$t = 2.46$ $p = 0.02$
Protein-bound iodine µg/100 ml	4.8±0.12* (3.0-7.8)	4.7±0.30 (2.4-7.4)	-
Renal iodide clearance ml/min	25.3±1.8 (11.7-41.3)	28.0±3.1 (17.3-38.9)	-

* 84 cases (Table 2.10)

The individual values are shown in Tables 2.1 and 2.7.

Table 2.9

Iodine content of milk

	No. of samples tested	Mean	Range (µg/kg)
Milk obtained in Glasgow	10	64	26 - 134
10.3.61	2	127	124 - 133
26.4.61	2	76	75 - 78
24.5.61	2	46	46 - 47
11.9.61	2	27	26 - 29
Milk obtained in Reykjavik	8	216	121 - 330
1.5.62	2	121	
11.1.63	2	204	203 - 204
15.2.63	2	323	316 - 330
22.3.63	1	243	
2.4.63	1	189	

ultimate effect of a high-normal dietary intake of iodine on thyroid function and iodine metabolism. However, the possible influence of race and climate must be remembered. Climatic conditions bear very little relation to the temperature of the immediate environment of the body, which is very similar in cold or intemperate climates. Nor are ethnic differences between Glasgow and Iceland* likely to be associated with significant differences in iodine metabolism.

The relation between the PII and the thyroid radioiodine clearance in females with normal thyroid function is shown in Fig 2.9 ($p<0.01$), and that between PII and AIU in Fig 2.10 ($p<0.001$). The results obtained in Iceland thus confirm the impression gained from analysis of the Glasgow data (p 69) that in normal subjects when the PII is relatively high the thyroid clearance is relatively low, but the adjustment is incomplete. Hence relatively high PII levels are associated with a low thyroid clearance and a raised AIU.

In the total group of 41 subjects there was no relation between the amount of iodine taken up by the thyroid (AIU) and the amount of hormone produced, as reflected in the PBI concentration. The additional iodine taken up is not stored, since the thyroid gland in Iceland contains only the normal amount of iodine (Sigurjonsson 1961). It therefore seems that there is a varying utilization of iodine: when the PII increases beyond a limit the AIU also increases, but decreased utilization of the trapped iodine maintains a normal level of hormone synthesis. This

* The inhabitants of Iceland are of Norwegian, Danish, Scottish and Irish stock (Encyclopedia Brittanica).

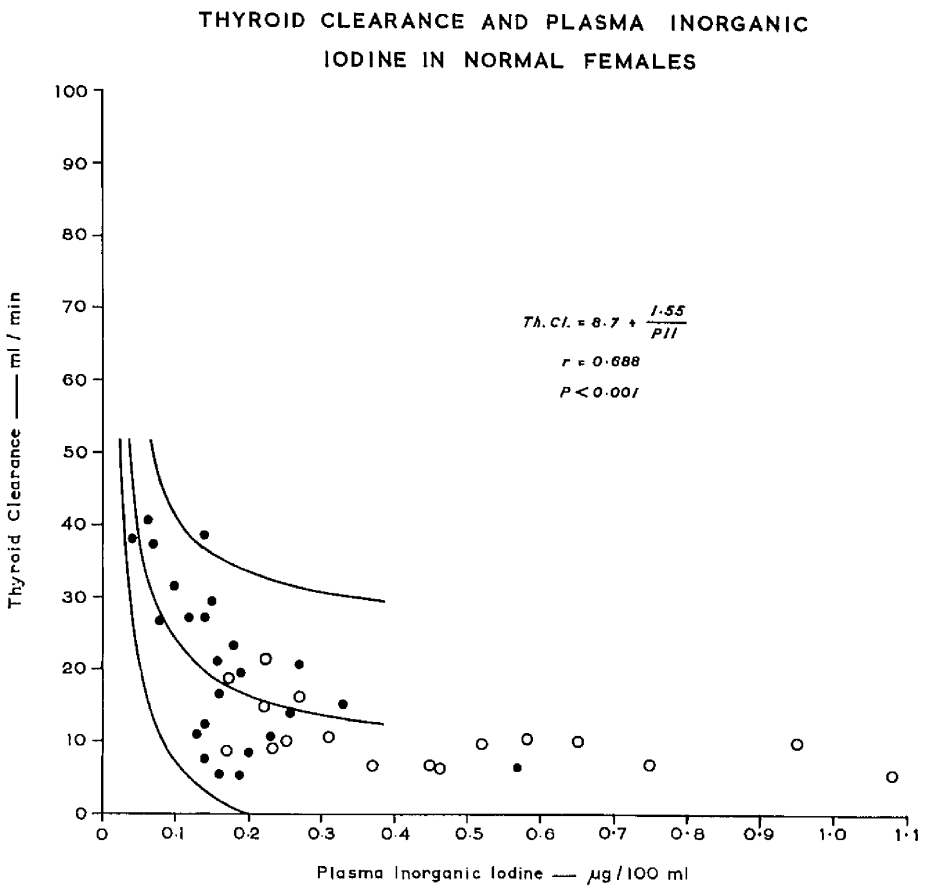

Figure 2.9

Relation between plasma inorganic iodine and thyroid radioiodine clearance in normal females living in Glasgow and in Reykjavik

● Glasgow.

○ Reykjavik.

The regression equation was calculated for the Glasgow group, but would also be appropriate for the Icelandic group.

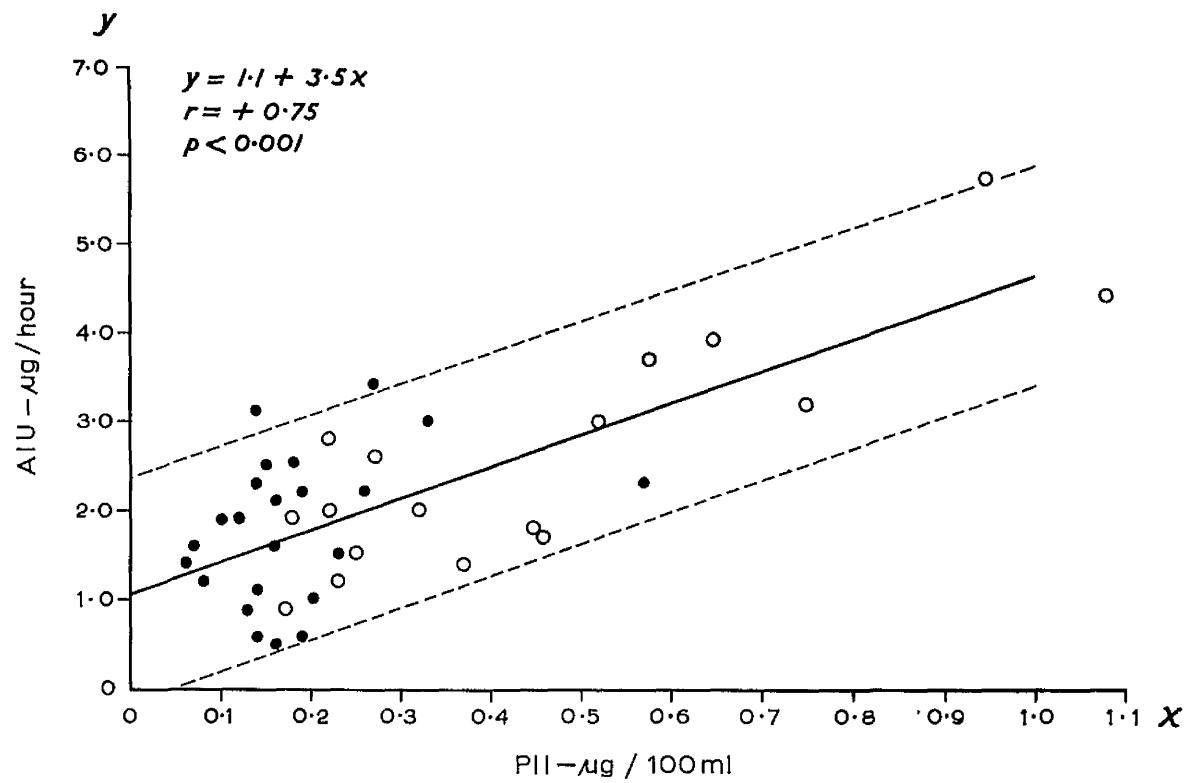

Figure 2.10

Relation between plasmainorganic iodine and absolute iodine uptake in normal females, living in Glasgow and in Reykjavik

● Glasgow.

○ Reykjavik.

The regression line ± 2 SD is shown.

suggests that organic-binding reactions may play a rate-limiting role in hormone synthesis, as proposed by Ingbar and Freinkel (1956).

CIRCULATING THYROID HORMONE

The metabolic effects of the circulating thyroid hormone depend upon its concentration, composition, and degree of protein binding.

Protein-bound iodine (PBI)

A convenient way of measuring the concentration of circulating thyroid hormone in the plasma or serum is the estimation of the protein-bound iodine (PBI). More than 20 years ago Turner et al (1940) found a mean normal value of 6.3 μg/100 ml. More refined techniques give slightly lower values. Thus Kydd et al (1950) established a normal range of 3.8 to 7.8 μg/100 ml and Blackburn and Power (1955) found a mean normal value of 5.2 and a standard deviation of 1.2 μg/100 ml. Earlier results often carried out by less reliable techniques have been revieved by Winikoff (1954).

Current techniques may give false high results if the plasma contains organic iodine compounds or iodide in excess. Mercurial compounds on the other hand interfere with the catalytic reaction on which the determination is based and so lead to false low values (Meyers and Man 1951).

To circumvent the first difficulty measurements of the butanol-extractable iodine (BEI) have been proposed (Man and Bondy 1957). This method is based on the fact that the thyroid hormone (T_3 and T_4) in the plasma is extractable with butanol whereas iodide and other circulating iodinated compounds are not. Thus these contaminating compounds are excluded from the estimation which

therefore approximates more closely to the concentration of circulating thyroid hormone. Abnormal iodoproteins, which occur in several thyroid disorders, are not included in the BEI estimation, and the concentration of these abnormal iodoproteins can be measured as the butanol-insoluble iodine (BII). The butanol-extraction method is rather elaborate for routine clinical use in spite of the simplification in technique proposed by Posner (1961) and most centres prefer the simpler PBI technique. Values for butanol-soluble (or butanol-extractable) iodine levels are usually about 0.6 µg/100 ml lower than the corresponding PBI values (Men et al. 1951), the upper limit of the normal range being approximately 6.5 µg/100 ml. Even this technique, however, may be invalidated by the administration of massive doses of organic iodine compounds but to a lesser extent than the usual PBI determinations.

Ion exchange resins can be used for the estimation of both the PBI and the PBI ^{131} (Scott and Reilly 1954; Blanquet et al. 1955, 1960; Zieve et al. 1955, 1956; Fields et al. 1956; Ingbar et al. 1957; Galton and Pitt-Rivers 1959a, b; Wynn et al. 1959). Farrell and Richmond (1961) working in our department have developed this technique and have shown that iodide is more effectively removed than by the conventional trichloroacetic acid precipitation method. Their method which involves the use of

Amberlite anion exchange resin, is described in Chapter 1. Galton and Pitt-Rivers (1959a, b) have used Dowex-1 resin and have found that acetic acid eluted thyroglobulin, MIT and DIT at pH 3.6, 3.0 and 2.2 respectively, whereas T_4 and T_3 were eluted at pH 1.4. Blanquet et al. (1960) use resin columns of Dowex-1 and Dowex-50, and so distinguish three radioiodinated fractions, one containing iodide and the other two organic fractions. Pileggi et al. (1961) reported that their resin method eliminates inorganic iodine, iodotyrosines and some exogenous organic compounds, and suggest that when these contaminants are present the resin method is more useful than the conventional PBI or BEI methods. From our own experience we have no doubt that inorganic iodine in amounts of up to 10 µg/100 ml can be effectively eliminated by the use of a suitable resin, but the removal of other compounds using various resins requires further investigation. Another technique is based on gel filtration, which can be used to separate the thyroid hormones from iodide in serum (Jacobsson and Widström 1962), and recently neutron activation analysis (Smith et al. 1962) has been successfully employed to measure the PBI.

Table 2.10shows our results of PBI estimations in 130 subjects without evidence of thyroid disease. There is no consistent variation with age or sex. Our normal mean is 4.9 and the standard deviation 1.15 µg/100 ml. If the distribution was statistically

Table 2.10

Normal protein-bound iodine values in µg/100 ml grouped according to age and sex.

Age Yr	Males (46 cases)	Females (84 cases)	Total (130 cases)
10 - 19	4.6 (4.0 - 5.3)	4.9 ± 0.41 (3.7 - 6.2)	4.8 ± 0.33 (3.7 - 6.2)
20 - 29	5.2 ± 0.47 (3.3 - 6.6)	5.3 ± 0.34 (4.3 - 6.9)	5.2 ± 0.28 (3.3 - 6.9)
30 -39	5.5 ± 0.54 (3.4 - 6.9)	5.0 ± 0.38 (3.0 - 7.8)	5.2 ± 0.31 (3.0 - 7.8)
40 - 49	5.0 ± 0.24 (4.1 - 6.0)	4.7 ± 0.25 (3.1 - 5.9)	4.8 ± 0.18 (3.1 - 6.0)
50 - 59	4.9 ± 0.34 (3.2 - 6.9)	4.6 ± 0.27 (3.0 - 6.9)	4.7± 0.20 (3.0 - 6.9)
60 - 69	5.1 ± 0.46 (3.3 - 6.5)	4.9 ± 0.23 (3.0 - 7.5)	5.0± 0.21 (3.0 - 7.5)
70 - 79	5.5 (3.6 - 9.3)	4.3 ± 0.60 (3.0 - 5.8)	4.8 ± 0.82 (3.0 - 9.3)
80 - 89	-	5.3 (5.1 - 5.6)	5.3 (5.1 - 5.6)
Total	5.1 ± 0.19 (3.2 - 9.3)	4.8 ± 0.12 (3.0 - 7.8)	4.9 ± 0.10 (3.0 - 9.3)

Results are shown as mean ± S.E., and the observed range is shown in brackets.

normal the 95% confidence limits would be 2.6 to 7.2 µg/100 ml, but it is not. In practice a better separation between normal subjects and patients with hypothyroidism and thyrotoxicosis is achieved by using a normal range of 3.0 to 7.5 µg/100 ml.

Gaffney et al. (1960) also found that age had no influence on the PBI levels of men aged 18 to 94 years, but noted biological day to day variations (0.6 to 1.2 µg/100 ml) which were greater than possible technical inaccuracies (0.3 to 0.4 µg/100 ml). High PBI values, averaging 9.1 µg/100 ml, have been reported in neonates 25 hours old (Fisher et al. 1962). Day to day fluctuations of the PBI had been previously reported by Margolese and Golub (1957). These authors also found higher values in their female subjects during the luteal phase of the menstrual cycle. The BEI may be on average, slightly higher in men than in women (Man (1962). Although day to day variations seem well established, Schatz and Volpe (1959) could not find any consistent variation within the same day, as for instance between morning and evening. A racial or dietary factor influencing PBI levels is suggested by the finding of increased values (up to 9 µg/100 ml) in some Eskimo tribes, but not in white soldiers living in the Arctic (Gottschalk and Riggs 1952). Seasonal variations of the order of 2 µg% have been reported in Japanese males. The levels were lowest in summer and winter and highest in spring and autumn.(Watanabe et al. 1963).

The PBI concentration does not show a linear relation with the amount of thyroid hormone produced per day, since it is also influenced by the rapidity of peripheral catabolism and excretion of the hormone. Generally speaking the daily production of thyroid hormone is proportional to the square of the PBI concentration (Riggs 1952) but this does not hold when the thyroxine-binding capacity of the plasma is altered.

Composition of the circulating organic iodine.

The circulating thyroid hormone is mainly thyroxine (T_4), which normally accounts for almost all the PBI (Taurog and Chaikoff 1948; Laidlaw 1949). In addition Gross and Pitt-Rivers (1952) found 3,5,3'-L-triiodothyronine (T_3) in the plasma of patients with thyrotoxicosis or thyroid cancer, and concluded that T_3 is also a normal constituent of the PBI. These results have been confirmed by many other workers and it seems that the PBI normally consists mainly of thyroxine but there are also small amounts of T_3 and perhaps traces of other unidentified iodinated substances as well (Dinglodine et al. 1955; Arons and Hydovitz 1959; Bird and Farran 1960; Beraud 1960; Varnotti et al. 1961). When thyroid activity is increased as in thyrotoxicosis and after the administration of TSH larger amounts of T_3 tend to be produced (Hydovitz and Arons 1957).

It is clear that the proportion of the various iodinated compounds in the PBI is not the same as the proportion of these

compounds secreted by the thyroid gland, since the plasma concentration depends on both the amount secreted and its rate of disappearance. Thus Pitt-Rivers and Rall (1961) have shown in rats that although the T_3 concentration in the plasma is approximately one twentieth of that of T_4 these two compounds contribute about equally to the biological activity of the thyroid hormone.

Injected iodotyrosines are rapidly deiodinated and do not remain long in the circulation (Stanbury et al 1956a). Therefore the presence of iodotyrosines in the plasma in more than trace quantities would seem unlikely, even if substantial amounts are secreted by the thyroid. Recent work on this subject, however, has been confusing and contradictory. Thus, although MIT and DIT are not detectable by radiochromatography, nevertheless significant amounts of these have been detected by the use of chemical chromatography (Warner and Block 1959), by double isotope dilution techniques (Beale and Whitehead 1960), and by neutron activation analysis (Dimitriadou et al 1962a, b). The reason for this discrepancy is not yet apparent. It may be that results of chemical chromatography are subject to artefacts (Dimitriadou et al 1960a), but this seems an unlikely explanation for all three methods. A more probable view is that the iodotyrosine-like material detected by the latter methods is not labelled by I^{131} because it is not secreted by the thyroid. In this case it may be a peripheral

breakdown product of thyroxine (Dimitriadou et al 1962b).

If these recent findings were confirmed they would necessitate a revision of our present concept that the PBI consists almost entirely of T_4 and T_3 and that iodotyrosines, if present at all, exist only in traces. Perhaps application of fresh techniques, such as analysis with ion-exchange resins (Pitt-Rivers and Sacks 1962) or modified charcoal (Posner and Pimental 1962) might help to resolve this controversial problem.

Variations in the chemical composition of the PBI which are of biological significance are rare, but when they occur they are of considerable clinical importance. If the PBI is composed largely of biologically inactive compounds a normal or even a high level may coexist with clinical hypothyroidism. On the other hand, if it consists mainly of T_3, which is biologically more active than T_4, a normal or even a low level may coexist with clinical hyperthyroidism. This may happen not only after T_3 administration but occasionally in the course of thyroid disease. Thus T_3 as the main circulating thyroid hormone has been reported in a case of non-toxic goitre (Rupp et al 1959) and in others with thyrotoxicosis (Rupp and Paschkis 1961; Shimaoka 1963). A compound resembling T_3 has also been noted in a case of nodular non-toxic goitre by Werner et al (1960b).

Thyroxine binding in the plasma.

The circulating thyroxine is not free in the plasma, but bound with the thyroxine-binding protein (TBP), which moves

electrophoretically between the α_1 and α_2 globulin fractions or Cohn Fraction IV-6 and IV-9 (Gordon et al. 1952; Horst and Rösler 1953; Freinkel et al. 1955) and has an isoelectric point close to pH 4 (Robbins et al. 1955). Thyroxine may also be bound by pre-albumin (Ingbar 1958) and albumin (Sterling et al. 1962). Christensen and Litonjua (1961) reported that the pre-albumin binding is negligible in the normal pH range and therefore of no physiological importance, but more recent work (Hollander et al. 1962) favours the view that pre-albumin has a definite physiological role, and is not simply an artefact produced by certain buffer systems. Blumberg et al. (1961) compared the results of two-dimensional gel and paper electrophoresis of human serum. Thyroxine-binding pre-albumin as seen on paper electrophoresis using an ammonium carbonate buffer is probably identical with band 1 (the fastest moving thyroxine band) in starch gel electrophoresis using a borate buffer, whereas thyroxine-binding globulin corresponds to band 4 of starch gel electrophoresis. This subject remains a difficult one since many technical factors, including the use of various buffers, may influence the in vitro protein binding of the thyroid hormones (Hamolsky and Freedberg 1960; Tata et al. 1961; Van den Schrieck et al. 1961).

The concentration of the thyroxine-binding protein determines to some extent the rate of metabolism of the circulating thyroid hormone since when thyroxine is more firmly bound in the plasma a

smaller proportion undergoes active metabolism (Tata 1960). Thus a small proportion of the total circulating thyroxine, less than 0.1%, is free and not bound to proteins. The proportion of this free fraction is directly related to the total concentration of thyroxine in the plasma and inversely related to the concentration of the thyroxine-binding protein. This free fraction is probably the active form of the hormone (Robbins and Rall 1957) and therefore of greater clinical importance than the PBI. The measurement of free thyroxine, however, is difficult and previous attempts (Christensen 1959, 1960a) have not always given clear-cut results. Recently important progress has been made by Sterling and Hegedus (1962). These authors repeatedly verified the existence of free thyroxine in human serum by dialysis through cellophane: the values were expressed as per cent of total thyroxine concentration of the serum. The mean ± SD for each group were: normal 0.11 ±0.016; thyrotoxicosis 0.23 ± 0.044; hypothyroidism 0.070±0.011; pregnancy 0.058 ± 0.014%.

The influence of thyroxine-binding proteins on PBI levels is illustrated by the alterations during pregnancy. Non-pregnant women have a TBP concentration not significantly different from men (Tanaka and Starr 1959a). The thyroxine-binding protein is increased in pregnancy (Dowling et al. 1956a) and this leads to increased PBI levels (about 2 µg/100 ml above the normal range) although the free thyroxine remains within normal limits; the high

thyroxine-binding protein concentration decreases the proportion of free/total thyroxine, but since the total thyroxine is increased, the absolute amount of free thyroxine presumably remains normal, and the person is euthyroid in spite of the high PBI. The opposite picture is seen after androgen administration which decreases the serum PBI (Keitel and Sherer 1957), but since it also decreases the thyroxine-binding protein concentration in the plasma (Federman et al 1958) the absolute amount of free thyroxine is normal and this explains the persistence of euthyroidism in spite of a low PBI.

Alterations in TBP occur not only physiologically as in pregnancy but also after the administration of certain drugs and in disease. Beierwaltes and Robbins (1959) report the case of a 48 year old male with greatly increased TBP leading to PBI values of 11.8 to 16.0 μg/ml; he was euthyroid, had a normal thyroid uptake and the quantity of thyroxine degraded daily was normal, but the radio-triiodothyronine red cell uptake was low; one of three children of this patient was similarly affected and this points to a familial defect. In another family four members in three generations had increased serum thyroxine-binding capacity and PBI (Florsheim et al 1962). The opposite abnormality, that is, a low PBI due to deficient thyroxine-binding globulin can also occur (Boisel et al 1962).

Drugs which raise the PBI include oestrogens (Engstrom and Markardt 1954). Dowling et al. (1956b) have shown that TBP may also be raised by these substances. Androgens have the opposite effect (Federman et al. 1958). The doses of oestrogens shown to affect the TBP are of the order of 30 mg of stilboestrol daily, which is outside the physiological range. Since there is no sex difference in the PBI or TBP it seems unlikely that they are influenced by variations within the physiological range. A full review of the action of oestrogens and androgens has been presented by Engbring and Engstrom (1959).

Salicylates depress PBI levels and this occurs even in thyroidectomised rats maintained on a constant amount of exogenous thyroxine (Good et al. 1960). This may be related to the finding of Wolff et al. (1961) that salicylates and other drugs which lower the PBI (2,4-dinitrophenol, diphenyl-hydantoin, dl-tetrachlorothyronine) displace T_4 from pre-albumin or thyroxine-binding globulin. These workers however carried out their experiments at a pH of 8.4 which may not be relevant to physiological conditions. Morreale de Escobar and Escobar del Rey (1961a) found in rats that 2,4-dinitrophenol decreases the PBI in serum without decreasing the concentration of iodine compounds in the peripheral tissues, and also (1961b) that 2,4-dinitrophenol increases the uptake of radio-T_4 by erythrocytes. One might interpret these findings as showing a

decreased binding of thyroid hormone by plasma proteins, but this was not the conclusion reached by those authors, since they found in electrophoretic studies (in contradiction to Wolff et al. 1961) that 2,4-dinitrophenol did not change the repartition of T_4 among the various plasma proteins. This, however, does not exclude the possibility that 2,4-dinitrophenol decreases thyroxine-binding by all the proteins uniformly and so the repartition would be the same, although the total binding capacity of the plasma would be diminished.

5,5'-diphenylhydantoin has been reported to displace l-thyroxine from thyroxine-binding globulin in vitro, raise the level of free thyroxine, and increase the red cell uptake of labelled thyroxine (Oppenheimer and Tavernetti 1962). Penicillin has been found to interfere with thyroxine-binding by pre-albumin (Surks and Oppenheimer 1962).

Disease. In hypothyroidism the concentration of TBP is increased (Robbins and Rall 1957; Tanaka and Starr 1959a) but it is unchanged in thyrotoxicosis (Robbins and Rall 1957). Although TBP is usually normal in thyrotoxicosis Cavalieri (1961) reported two sisters, who were thyrotoxic but had a normal PBI level; this was explained by the decrease in thyroxine-binding by the plasma of both these patients and illustrates the statement that the PBI is a good index of thyroid function only when the TBP is within normal

limits. TBP is also increased in hepatic cirrhosis (Tanaka and Starr 1959a). Vannotti and Beraud (1959) have reported that acute liver damage, e.g. infectious hepatitis, raises both the PBI and the thyroxine-binding protein concentration of the serum. In the nephrotic syndrome the PBI is often low although patients are not clinically hypothyroid. This is probably a reflection of the low level of thyroxine-binding which has been demonstrated by Robbins and Rall (1957) and Christensen (1960a).

Triiodothyronine also moves electrophoretically with the inter-α-fraction but it is less firmly bound than thyroxine and a considerable amount is also found in the other protein fractions as well (Dingledine et al. 1955). Christensen (1960b) reports that the proportion of free to total T_3 is 15 times greater than that of thyroxine and this could account for the faster disappearance rate of T_3 from the plasma and its more rapid metabolic effects.

EXCRETION OF IODINE

Iodine is lost from the body chiefly through the kidney and to a lesser extent in the faeces. The amount varies widely: the rate of excretion influences the body stores and the iodine requirements. Urinary iodine is derived from the plasma inorganic iodine whereas faecal excretion is mainly the result of incomplete reabsorption of thyroxine or its conjugates which have passed into the alimentary tract with the bile, although a part may also arise from incomplete absorption of iodine in organic form in foodstuffs. Small amounts are present in sweat (Spector et al 1945; Harden and Alexander 1963). The claim that considerable quantities of iodine escape in the expired air (Salter et al 1949) has not been substantiated (Riggs 1952).

URINARY EXCRETION OF IODINE

Urinary iodine is derived from the plasma inorganic iodine (PII). Iodide is filtered through the glomerular membrane, and part is reabsorbed in the tubules; hence the renal iodide clearance is smaller than the glomerular filtration rate. Williamson et al (1962) used the stop-flow technique to determine the site of renal tubular reabsorption of radioiodine in dogs. In these

circumstances the pattern of radioiodine reabsorption seemed to be qualitatively similar to that of chloride or sodium, although iodide was reabsorbed to a lesser extent in both distal and proximal segments. Large doses of iodide, perchlorate, or thiosulphate did not produce a significant change. These authors concluded that iodide is reabsorbed in both proximal and distal portions of the renal tubule.

Composition of the urinary iodine.

The iodine in the urine of normal persons is almost entirely in inorganic form. This was first shown using chemical methods in 1934 (Elmer and Schops 1934; Davison and Curtis 1939) and was later confirmed by radioisotopic techniques (Albert et al 1949; Albert and Keating 1949, 1952; Myant and Pochin 1950; Rall 1950; Berger and Peyrin 1957). Even injected MIT and DIT appear in the urine normally as iodide (Stanbury et al 1956a) and it is now accepted that almost all of the urinary iodine is in the form of iodide (Riggs 1952; Pitt-Rivers and Tata 1959).

It must be noted, however, that iodine compounds may be present in the urine in organic form in special circumstances. Thus a large amount may be demonstrated in the urine of persons with goitre due to dyshormonogenesis and especially in the type due to deiodinase deficiency (p223). Smaller quantities of organic compounds may be found in thyrotoxicosis (Rall 1950; Berger and Peyrin 1957). Also, after the ingestion or injection of non-hormonal organic iodine compounds, for instance after cholecystography or pyelography,

much iodine appears in the urine in organic form. To detect such cases we have used a resin column to divide the urinary iodine into organic and inorganic fractions (p22). At the moment this method is not sufficiently accurate to give quantitative results but it is a useful screening procedure. It serves to detect cases in which organic iodine compounds are present in more than trace amounts and where PII estimation based on the specific activity of the urinary iodine would be inappropriate. Our method is similar in principle to that used by Fletcher (1957) for the separation of radioactive iodine compounds in the urine.

Quantity of the urinary iodine.

The "normal" amount of iodine excreted in the urine in 24 hours varies greatly from individual to individual and from region to region depending on the dietary intake of iodine. Thus it is greater where much fish is consumed or where the household salt is iodised and it is lower in places where iodine deficiency is prevalent. Von Fellenberg (1926), a pioneer in the investigation of iodine metabolism, found a mean daily urinary output of 17 and 19 µg iodine in the goitrous regions of Munzenschwil and Koisten respectively, but 112 µg/day in Forte dei Marmi where goitre was absent. In Ohio Curtis et al. (1937) found a range of 7 to 196 with a mean of 51 µg/day, which they compared with means ranging between 27 and 64 µg/day, recorded by other authors in other goitrous regions, and means between 72 and 343 µg/day, recorded

in goitre-free regions. A more extensive review has been published by McClendon (1939) which also showed a negative correlation between the prevalence of goitre in a community and the 24 hour urinary iodine excretion. Riggs (1952) who compiled his data from the literature concluded that in regions free from endemic goitre the overall mean urinary iodine excretion was 150.3 µg/24 hr.

The normal 24 hour excretion of iodine in our cases has ranged from 33 to 171 µg of iodine daily, although one apparently normal subject with a low PII of 0.06 µg/100 ml had a 24 hour urinary excretion of only 25 µg/day. These values show that most of our normal cases had values rather lower than the mean iodine excretion found in the U.S.A. and this is probably due to the widespread use of iodised salt in North America.

Relation between urinary iodine and plasma inorganic iodine (PII).

There is no doubt that the 24 hour urinary excretion of iodine is a valuable index of iodine deficiency and has been successfully used for this purpose in several studies. However for the study of individual cases the PII seems better. These parameters correlate well, but exceptions exist since the PII bears in addition an inverse relation to the renal clearance of iodide (p119). Fig2.11 shows the observed relation between the PII

Table 2.11

Plasma inorganic iodine and 24 hour urinary excretion of iodine in 37 patients

No.	Name	Plasma inorganic iodine µg/100 ml	24 hr urine excretion of iodine µg	Other details
Normal thyroid function				
1	J.P.	0.25	75	Table 2.2
2	J.R.	0.34	99	" "
3	D.D.	0.35	61	" "
4	E.M.	0.39	171	" "
5	M.S.	0.14	44	" "
6	J.B.	0.16	87	" "
7	C.W.	0.57	104	" "
8	C.D.	0.11	40	" "
9	D.C.	0.25	151	" "
10	S.B.	0.18	87	27 yr M. medical staff
11	M.G.	0.16	46	Table 2.2
12	T.F.	0.18	97	" "
13	J.F.	0.14	51	" "
14	S.C.	0.18	59	" "
15	J.O.	0.14	33	" "
16	J.G.	0.94	181	Had taken KI mixture
Simple goitre				
17	M.M.	0.07	34	Table 4.3
18	I.M.	0.19	92	" "
19	E.F.	0.04	44	" "
20	E.G.	0.10	87	" "
21	E.D.	0.02	70	" "
22	A.G.	0.02	56	" "
23	E.W.	0.06	30	" "
24	V.P.	0.04	23	" "
25	J.S.	0.01	15	" "
26	A.M.	0.06	56	" "
27	E.D.	0.04	63	" "
28	J.R.	0.12	53	64 yr F. Th.Cl.41 ml/min goi. 75 g.
29	M.M.	0.03	56	19 yr M. Th.Cl. 179 ml/min goi. 75 g.
Thyrotoxicosis				
30	M.W.	0.28	101	Table 4.1
31	E.A.	0.13	40	" "
32	H.S.	0.02	10	" "
33	J.M.	0.08	53	" "
34	A.K.	0.46	153	3 4 yr F. PBI 9.8 µg/100 ml
35	M.M.	0.32	80	27 yr F. PBI 12.4 µg/100 ml
36	A.G.	0.65	155	19 yr F. PBI 9.2 µg/100 ml
37	M.L.	0.01	6	26 yr F. PBI 7.9 µg/100 ml

PLASMA INORGANIC IODINE AND 24 HOUR URINARY EXCRETION OF IODINE

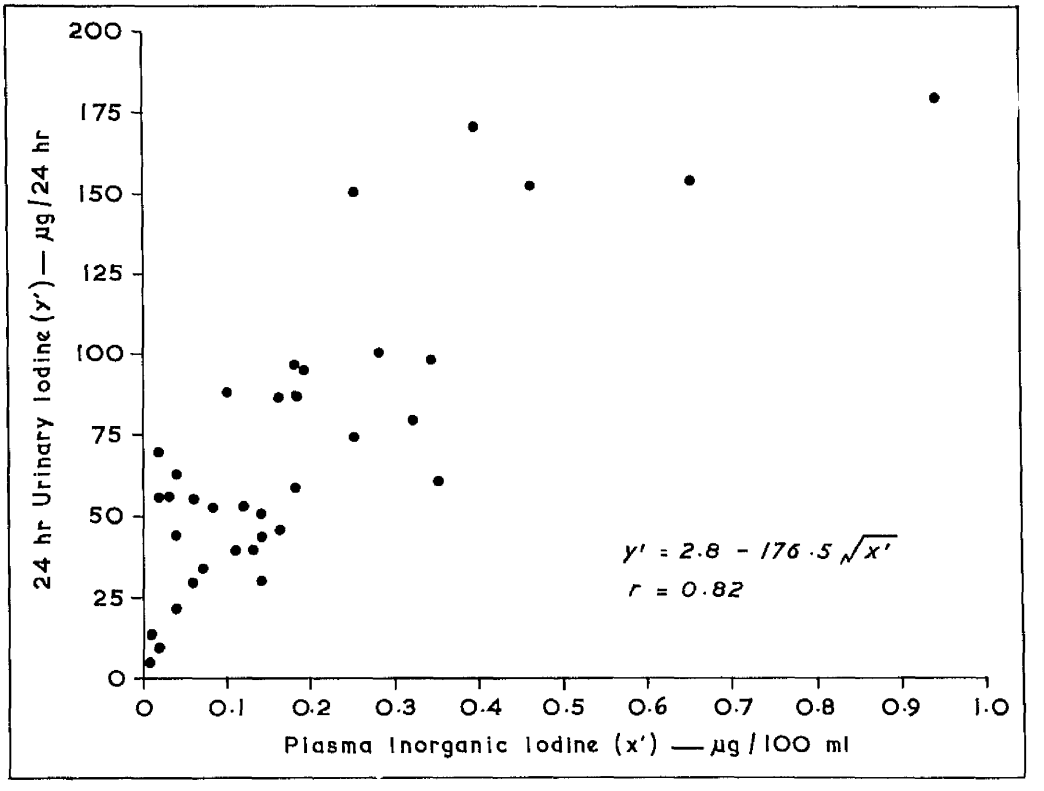

Figure 2.11

Relation between the plasma inorganic iodine and the 24 hour urinary excretion of iodine

The results obtained in 37 patients show a very significant correlation ($r = 0.82$, $p < 0.001$), but it is not a straight-line relation.

and the 24 hour urinary iodine excretion in 37 of our patients (Table 2.11). There is obviously a highly significant relation ($p<0.001$), but not a straight line one. This lack of linearity is due to two factors. First, patients with a low PII have on the average a slightly higher renal clearance, and this results in agreater proportional decrease in PII than in the 24 hour urinary iodine excretion. Secondly, the 24 hour urinary excretion is proportional to the mean PII level of the patient throughout the day, whereas the PII recorded by us is the fasting one. The fasting PII may differ slightly from the mean daily PII, and this would again distort the linear relation. Since the reported mean renal clearance rates of iodide do not differ from one country to another the mean 24 hour urinary excretion of sufficiently large groups will bear a close and linear relation to the mean PII in each group. However since there are wide variations in the renal clearance of individuals, iodine deficiency in an individual case can be deduced more accurately from the PII than from the 24 hour urinary excretion.

RENAL IODIDE CLEARANCE

The rate at which the plasma is cleared of iodide by the kidneys can be calculated from the Van Slyke clearance formula using the radioactivity of the plasma and urine as an index of the relative concentrations of iodide in these two body fluids. The concentration of radioiodide in the plasma after a tracer dose does not remain constant, but falls with time and the effect of this on the calculation of the renal clearance has been discussed by Berson et al (1952) and Alexander et al (1962). The formula and technique which we have used are described in Chapter 1.

Table 2.12 shows the results obtained in normal subjects by different authors. The standard deviation usually given is not entirely appropriate since the distribution is of lognormal rather than normal type. Table 2.13 shows our renal iodide clearance determinations in 23 male and 23 female subjects, none of whom had evidence of thyroid or renal disease. Males on the whole had higher values ($p < 0.001$) presumably because of their larger body size. The clearance was not related to age except that lower values were found over the age of 60, both in males ($p < 0.02$) and females ($p < 0.01$). If we define the normal range of renal clearance as the mean $\pm$ 2 S.D. (after logarithmic conversion) we obtain a range of 14.7 to 58.5 ml/min (Alexander et al 1962). In practice we have adopted 15.0 to 55.0 ml/min as our normal range and this includes

Table 2.12

Renal clearance of iodide. Normal values quoted in the literature, in ml/min.

Author	No. of cases	Mean	S.D.	S.E.	Range
Myant et al. 1950	7	31.0			11.0 to 44.0
McConahey et al. 1951	9	35.3		3.1	
Berson et al. 1952	87				10.6 to 69.0
Perry and Hughes 1952	11	31.4		2.0	
Cassano et al. 1957 a, b	5	35.0	6.9		
Author's study	46	31.1	11.2	1.7	11.7 to 61.8

Note: The distribution is not statistically a normal one, and the use of the S.D. is therefore not entirely appropriate.

Table 2.13

Normal renal clearance values in ml/min grouped according to age and sex.

Age	Males (23 cases) mean ± S.E.	Females (23 cases) mean ± S.E.	Total (46 cases) mean ± S.E.
0 - 19	27.0	31.5 (30.2 - 32.7)	30.0 ± 1.62 (27.0 - 32.7)
20 - 39	40.6 ± 3.67 (25.9 - 61.8)	25.0 ± 5.80 (15.7 - 41.3)	35.8 ± 3.62 (15.7 - 61.8)
40 - 59	38.8 ± 3.53 (17.9 - 55.8)	28.4 ± 2.06 (19.0 - 37.4)	33.3 ± 2.29 (17.9 - 53.8)
60 -	27.2 ± 2.25 (21.0 - 30.8)	19.3 ± 3.41 (11.7 - 30.5)	22.2 ± 2.52 (11.7 - 38.5)
Total	36.9 ± 2.25 (17.9 - 61.8)	25.3 ± 1.80 (11.7 - 41.3)	31.1 ± 1.66 (11.7 - 61.8)

The observed range is shown in brackets below the mean ± S.E.

The individual values are shown in Table 2.1.

44 of 46 normal cases.

Factors influencing the renal iodide clearance.

Bricker and Hlad (1955) established that the renal iodide clearance was unaffected by increased rates of urine flow and was independent of the clearance of sodium, chloride and potassium. The same authors (Hlad and Bricker 1954) have reported a linear relationship between renal iodide clearance and glomerular filtration rate. The high values of renal clearance found in hyperthyroidism and the low in hypothyroidism could be explained in this way. Low renal iodide clearances have been found in renal insufficiency by McConahey et al. (1951) and by Perry and Hughes (1952). These last authors suggested that the decreased renal clearance in patients with renal insufficiency was due both to decreased glomerular filtration rate and to increased tubular reabsorption. A decreased renal iodide clearance has been reported in the nephrotic syndrome (Fiaschi et al. 1959).

Cassano et al. (1957a, b) found increased renal iodide clearances during puberty, in pregnancy, and in hyperthyroidism, acromegaly and Cushing's syndrome, and decreased values in hypothyroidism, hypopituitarism and renal disease. These observers suggest that an increase in renal iodide clearance which may be of familial origin may lead to a low PII and so to iodine deficiency goitre. This subject is discussed more fully in Chapter 4 where it is concluded that although a high renal clearance of iodide is a rare cause of iodine-deficiency goitre per se, it is nevertheless a significant contributory factor in many

persons on a low-normal dietary iodine intake.

If an increased renal clearance of iodine is contributing to the production of iodine-deficiency goitre it is clearly desirable to know what factors influence it. Decreased clearance of iodide has been reported in patients taking a low-salt diet and conversely the clearance is said to be increased by an increase in sodium chloride intake (Baschieri et al. 1958, Cassano et al. 1959a, b). A diminished renal iodide clearance was found in rats after protein starvation (Aschkenasy and Guerin 1960), and it was suggested that this is the cause of the high plasma radioiodine values observed under similar conditions (Aschkenasy et al. 1959).

Animal experiments have shown an increase in renal clearance after administration of propylthiouracil (Brown 1956), and a similar effect has been also suggested for perchlorate (Halmi et al. 1956) and calcium (Simpson 1947). However, Malamos and Koutras (1962) did not find any increase in the renal iodide clearance in man after administration of calcium (both acute and chronic administration), potassium perchlorate, carbimazole, and sodium chloride.

It is theoretically possible that some antithyroid drugs or natural goitrogens may, in addition to their direct effect on the thyroid, induce an iodine-deficiency state through a renal leak of iodine, but there is no good evidence of this at present.

EXCRETION OF IODIDE IN THERMAL SWEAT

Information regarding the iodide content of human sweat is very scanty, mainly because of the technical difficulties involved in measuring the very small quantities of iodide normally present. Spector et al. (1945) attempted to measure the iodide content of sweat in four subjects using direct chemical assay, but did not relate it to plasma levels. Nelson et al. (1947) gave eight subjects large doses of iodide and were thus able to raise the sweat and plasma iodide to levels measurable by chemical methods. After administration of I^{131} to children, Brodkey and Gibbs (1960) found a lower concentration of radioiodine in the sweat than in the plasma. Such isotopic measurements permit only the relative amounts of iodide in the sweat and in the blood to be determined. Using a combination of chemical and radioisotopic techniques, similar in principle to that employed to estimate the plasma inorganic iodine (PII), it is possible to make a much more complete study of iodide excretion in the sweat. In this way the iodide excreted in sweat (SI) in µg/hr can be measured, and related to the PII concentration and to the iodide lost in the urine during the same time interval.

Methods

Theoretical considerations

Sweat is formed from a precursor fluid similar in composition

to plasma (Bulmer and Forwell, 1956). Since the sweat glands and tubules cannot distinguish between radioactive and stable iodine atoms, the specific activity of the iodide (proportion of the radioactive to total iodide atoms) in the sweat is the same as the specific activity in the plasma.

$$1 \qquad \frac{I^{132}\ \text{sweat}}{SI} = \frac{I^{132}\ \text{plasma}}{PII}$$

The plasma inorganic iodine is normally too small to be measured chemically but can be calculated indirectly from measurements of urinary iodide (p. 11).

$$2 \qquad \frac{I^{132}\ \text{plasma}}{PII} = \frac{I^{132}\ \text{urine}}{\text{Urinary iodide}}$$

and

$$3 \qquad \frac{I^{132}\ \text{sweat}}{SI} = \frac{I^{132}\ \text{urine}}{\text{Urinary iodide}}$$

Subjects studied

The main group of subjects studied was eleven ward patients, all having PII concentrations within the physiological range of 0.03 - 0.60 µg/100 ml.

Physical data for these subjects are shown in Table 2.14

To validate the specific activity method a further seven euthyroid ward patients were given potassium iodide orally, in doses ranging from 1 to 25 mg for 24 hours prior to the period of sweating. The plasma and sweat iodide were thus raised to levels at which conventional chemical methods of assay could be used in addition to measurement by the specific activity method.

Table 2.14

Physical data

Patient	Sex	Age (yr)	Height (cm)	Weight (kg)	Surface area* (sq metres)
1	M	59	164	67	1.72
2	M	48	166	77	1.84
3	M	64	170	74	1.85
4	M	53	174	78	1.92
5	M	27	163	102	2.09
6	M	69	157	81	1.82
7	M	65	165	67	1.74
8	F	45	155	51	1.48
9	F	60	165	71	1.78
10	F	41	163	54	1.57
11	F	49	159	60	1.61

* Surface area predicted by Du Bois's formula.

Procedure

A tracer dose of 100 μc of radioiodine (I^{132}) was given orally with the subject fasting. One hour later the subject was covered with two woollen blankets and one electric blanket in a bed which had been preheated. During the subsequent two hours sweat was collected in polythene bags placed round the arms to the axillae and round the legs to the knees. The volume of sweat was calculated for each arm and leg from the difference in weight of the polythene before and after sweating (1.0 G = 98 ml). The bags and liquid were counted in a well-type scintillation counter and the % dose I^{132}/ml sweat was calculated. The sweat was subsequently filtered and its urea content estimated by the method of Skeggs (1957). Urine was collected over the same 2 hour period and its radioactivity and chemical iodine content were measured. Chemical estimation was by the chloric acid digestion method (Farrell and Richmond, 1961) omitting resin column treatment. The concentration of iodide in the sweat (SI) was calculated from equation (3)

$$SI(\mu g/100\ ml) = \frac{\%\ dose\ I^{132}/ml\ sweat \times urinary\ iodide(\mu g/100\ ml)}{\%\ dose\ I^{132}/ml\ urine}$$

Plasma radioactivity was measured at the midpoint of sweating and the PII was calculated (p 17). Plasma radioactivity at this time can be assumed to be entirely due to inorganic iodine and to be the mean radioactivity of the plasma over the period of sweating (p13). Weiner (1945) has shown that the volume of sweat excreted by the area enclosed in polythene (arms and legs from feet to knees) is 26% of the whole

body sweat, thus one can calculate the total quantity of body sweat excreted in our subjects. The plasma iodide clearance to sweat was calculated from the formula:-

$$\text{Sweat clearance (ml min)} = \frac{\text{Total body sweat (ml)} \times \%\ \text{dose } I^{132}/\text{ml sweat}}{\%\ \text{dose } I^{132}/\text{ml plasma} \times \text{time of sweat collection(mins)}}$$

The volume of urine excreted during the 2 hour period was measured and the renal excretion of iodide and renal clearance of iodide were calculated (p 18).

Results

The results are shown in Tables 2.15-2.17 and Figs. 2.12 and 2.13. All values are expressed as mean ± standard error of mean. Preliminary observations designed to test the validity of the specific activity method are shown in Fig. 2.12. In the seven subjects given iodide supplements a close linear correlation ($r = 0.99$, $p < 0.001$) was found between simultaneous direct chemical and indirect radioisotopic estimations of the sweat iodide. The agreement between the concentration of iodide in the sweat from opposite arms and from opposite legs in the same subject, $p < 0.001$ (Table 2.15), is further confirmation of the reproducibility of the method.

The concentration of iodide in the sweat was 0.167 ± 0.035 µg/100 ml. The rate of sweating from the arms and legs of the subjects ranged from 30 to 203 ml per 2 hrs, mean 90.5 ± 16.9 ml. There

Table 2.15

Sweat iodide excretion

	Sweat vol. (ml)					Sweat iodide (µg/100 ml)					Iodide excreted(µg/2hr)				
Patient	*RA.	LA.	RL.	LL.	Total	RA.	LA.	RL.	LL.	Mean	RA.	LA.	RL.	LL.	Total
1	51.0	56.0	43.4	52.5	202.9	.08	.08	.07	.07	.08	.041	.045	.030	.037	.153
2	23.8	22.8	10.4	10.6	67.6	.27	.25	.17	.17	.23	.064	.057	.018	.019	.158
3	15.3	11.6	3.0	4.5	34.4	.19	.16	.13	.14	.17	.029	.019	.004	.006	.058
4	11.2	4.2	6.0	8.6	30.0	.38	.49	.31	.28	.35	.043	.021	.019	.024	.107
5	39.8	27.8	42.8	35.8	146.2	.02	.03	.06	.02	.03	.006	.008	.025	.007	.046
6	27.2	25.8	23.1	23.4	99.4	.24	.24	.20	.23	.22	.065	.062	.046	.054	.227
7	18.8	20.2	10.5	10.6	60.0	.34	.26	.38	.38	.31	.064	.053	.040	.040	.197
8	11.8	12.5	-	-	-	.13	.18	-	-	.16	.015	.023	-	-	-
9	12.0	12.8	32.3	36.8	93.9	.12	.17	.16	.14	.15	.014	.022	.052	.052	.141
10	18.7	21.2	31.3	39.3	110.4	.11	.09	.05	.06	.07	.021	.019	.016	.024	.080
11	5.0	11.5	22.2	21.6	60.3	.07	.06	.06	.07	.06	.003	.007	.013	.015	.038
Mean	22.28	21.39	22.50	24.37	90.51	.182	.183	.159	.156	.167	.0350	.0313	.0263	.0278	.1205
S.E. of the mean	4.42	4.50	4.67	5.09	16.9	.039	.043	.036	.036	.035	.0076	.0065	.0049	.0055	.0205

* RA = Right Arm, LA = Left Arm, RL = Right Leg, LL = Left Leg. (Case 8 omitted from calculations).

Table 2.16

Sweat iodide and plasma inorganic iodine

Patient	Sweat Iodide (SI) µg/100 ml	Plasma Iodide (PII) µg/100 ml	SI / PII	Sweat Iodide Clearance ml/min
1	.08	.21	.38	2.60
2	.23	.33	.70	1.66
3	.17	.20	.85	1.01
4	.35	.52	.67	0.73
5	.03	.33	.10	0.48
6	.22	.35	.63	2.18
7	.31	.43	.72	1.50
8	.16	.29	.55	0.62
9	.15	.19	.79	2.60
10	.07	.10	.70	2.60
11	.06	.15	.43	0.83
Mean	.167	.201	.589	1.53
S.E. of mean	.033	.038	.066	0.26

Table 2.17

Comparison between urine and sweat excretion of iodine

Patient	Estimated total sweat iodide excretion µg/2 hr	Urine Vol. ml/2 hr	Urine Iodide excretion µg/2 hr	Sweat Clearance ml/min	Renal Clearance ml/min	Sweat iodide excretion / Urine iodide excretion
1	0.63	86	7.74	2.60	30.7	0.08
2	0.65	698	26.94	1.66	53.2	0.03
3	0.24	220	11.00	1.01	46.8	0.02
4	0.41	190	16.34	0.73	26.1	0.03
5	0.19	143	12.16	0.48	30.2	0.02
6	0.95	104	10.40	2.18	24.8	0.09
7	0.82	99	21.78	1.50	42.4	0.03
8	0.31	280	9.52	0.62	27.2	0.02
9	0.58	312	15.60	2.60	67.0	0.04
10	0.33	320	6.08	2.60	49.2	0.05
11	0.16	233	8.62	0.83	48.0	0.02
Mean	0.479	244.1	13.29	1.53	40.51	0.039
S.E. of mean	0.080	52.0	1.92	0.26	4.12	0.007

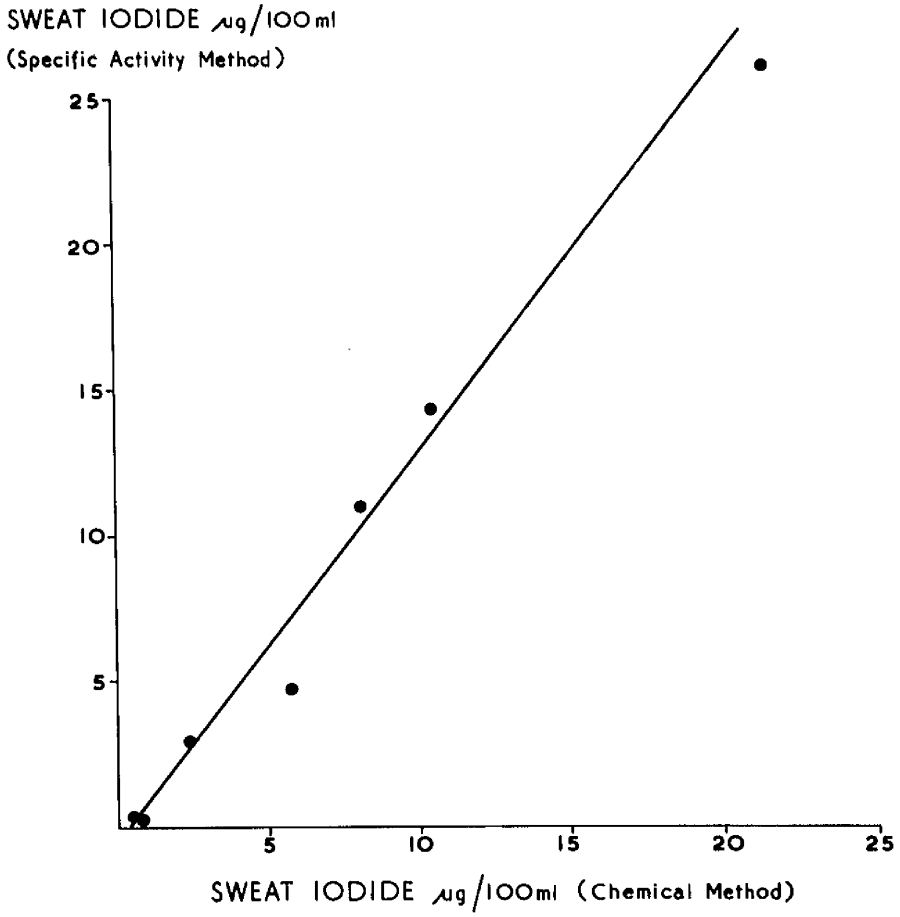

Figure 2.12

Comparison of direct and indirect estimations of the sweat iodide concentration

There is a very significant correlation.

Regression equation: $y = 0.51 + 1.28x$

$r = 0.99$

$p < 0.001$

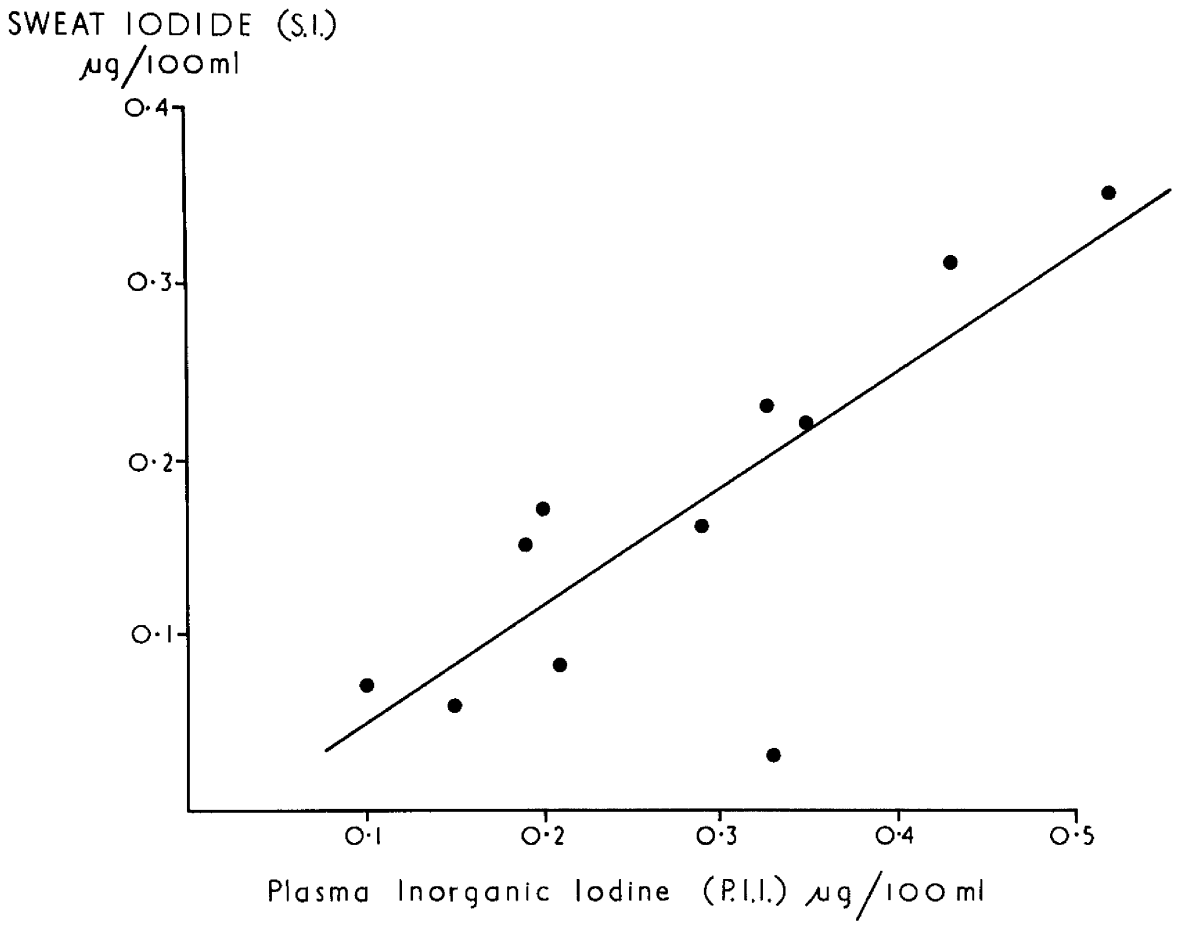

Figure 2.13

Relation between plasma inorganic iodine and the sweat iodide concentration

Regression equation: $y = 0.66x - 0.02$

$r = 0.76$

$p < 0.01$

was no significant difference between the volume of sweat excreted from one arm compared with the other, and from one leg compared with the other leg. The mean iodide excretion from arms and legs per 2 hours was 0.121 ± 0.0205 µg. The relation between SI and PII is shown in Table2.16 and Fig.2.13. The regression equation is $y = 0.66x - 0.02$, $r = 0.76$ $p < 0.01$. The ratio SI/PII was 0.59 ± 0.06, range 0.10 to 0.85. The sweat clearance of iodide was 1.53 ± 0.26 ml /min. The loss of iodide in the sweat varied from 2 to 9% of that excreted in the urine.

Discussion

Discussion

There are two possible sources of error in estimations of the iodide concentration in sweat. The first difficulty is the accurate collection of the sweat, the second lies in the measurement of the very small quantity of iodide present in the collected sweat. Sweat collected from the arms can be assumed to be representative of whole body sweat (Johnston et al 1944; Ladell 1948). Although Ladell (1948) found sweat collected in polythene bags to be of a similar concentration to sweat obtained by body washings, it has been suggested that sweat collected in bags is more concentrated (Dill et al 1938; Kleeman et al 1953; Van Heyningen and Weiner 1952). One possible explanation is that water vapour condensing on the polythene is inadequately mixed

with the remainder of the sweat. This is especially likely in experiments where sweat is repeatedly drained from the bag in the course of the experiment. On the other hand, measurement of total body sweat loss by washings may give falsely low values because of incomplete collections. These sources of error are eliminated using the method we describe; the concentration of sweat iodide is calculated from the total iodide present as measured radioisotopically, and the volume of \sweat is measured by bag weighings. Direct chemical measurement of the iodide concentration in sweat and plasma is inaccurate at physiological levels. Specific activity methods have been applied to the measurement of the plasma iodide (p 11), and this method can equally well be applied to measurement of the sweat iodide. An additional advantage of a radioisotopic method is that any exogenous iodine in the skin, contaminating the sweat, is not measured.

In the present experiment at the highsweat rate induced, the iodide losses in the sweat over the 2 hour period was 0.479 ± 0.090 µg /100 ml. This was 2 to 5% of the urinary iodide excretion over the same period, and compares with an optimal daily intake of about 160 µg to 200 µg (p 155). The loss of iodide in the sweat at least in temperate climates is therefore insignificant.

We have shown that the sweat iodide is related to the plasma iodide, the ratio SI/PII being 0.10 to 0.85 with a mean of 0.59. This is somewhat higher than the ratio 0.05 to 0.36, mean 0.17 obtained by

Brodkey and Gibbs (1960) in normal children by measuring the radioactivity in sweat and plasma after a tracer dose of radioiodine. However, we have found that considerable quantities of radioactive iodine may be lost by adsorption on to polythene or glass surfaces and this may partly account for their lower figures since in the description of their method no mention was made of this adsorbed radioactivity. On the other hand, as Brodkey and Gibbs suggest, the concentration of iodide in sweat may vary with age.

Summary

The concentration of iodide in thermal sweat (SI) has been measured in 11 subjects with normal plasma inorganic iodine levels (PII) using a combination of chemical and radioisotopic techniques and was found to be 0.17 ± 0.033 µg/100 ml.

Sweat iodide clearance was 1.53 ± 0.26 ml/min.

The ratio of sweat iodide/plasma iodide concentration varied between 0.10 and 0.85 (mean 0.58).

The loss of iodide during severe sweating varied between 2% and 9% of that excreted in the urine. It is concluded that in temperate climates loss of iodine in the sweat is not an important factor in producing a state of iodine deficiency.

Chapter 3 - IODINE REQUIREMENTS IN MAN

Chapter 3 - IODINE REQUIREMENTS IN MAN.

Various methods are available to determine the requirements of essential dietary constituents in man. If the intake is known and the excretion in the urine, faeces, sweat and breath can be measured, a balance can be calculated. It can reasonably be assumed that a negative balance of an essential nutrient cannot be sustained over a long period without depletion of body stores and ultimate ill health. Alternatively if it is known that a detectable abnormality results from long continued deficiency of a given substance, a survey of the dietary intake in patients with and without the abnormality may give a clue to the minimum requirement of the nutrient.

Dietary Intake.

The evaluation of the iodine intake of an individual is notoriously difficult since, in addition to the general difficulties of diet surveys, the iodine content of the same food varies considerably depending on the place and season in which it is produced. It is therefore necessary to have available the results of recent analyses of the major iodine-containing food items in the locality in which the survey is carried out. For instance, feeding chickens with fish may raise the iodine content of both poultry and eggs. Direct analysis of the food consumed in a metabolic ward is more accurate but is still very unsatisfactory if the information desired is the iodine intake

under normal conditions, and not that in a metabolic ward.

The calculation of the iodine intake, using a diet history in conjunction with tables giving average iodine content of foodstuffs, is subject to large errors. Nevertheless, statistically valid comparisons can be made if groups of patients from the same locality are adequately randomised and investigated in the same way. Thus even if the figures are not accurate in an absolute sense, they are useful as evidence of differences between groups.

Sea food is the only really rich source of iodine, and since its consumption varies markedly from subject to subject according to individual preferences and from community to community according to general availability, it is obvious that differences in iodine intake in areas in which iodine is not added to the salt are to an important extent due to differences in fish consumption. Thus the high prevalence of goitre in mountainous regions is due not only to the low iodine content of the locally grown food but also to the scarcity of sea fish (Lidgas 1953). Nevertheless milk and eggs also contain significant amounts of iodine, and therefore persons not taking either fish or iodised salt do not necessarily develop an iodine deficiency state.

The Chilean Iodine Educational Bureau (1952) has calculated from figures provided by the British Ministry of Food that the average urban working-class diet in Britain contains 565 µg of iodine per week or 80 µg per day. This figure is lower than the one obtained

from our dietary surveys in Glasgow and also much lower than what we consider to be the optimal amount (p155).

Our Glasgow survey was based on diet histories taken by Miss I. Dallas, dietician to the Western Infirmary. The iodine content of the diet was calculated from Tables 3.1 and 3.2, and for other food items the tables of the Chilean Iodine Educational Bureau (1952) were used. We recorded the average dietary iodine intake of 67 normal subjects, 24 males and 43 females (Table 3.3) and found the mean to be 290 ± 19.3 µg/day. This figure is much higher than the estimate previously mentioned and comparison with the 24 hr urinary iodine excretion shows that our estimation of the dietary iodine intake is unduly high. Dietary intake of iodine in equilibrium equals excretion of iodine, and as we have seen, the greater part of this is in the urine. One would expect, therefore, to find the dietary intake alittle higher than the 24 hr excretion of iodine. This is not the case in our survey and we believe that the discrepancy between dietary intake and urinary iodine excretion should be attributed to a systematic overestimation in the diet history and not an underestimation of the 24 hr urinary iodine excretion. We have good evidence about the reliability of the urinary iodine estimation (Richmond 1962). On the other hand, diet histories are subject to the following inaccuracies: (1) measurement of the iodine content of the food is subject to greater technical error than measurement of urinary iodine. (2) The iodine content of food may vary considerably from sample to sample (Richmond 1962). (3) It is difficult to be sure about the iodine concentration of food

Table 3.1

Iodine content of food obtained in Glasgow

	No. of samples tested	Mean µg/kg	Range µg/kg
Milk	10	64	26 - 134
10.3.61	2	127	124 - 133
26.4.61	2	76	75 - 78
24.5.61	2	46	46 - 47
11.9.61	2	27	26 - 29
Eggs (whole)	5	247	142 - 373
Fish			
Haddock	3	8250	6590 - 9860
Herring	4	400	210 - 700
Whiting	7	1750	650 - 3610
Mussels	1	850	
Food additive (alginate)			5300 - 92,000

Table 3.2

Average iodine content of some everyday foods

These figures are the means of selected figures from the Tables in "Iodine Content of Foods", Chilean Iodine Educational Bureau (1952). The observations described on p.140 indicate that use of the Table overestimates the dietary intake of iodine.

TABLE 11. *Average iodine content of some everyday foods*

	Iodine content (μg/kg)	
	Fresh basis	Dry basis
MILK & MILK PRODUCTS		
Milk (cow's)	35	
Cheese	51	
Butter	56	
Mean	47	
EGGS		
Hen's eggs Mean	93	
MEAT & MEAT PRODUCTS		
Mutton	27	
Beef	28	
Veal	28	
Pork	45	
Bacon	77	
Lard	97	
Mean	50	
FISH		
(i) Marine Fish		
Sole	163	1072
Sea bass	250	471
Sardines	284	745
Mackerel	371	1031
Halibut	520	2225
Herring	520	1358
Sea perch	742	3105
Cod	1463	7493
Haddock	3180	15941
Mean	832	3715
(ii) Anadromous Fish		
Sea trout	330	1028
Salmon	341	1030
Mean	330	1029
(iii) Freshwater Fish		
Carp		68
River bass	71	115
Lake trout		88
River perch	40	194
Mean	30	116
FISH OILS		
Salmon oil	2450	
Cod-liver oil	8387	
All others taken together	3052	
Mean	4630	

	Iodine content (μg/kg)	
	Fresh basis	Dry basis
SHELL FISH		
Crab and crabmeat	308	1292
Oysters	577	4712
Clams	783	3595
Lobster	1020	4744
Shrimps	1300	4987
Mean	798	3866
CEREAL GRAINS & PRODUCTS		
Rice	22	39
Maize	27	43
Wheat	37	44
Flour	42	
Bread	58	
Barley	58	92
Oats	60	91
Rye	72	84
Mean	[illegible]	65
VEGETABLES		
Mangolds	11	192
Gourds, pumpkins, marrow	12	660
Cauliflower	12	[illegible]
Beetroot	21	233
Onions	22	204
Cucumber		400
Lettuce		668
Carrots		[illegible]
Turnips	[illegible]	343
Asparagus	42	[illegible]102
Potatoes	45	[illegible]
Cabbage	52	[illegible]
Spinach (* [illegible] from the	201	1636
*	29	385
LEGUMES		
Peas	23	223
Beans	36	245
Mean	30	234
FRUITS		
Pears	10	[illegible]
Tomatoes	17	[illegible]96
Apples	16	277
Cranberries	29	100
Mean	18	159

Table 3.3a

Dietary iodine intake in μg/day in normal males*, estimated from diet history

20 - 39 yr	40 -59 yr	60 - 81 yr
357	359	236
406	229	80
232	231	288
	359	284
	518	410
	287	75
	60	412
	399	
	340	
	480	
	478	
	609	
	256	

* These subjects were relatives and visitors of ward patients. They were unselected except insofar as they volunteered for the study.

Table 3.3b

Dietary iodine intake in µg/day in normal females*, estimated from diet history

20 - 39 yr	40 - 59 yr		60 - 79 yr
144	320	244	215
257	360	401	220
245	328	275	38
467	400	48	316
336	237	209	308
215	522	200	442
	374	222	102
	348	228	
	1069	282	
	192	131	
	223	173	
	251	260	
	308	260	
	554	331	
	241	262	

* These subjects were relatives and visitors of ward patients. They were unselected except insofar as they volunteered for the study.

items not analysed in Glasgow, but taken from tables, since the same food item may show considerable variation (Chilean Iodine Educational Bureau 1952). (4) Diet histories in themselves carry a considerable error. For these reasons the figures obtained from diet surveys, ours and others, have a wide margin of error.

With these limitations in mind we may compare the dietary iodine intake of various groups, although the figures recorded should not be accepted in an absolute sense. Males on the whole seem to ingest more iodine then women (Table 3.4). The difference is not statistically significant ($p<0.3$) but since the difference is found in all age groups it seems likely that it is real. It may be due to the larger caloric intake of men. Subjects over 60 years of age seem to take less iodine ($p<0.2$).

The great individual variations in iodine intake are shown in Fig 3.1 which compares the iodine intake of normal subjects and patients with simple goitre from the same district. The latter lies at the lower end of the normal distribution curve (see also p205).

Calculation of iodine requirements based on epidemiological data.

The assessment of iodine requirements in man is difficult. It has been assumed that the minimum iodine requirement is that amount of iodine which will prevent the occurrence of iodine-deficiency

Table 3.4

Dietary iodine intake in µg/day in normal subjects according to age and sex

Age	Males (24 cases)	Females (43 cases)	Total (67 cases)
20 - 39	332 (232 to 406)	277 ± 46.8 (144 to 467)	295 ± 34.2 (144 to 467)
40 - 59	354 ± 40.4 (60 to 609)	308 ± 32.0 (48 to 1069)	322 ± 26.7 (48 to 1069)
60 -	269 ± 46.8 (75 to 412)	234 ± 51.5 (38 to 442)	253 ± 34.9 (38 to 442)
Total	323 ± 28.0 (60 to 609)	273 ± 26.6 (38 to 1069)	290 ± 19.3 (38 to 1069

The range is shown in brackets below the mean ± S.E.

The individual values are shown in Tables 3.3a and 3.3b.

MEAN DAILY IODINE INTAKE IN NORMAL SUBJECTS AND PATIENTS WITH SIMPLE GOITRE

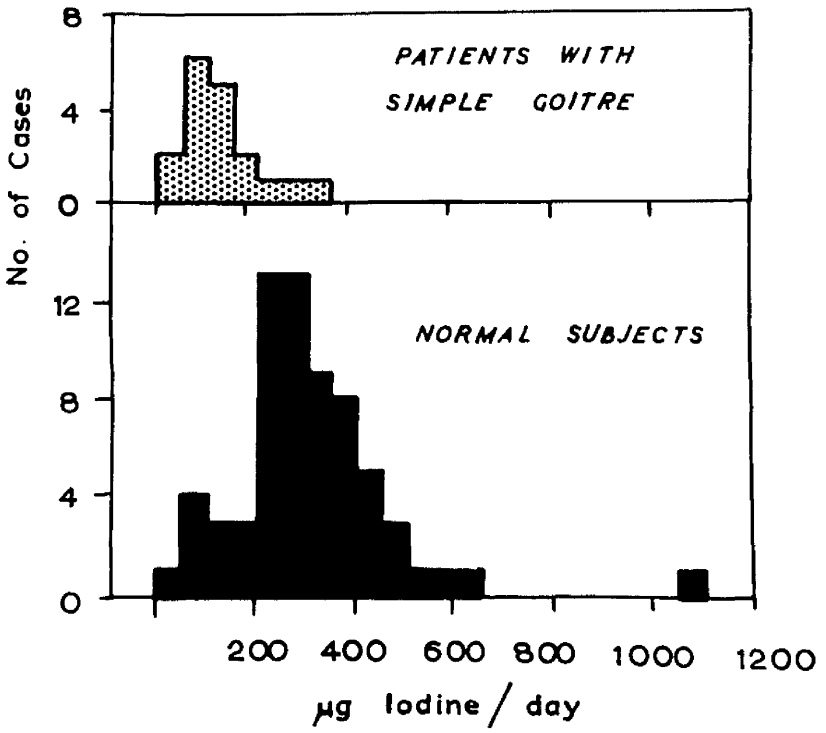

Figure 3.1

Mean daily iodine intake estimated from diet histories

Normal persons have a mean daily intake of 290 ± 19.3 µg. Patients with simple goitre have an iodine intake usually lying at the lower end of the normal curve. The difference between the means of the two groups is highly significant.

goitre. On this basis figures have been derived from calculation of the quantities of iodine present in iodised salt, since this salt is known to have produced a dramatic fall in the prevalence of non-toxic goitre. The lowest level used with striking effect is in Switzerland, and here the additional amount of iodine supplied averaged 76 μg per head of the population daily. On the basis of this type of evidence Matovinovic and Ramalingaswami (1960) conclude that the human requirement for iodine is less than 100 μg a day. On the other hand, after an extensive review of the subject, Kutschora-Aichbergen (1962) concluded that the physiological requirement of iodine is of the order of 200 μg per day, or 70 mg per year. The figure of 200 μg per day has also been proposed by Curtis and Fortman (1943, 1949) as the optimum daily iodine intake, but the basal (minimum) intake accepted by these authors was 44 to 75 μg daily.

The Committee on Nutrition of the British Medical Association (1950) set the minimum daily requirement at 100 μg for adults and 150 μg for children, adolescents and in pregnancy. The Nutrition Board of the National Research Council of the U.S.A. give the optimum figures as 150 to 300 μg for an adult and the value of 400 μg is approved by the Food and Agriculture Organisation of the United Nations (1954).

The unsatisfactory nature of the evidence provided by epidemiological dietary surveys is illustrated by our own survey in

Glasgow. We found that patients with iodine-deficiency goitre had a mean dietary intake of 79 ± 20 µg/day, the highest individual value being 134 µg/day. However, this figure was not in keeping with the 24-hr urinary excretion of iodine (p140), giving systematically higher values. Furthermore this dietary survey does not given an estimate of the individual variations in iodine requirements. One can conclude that such surveys are useful only for comparison between groups (e.g. with and without goitre) but do not provide reliable absolute figures.

Calculation of iodine requirements based on quantitative studies of iodine metabolism.

A fresh approach to the problem can be made by basing the estimate of iodine requirement on the intake which is needed to maintain the PII within the normal range of 0.08 to 0.60 µg/100 ml. This calculation of the iodine requirement is, however, considerably influenced by the renal iodide clearance rate. The renal clearance of iodide does not decrease when the PII falls nor does it increase when the PII rises. Unlike chloride (Fig 3.2) there is no homeostatic renal mechanism to keep the PII constant, and so the PII fluctuates with the dietary intake of iodine. When the dietary intake is deficient the thyroid compensates by increasing its iodide clearance but the renal clearance does not alter. Fig 3.2

DIFFERENCE BETWEEN ADAPTION TO CHLORIDE AND IODIDE DEFICIENCY

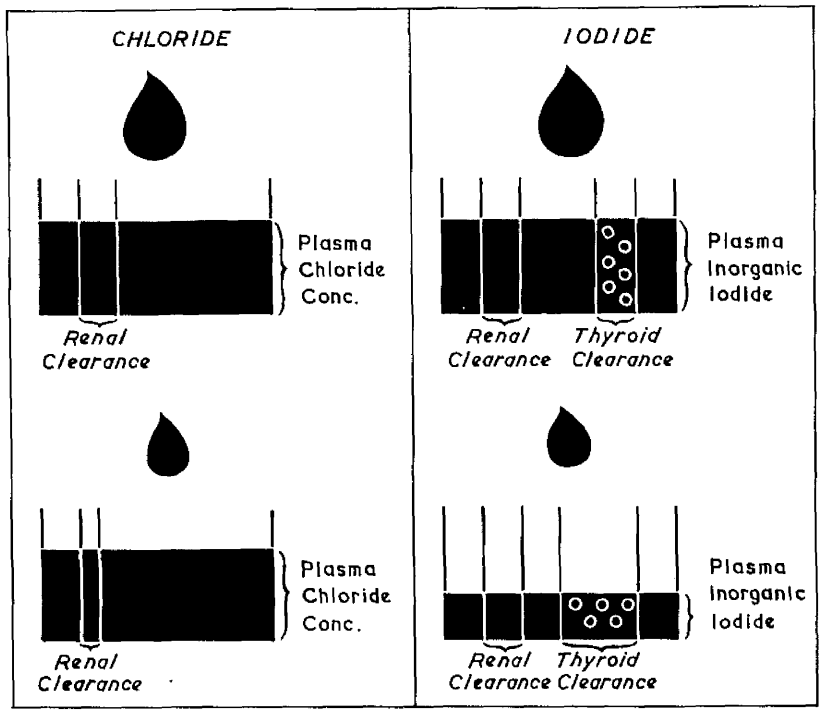

Figure 3.2

Adaptation to chloride deficiency

When dietary chloride intake is diminished there is no decrease in the plasma chloride level. This is achieved by a renal homeostatic mechanism: the renal chloride clearance decreases in proportion to the chloride intake and so the urinary chloride excretion also decreases in proportion, without any alteration in the plasma chloride level.

Caption continued overleaf

Caption to Figure 3.2 (continued)

Adaptation to Iodide deficiency (weeks or months)

When dietary iodide intake is diminished the plasma iodide (PII) decreases in proportion because there is no renal homeostatic mechanism: the renal iodide clearance remains unchanged. Note that the urinary excretion of iodide decreases in proportion to the iodide intake, but this is achieved by a reduction in the plasma inorganic iodine, whereas in chloride deficiency this is achieved by reduction of renal chloride clearance. The simplified general formula is, dietary intake = urinary excretion = plasma concentration x renal clearance. In iodide deficiency the plasma concentration falls and the renal clearance remains constant, whereas in chloride and sodium deficiency the plasma concentration remains constant and the renal clearance decreases. Note, however, that although there is no general renal mechanism for the adjustment to iodide deficiency, there is a thyroid mechanism: in iodide deficiency the thyroid clearance rises as the plasma inorganic iodine (PII) falls and thus keeps the absolute iodine uptake (AIU) within the normal range. Thus in the case of sodium and chloride the homeostatic mechanism (renal) protects the whole body, whereas in the case of iodide the mechanism (thyroid) acts only locally.

illustrates how the increase in thyroid iodide clearance compensates for the low PII. This increase in thyroid clearance is usually accompanied by goitre formation (p210).

We can therefore define the minimum iodine requirement as that amount of iodine which is necessary to maintain a normal PII and so avoid the formation of an iodine-deficiency goitre. We have found that the lower limit of the normal PII is 0.08 µg/100 ml (p43). Since, however, there is some overlap between the normal range and that observed in iodine deficiency goitre we suggest that the minimum PII value which protects a person from iodine-deficiency goitre is 0.10 µg/100 ml. With a renal clearance of iodide of 34 ml/min the 24 hour urinary excretion of iodine at a PII of 0.10 µg/100 ml is 50 µg/day. Allowing 20µg for faecal excretion this leads to a figure of 70 µg/day, as the minimum iodide requirement for the average person. There is, however, a wide range of renal clearance, and while 42 µg/day would be enough for a person with a renal clearance of 15 ml/min, if the renal clearance were 55 ml/min 99 µg/day would be required, allowing in each case 20 µg for faecal excretion. The faecal iodine excretion, however, may reach 40 µg per day, and so the iodine requirements must be increased by another 20 µg/day. Such a person with a renal clearance of 55 ml/min would therefore require a minimum iodine intake of 120 µg a day to maintain the PII at the lower levels of the normal range (0.10 µg/100 ml).

These considerations show that the iodine requirements may differ widely even in perfectly healthy persons, since both the renal clearance of iodide and the faecal iodine excretion have a wide normal range. 70 µg daily is the average iodine requirement, but some persons need only 40 µg whereas others need as much as 120 µg. A PII of 0.10 µg/100 ml which was taken as the basis for our calculations must be considered the absolute rather than the safe minimum, and it would be better to aim at a PII level of 0.15 µg/100 ml or more. This would raise the desirable iodine intake from a minimum of 120 µg/day to the safer level of 160 µg/day. These values refer of course to amounts of inorganic iodine actually entering the body after ingestion of food. All the iodine present in food may not be available in absorbable form, in which case the minimum requirements would have to be adjusted upwards.

A calculation of iodine requirement based on an approach somewhat similar to our own made use of the 24 hr urinary excretion of iodine. It was found that when the 24 hr urinary iodine was less than 40 µg/day the radioiodine uptake was usually increased (Stanbury 1953). The iodine requirements were set at 100 µg daily, allowing for a margin of safety. If to the 40 µg iodine excreted daily in the urine, one adds 20 µg for faecal excretion, the value rises to 60 µg which is in good agreement with our own estimate of 70 µg as the average minimum iodine requirement.

Conclusion.

Looking at our own evidence as a whole, we arrive at a figure in the region of 160 µg a day as the minimum certainly safe amount of iodine which must be available in the individuals' diet if iodine deficiency goitre is to be avoided. This intake would maintain the PII in the normal range in almost the whole population, although a few exceptional individuals with abnormally high excretion rates of iodine would have a PII below 0.15 µg/100 ml. It might be advisable to raise this figure to 200 µg in children and during pregnancy.

It is important to keep this figure of 160 µg to 200 µg in mind when considering the adequacy of the dietary intake of iodine. Thus it can be seen that . consumption of sea fish two or three times a week provides the extra iodine necessary for the majority of the members of a community not receiving iodised salt. An estimate of the minimum requirement of iodine is also needed in deciding the amount of iodine which should be added to salt for goitre prophylaxis.

Chapter 4 - PATHOLOGICAL ASPECTS OF IODINE METABOLISM

continued overleaf

Chapter 4 (continued)

Chapter 4.

PATHOLOGICAL ASPECTS OF IODINE METABOLISM.

My objects in undertaking these studies were to establish the pattern of iodine metabolism in the various disorders of thyroid function, and to examine the value in clinical diagnosis, if any, of such measurements as the plasma inorganic iodine concentration, and the absolute uptake of iodine by the thyroid. The methods used have been described in Chapter 1.

The patients included in the investigation are first described, and the individual results are presented in tabular form. In the subsequent sections of this chapter these results are analysed and discussed in the light of previous work.

Patients studied

The complete series consisted of 107 patients with thyroid disease, and included 40 with thyrotoxicosis, 53 with simple goitre and 6 with hypothyroidism. The diagnosis was made on clinical grounds (Wayne, 1960), and confirmed in every case by estimation of the protein-bound iodine. When necessary we used, in addition I^{131} uptake tests at four and 48 hours and protein-bound I^{131} at 48 hours, thyroxine or tri-iodothyronine suppression tests, the perchlorate discharge test, the TSH stimulation test, estimation of the butanol-insoluble I^{131} and the intrathyroidal exchangeable iodine, thyroid auto-antibody studies, and

finally the response to treatment.

Patients with "simple goitre" i.e. non-toxic goitre excluding frank cases of dyshormonogenesis, auto-immune thyroiditis and goitrogen administration (p182) were divided into those with high thyroid radioiodine clearance (and uptake) values, and those with normal ones. Values of thyroid radioiodine clearance up to 40.0 ml per minute were considered to be normal. Although in practice the clearance values form a continuum, this separation serves a useful purpose, since in patients with a high radioiodine uptake the mechanism responsible for goitre formation is presumably still active, and also since these cases are more likely to be misdiagnosed as thyrotoxicosis on the basis of radioiodine uptake studies.

Patients with auto-immune thyroiditis attending this clinic have been thoroughly reported by Dr. W.W. Buchanan (M.D. thesis, 1962) and so will not be described in detail.

Three patients with iodide goitre were studied, both while taking and after discontinuing the large iodide loads which had resulted in goitre formation. Studies were also carried out on four proven cases of dyshormonogenesis - three of Pendred's syndrome and one of goitrous cretinism with an abnormal circulating iodoprotein. The cases of dyshormonogenesis (p217) and iodide goitre (p225) are discussed individually because of the small numbers of cases available for study.

No.	Name	Sex	Age yr.	Dur. goi. yr.	Dur. sym. yr.	D. I.	PBI µg%	24 hr. Iur µg	I^{131} test uptake 4 hr.	uptake 48 hr.	48 hr % dose/l. TPI	48 hr % dose/l. PBI	Stable iodine studies $2\frac{1}{2}$ hr upt.	Th.Cl.	PII	AIU	R.Cl.
1	M.W.	F	41	4/12	3/12	25	16.0			91.4			90.0	70.8	.13	5.5	44.2
2	A.M.	F	49	2	$1\frac{1}{2}$	27	12.0		100.0	100.0	0.47	0.45	84.9	133.6	.10	7.8	12.4
3	H.S.	F	27	$1\frac{1}{2}$	$1\frac{1}{2}$	36	4.8	9.5	100.0	100.0	0.50	0.43	100.0	778.7	.02	11.4	
4	A.H.	F	18	1/12	1/12	21	16.5						73.7	295.9	.25	44.4	34.4
5	E.M.	F	41	5	5	21			69.0	66.8	0.76	0.74	53.8	124.7	.09	6.7	42.7
6	M.T.	F	32	2	1	31	13.3		100.0	100.0	1.23	1.12	72.9	238.7	.05	7.4	28.7
7	E.L.	F	33	3/12	7/12	35	14.6						90.7	394.1	.14	33.3	46.7
8	M.W.	F	38	-	7/12	22	10.6			95.8	0.42	0.37	52.9	80.0	.24	11.7	39.4
9	I.S.	F	56	3	3	27	11.8		66.1	80.1	0.56	0.54	52.4	78.1	.15	7.0	23.1
10	J.S.	F	41	4	4	34	10.9		77.0	78.2	0.71	0.54	64.9	283.2	.11	18.7	60.4
11	A.R.	F	39	5/12	5/12	17	13.4		87.6	60.0	2.60	2.99	60.1	83.9	.11	15.5	43.5
12	S.L.	F	46	3/12	3/12	23	15.3							577.0	.13	45.0	41.0
13	E.C.	F	38	4	3	26	13.5						43.4	157.2	.22	20.3	
14	J.C.	M	71		1	10	10.5		67.8	70.9	1.68	1.68	39.0	61.4	.26	9.7	21.7
15	E.W.	F	55	6	6	28	10.4		98.4	82.5	1.57	1.51	91.6	298.0	.20	35.2	23.8
16	J.R.	F	29	5	5	30	9.7						82.4	263.0	.09	13.7	31.5
17	A.W.	F	52	6/12	6/12	21	12.4						59.4	84.0	.33	16.9	20.7
18	M.S.	F	34		6/12	25	9.2						60.5	88.0	.16	8.4	15.9
19	C.O.	F	25	1/12	2/12	28	9.5						78.4	357.0	.08	17.1	35.4
20	E.M.	F	28	3/12	3/12	13	9.7						44.2	134.0	.05	3.6	38.9
21	M.B.	F	46	1	2	17	10.2						64.2	385.0	.05	12.0	55.1
22	N.B.	F	44		3/12	30	13.6						92.0	1054.0	.07	45.5	81.2
23	M.B.	F	45	6/12	2	18	9.2		79.7	46.0	3.83	3.72	65.4	333.0	.05	10.2	31.6
24	W.D.	F	50	3/12	1	16	7.9		71.1	69.6	1.66	1.42	48.1	155.0	.10	8.9	19.8
25	J.M.	F	43			29	15.5	53					69.1	187.0	.08	8.9	48.5
26	R.C.	M	46	3/12	4/12	22	9.8						67.6	210.0	.25	31.5	
27	M.W.	F	42		8/12	20	9.6	lol					37.6	77.9	.28	13.3	17.4
28	E.A.	F	51	7	3	13	6.2	40	51.4	65.8	0.07	-	45.6	109.4	.13	8.7	40.8
29	J.N.	F	49	8		30	15.3	30					82.4	274.1	.31	51.0	16.7
30	I.S.	F	45	2/12	1	35	17.2						78.1	125.1	.46	34.5	13.1
31	J.H.	F	26				14.4						46.8	48.9	.15	4.4	27.0
32	M.E.	F	36		6/12	33	16.0	70					81.3	313.0	.09	17.5	37.8
33	N.C.	F	43	5/12	5/12	36	13.1						86.5	455.8	.11	28.7	30.6
34	M.E.	F	48		7/12	26	12.5						84.5	405.3	.11	27.7	23.9
35	I.A.	F	57			31	15.5						71.7	300.9	.17	30.7	21.6
36	M.C.	F	48	1		24	14.2						72.4	126.7	.16	12.2	32.2
37	H.M.	M	45		2	21	10.1						79.0	417.2	.03	7.5	57.5
38	B.T.	F	49			35	21.6						86.8	555.6	.17	56.0	70.2
39	M.D.	F	34	1/12		31	10.5						70.1	157.0	.31	29.7	51.5
40	C.H.	F	59	3/12	$1\frac{1}{2}$	24	12.6						83.8	313.0	.06	11.8	30.0

No suppression of thyroid uptake after administration of 120 µg T_3 daily for one week.

Table 4.2

Iodine metabolism in primary hypothyroidism

No.	Name	Th. upt. % dose	Th. Cl. ml/min	PII µg/100 ml	AIU µg/hr	PBI µg/100 ml	R. Cl. ml/min
1	M.L.	13.9	8.0	.01	0.05	0.9	13.9
2	H.M.	13.0	1.7	.13	0.13	0.5	30.0
3	J.M.	3.6	2.6	.037	0.06	0.5	20.3
4	A.B.	5.6	0.0	.26	0.0	1.6	13.7
5	E.M.	3.6	3.0	.15	0.27	0.9	19.1
6	S.C.	10.6	7.1	.25	1.1	1.0	28.3
Mean ± S.E.		8.2±1.8	3.7±1.3	.14±.04	0.3±0.16	0.8±0.24	19.2±3.9

Thyroid clearance > 40 ml/min
(For abbreviations and units used see p vi)

No.	Name	Sex	Age	Goitre Size g	Goitre Dur. yr.	24 hr Iur	PBI µg%	Diet µg	I^{131} test uptake % 4 hr	I^{131} test uptake % 48 hr	TFI	PBI	Stable iodine studies $2\frac{1}{2}$ hr	Th.Cl.	PII	AIU	R.Cl.	IEI mg
1	J.I.	F	27	75	10/12		6.8		73.2	84.5	0.47	0.47	41.5	146.2	.03	2.8		
2	B.G.	F	22	50			5.5		73.7	99.6	0.10	-	46.7	108.5	.03	2.0	35.3	
3	D.E.	F	36	75	24	70	5.9		99.6	99.9	1.41	0.26	67.6	142.1	.02	1.7	48.0	
4	A.G.	F	32	75	26	56	6.6		60.2	74.1	0.15	-	45.5	93.2	.02	1.1	63.4	14.6
5	M.L.	F	31	40			4.4		48.2	70.0	0.10	-	28.2	40.6	.06	1.5	38.6	
6	E.W.	F	56	100		30	5.5	134	46.7	74.0	0.12	-	37.6	61.3	.06	2.3	27.7	
7	J.W.	F	37	50									34.8	63.0	.04	1.4	15.4	15.4
8	M.E.	F	23	100	6/12		5.3						39.9	55.0	.05	1.8	33.9	
9	V.P.	F	23	75		23	5.3						39.2	64.0	.04	1.7	52.4	
10	M.M.	F	39	50			3.5						25.8	51.9	.04	1.3		
11	J.S.	F	21	100	6	15	3.0						66.1	93.8	.01	0.5	41.3	
12	A.M.	F	36	125	20	56	4.2		54.4		0.02	-	35.1	49.7	.06	1.9	43.8	
13	E.D.	F	18	50	4/12	63	5.1	109					27.4	42.0	.04	1.1	31.0	
14	G.M.	M	37	75			4.1		71.6	84.7	0.08	0.06	53.3	89.0	.03	1.6	19.0	6.3
15	J.L.	F	59	150	10	49	5.5	25	86.0	94.3	0.09	-	74.1	155.4	.06	5.7	30.7	10.0
16	M.M.	M	19	75			4.7	88					59.0	179.7	.03	3.1	38.8	
17	R.A.	F	19	50	2								52.0	74.5	.05	2.4		
18	MM.	F	45	150	30	34	4.9	41	55.0	70.6	0.07	-	42.4	68.6	.07	2.8	23.3	6.2
19	C.W.	F	29	100	6		4.5						43.1	53.8	.08	2.6	16.0	
20	J.J.	M	45	50			7.5						31.3	59.6	.08	2.8	26.2	
21	S.H.	F	25	200	2		4.2		38.8	54.8	0.10	-	29.1	57.6	.07	2.5	37.8	
22	I.M.	F	34	50			4.5						38.1	55.0	.07	2.4	35.6	
23	J.W.	F	19	50			2.7						35.6	58.1	.07	2.4	23.1	
24	T.M.	F	25	50	7/12		5.9						29.1	50.8	.08	2.3	32.3	

T_3 test: normal suppression of thyroid uptake. Perchlorate discharge test negative.

In every case the precipitin test was negative.

No.	Name	Sex	Age	Goitre Size g	Goitre Durn. yr	24 hr Iur	PBI µg%	Diet µg	I^{131} test Uptake % 4 hr	48 hr	TPI	PBI	Stable iodine studies $2\frac{1}{2}$ hr	Th.Cl.	PII	AIU	R.Cl.	IEI mg
1	I.M.	F	44	50		92			53.9	74.9	0.08	-	23.9	7.3	.19	0.9	27.2	
2	H.B.	F	25	50	3/12		5.5						23.4	20.2	.14	1.7	31.2	
3	C.W.	F	40	50	4/12		6.5		45.3	60.0	0.26	0.26	17.9	32.7	.22	4.3	14.1	
4	J.S.	F	71	50	20		5.1						7.0	15.4	.15	1.4	18.5	
5	M.K.	F	18	40			6.7						21.8	24.4	.15	2.2	32.1	
6	A.H.	F	31	125	17		5.5		48.9	57.7	0.07	-	33.1	39.6	.11	2.5	45.6	
7	J.T.	F	16	50	2		4.1						36.6	21.4	.09	1.2	63.7	
8	A.N.	F	37	75			5.8						18.2	21.7	.12	1.5		
9	M.Q.	F	32	50	2		5.7		99.0	69.9	0.14	-	31.9	29.1	.12	2.0	30.6	
10	M.W.	F	57	50	3		5.3		32.7	35.5	0.08	-	21.2	19.0	.09	1.0	28.7	
11	E.G.	F	34	75	3	87	2.7						34.7	33.7	.10	2.0	40.5	
12	R.M.	F	14	75	2/12		5.7	92					28.5	38.4	.08	2.0	37.7	
13	J.T.	F	16	50	5/12		6.7	276					11.8	11.4	.11	0.8	20.0	
14	J.M.	F	23	50	1		6.9	91					17.8	19.7	.11	1.3	25.6	
15	W.A.	M	34	100		46	6.7	338					17.5	22.4	.14	1.8	81.0	
16	E.C.	F	16	75			5.3	129					17.8	27.0	.08	1.3	39.3	
17	C.J.	F	15	75	5	45	6.2	226					10.8	12.9	.08	0.6	33.8	
18	M.G.	F	16	50			6.3						17.8	29.3	.35	6.2	33.0	
19	E.R.	F	23	75	3/12	28	5.5	77					23.0	37.1	.10	2.2	31.3	
20	B.J.	F	32	200	11		4.0	53	56.9	63.2	0.10	-	51.0	32.7	.03	0.7	39.8	
21	C.P.	F	32	50	2		5.4	160	54.1	67.1	0.03	-	38.6	34.1	.05	1.1		
22	E.F.	F	34	50		44	3.8	80					33.1	21.6	.04	0.5	35.2	29.6
23	A.W.	F	35	100	20		3.0						20.4	22.9	.03	0.4	31.1	
24	M.R.	F	44	75	8		5.3	158	53.8	68.5	0.09	-	30.4	25.4	.05	0.8	43.0	
25	J.P.	F	52	75	4	14	2.5						26.6	30.8	.02	0.4	30.0	
26	C.M.	F	34	75	5	6	4.9						24.2	33.1	.03	0.6	28.8	
27	W.C.	M	46	50	3/12		4.4						31.7	13.5	.07	0.6	30.1	
28	E.R.	F	40	50			3.8						22.8	38.8	.07	1.3	40.6	
29	I.R.	F	32	50			4.7	128					20.8	31.0	.07	1.3	58.0	

Klinefelter's syndrome.

In every case the precipitin test was negative.

THYROTOXICOSIS

Inorganic iodine metabolism

In thyrotoxicosis, the overactive gland takes up an increased quantity of iodide and produces an increased quantity of thyroid hormone. The thyroid clearance and uptake of radioiodine and the absolute iodine uptake (AIU) are increased and usually lie well above the normal range. Moreover the iodide which is taken up is quickly converted to thyroxine and rapidly released into the blood stream.

Measurements in 40 cases are shown in Table 4.1 and summarised in Table 4.4. Except for cases treated with iodine and not included in the Table, the thyroid clearance was always raised and exceeded 1000 ml/min in one case. The absolute iodine uptake (AIU) was also increased, exceeding 6 μg/hr in all except 4 cases.

The rise in AIU is sometimes not as marked as that of the thyroid clearance because the plasma inorganic iodide (PII) is slightly decreased. The decrease in PII is not statistically significant in our series, but is nevertheless suggestive ($p < 0.2$). It would be expected on theoretical grounds since in thyrotoxicosis not only are organic iodine compounds lost in the faeces and urine in excess (Berson and Yalow 1954; Van Middlesworth 1960), but the renal

Table 4.4

Iodine metabolism in 40 cases of hyperthyroidism

	Mean	S.E.	Range	Normal Range
Th. Upt. at 2½hr.	69.4	2.58	37.6 - 99.9	10.0 - 35.0%
Th. Cl.	280.8	33.97	48.9 - 1054.0	8.0 - 40.0 ml/min
PII	0.15	0.015	0.02 - 0.46	0.08 - 0.60 µg/100 ml
AIU	20.7	2.39	3.6 - 56.0	0.5 - 6.0 µg/hr
PBI	12.3	0.52	4.8 - 21.6	3.0 - 7.5 µg/100 ml
Renal clearance	35.3	2.59	12.4 - 81.2	15.0 - 55.0 ml/min

The individual values are shown in Table 4.1.

clearance of iodide is also slightly increased.

This increase in renal clearance is moreover greater than is suggested by the figures in Table 4.4, because in the thyrotoxic group the proportion of female subjects is much greater than in the control group, and normal males have a greater renal clearance than normal females. If we consider only female cases the figures are 35.1 ± 2.6 ml/min in the toxic cases and 25.3 ± 1.8 ml/min in the normal ones. The difference is statistically significant ($t = 3.09$, $p < 0.01$). The increased renal iodide clearance in thyrotoxicosis has been attributed not to a specific action of thyroxine but to an increased glomerular filtration rate (Hlad and Bricker 1954). High values for the renal clearance in thyrotoxicosis (46.4 ± S.D. 7.6 ml/min) were found by Cassano et al (1957). McConahey et al (1951), on the other hand, recorded normal values but they studied only a few cases, and did not allow for sex differences.

Although the PII is usually normal or low-normal in thyrotoxicosis, it is usually raised in patients who have received moderate amounts of exogenous iodine. In these patients the thyroid clearance and uptake may lie within the normal range or even below it.

Figs 4.1 and 4.2 showthat the absolute iodine uptake (AIU) is of considerable value in the diagnosis of thyrotoxicosis, since thyrotoxic patients have a much larger AIU than euthyroid subjects, whether or not they have goitre or a high radioiodine uptake. All the patients represented in Fig 4.1 had a high radioiodine uptake. Estimation either of the protein-bound iodine (PBI) or of the AIU separates the

ABSOLUTE IODINE UPTAKE AND PROTEIN-BOUND IODINE IN THYROTOXICOSIS AND SIMPLE GOITRE

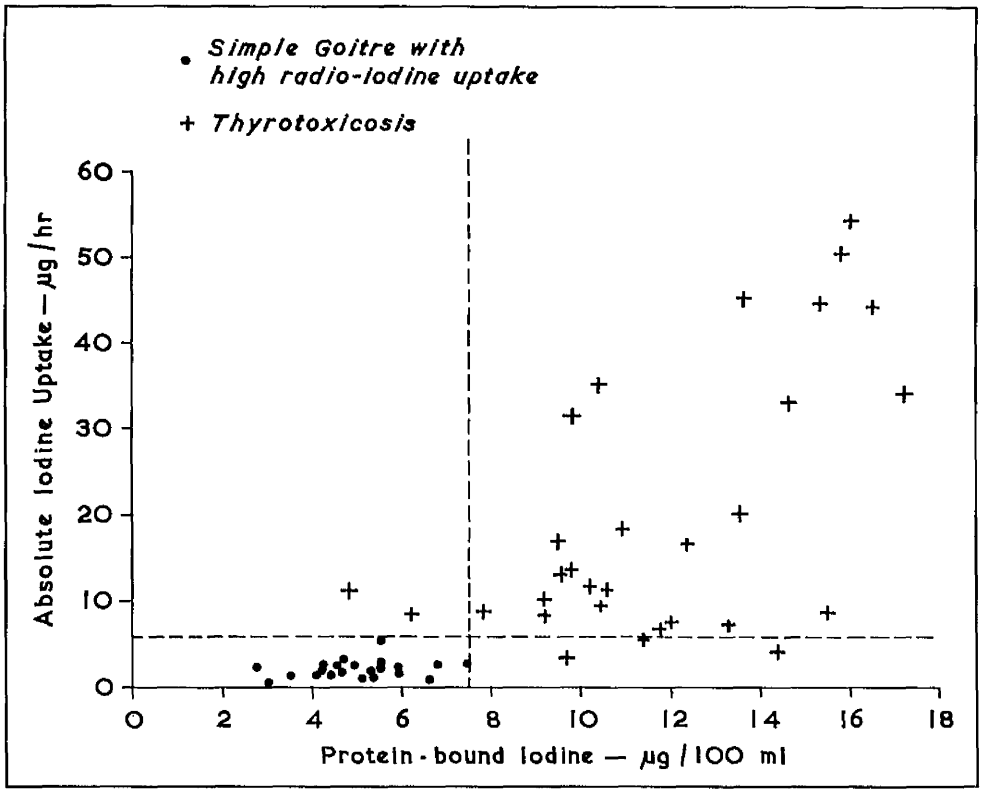

Figure 4.1

Absolute iodine uptake (AIU) and PBI in iodine deficiency goitre and in thyrotoxicosis

All the patients shown in this figure have a high radioiodine uptake. Both the AIU and PBI give a good separation between patients with iodine deficiency goitre and those with thyrotoxicosis. A small overlap occurs with either test, but when both are used the diagnostic accuracy is increased.

RADIOIODINE UPTAKE (2½ hr) AND ABSOLUTE IODINE UPTAKE IN THYROTOXICOSIS AND SIMPLE GOITRE

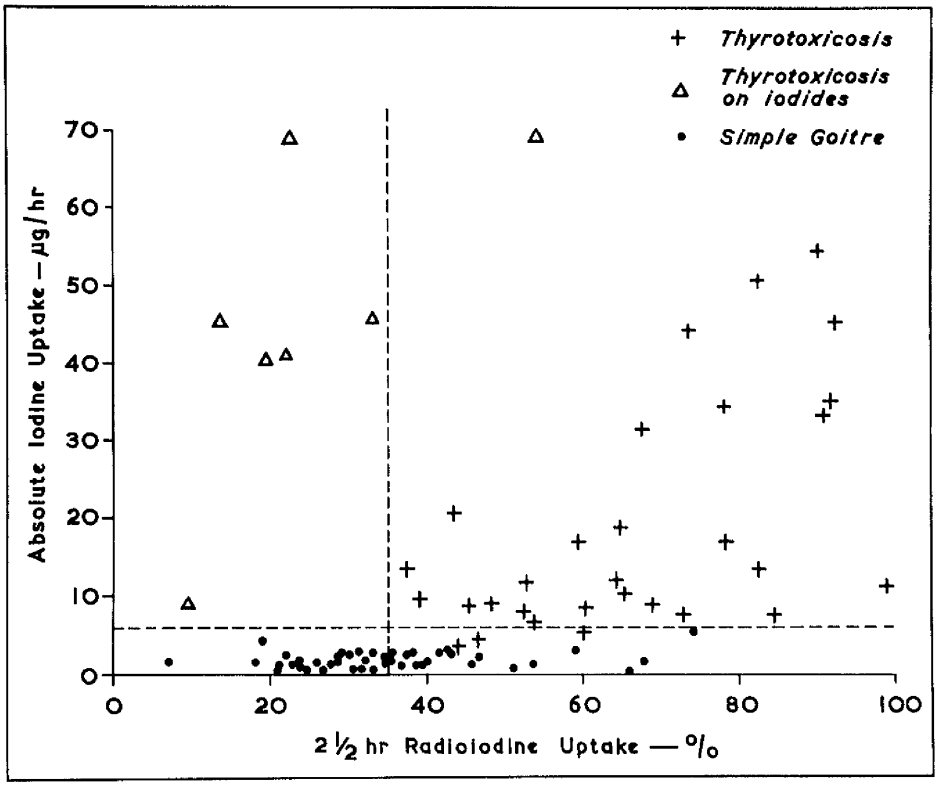

Figure 4.2

Radioiodine uptake and absolute iodine uptake in simple goitre and in thyrotoxicosis

The AIU gives a good separation of patients with simple goitre from those with thyrotoxicosis. In contrast, a good seperation is not obtained with the 2½ hr I^{132} uptake because a large proportion of patients with simple goitre show increased values, whereas thyrotoxic patients receiving iodides usually show normal or low values.

thyrotoxic and euthyroid patients quite well, but if both are estimated greater precision is achieved. No thyrotoxic patient had both normal PBI and normal AIU.

Fig 4.2 shows the AIU and the 2½ hr uptake of radioiodine in 37 thyrotoxic patients, including seven who had been receiving iodine in some form, and in 45 patients with simple goitre. Nineteen patients with simple goitre had a high radioiodine uptake, whereas six thyrotoxic patients had normal or low values. The AIU gave much more reliable results, since there were no abnormally high values in the group with simple goitre, and only three normal values in the thyrotoxic group.

Organic iodine metabolism

Both the large amount of thyroid hormone produced by the over-active gland and the rapid intrathyroidal turnover rate of iodine contribut to the high PBI^{131} found in thyrotoxicosis. Thus the PBI^{131} values estimated 48 hr after the administration of the isotope almost always exceed 0.4% of the dose per litre (Wayne 1954, 1960). This is in striking contrast to normal persons in whom the PBI^{131} is almost always less than 0.2% of the dose per litre, and with tracer doses is usually undetectable.

The serum PBI is almost always increased in thyrotoxicosis and in our cases was on the average raised by a factor of two and a half. This increase is not, however, proportional to the increase in the AIU which was on the average increased nine times. A straight line relation would not be expected since the peripheral degradation of thyroxine is accelerated in

thyrotoxicosis. A more nearly linear relation is obtained if the AIU is plotted against the third power of PBI, shown in Fig 4.3. The significant correlation between AIU and PBI in thyrotoxicosis is in contrast to the findings in euthyroid subjects (p69). The better correlation in thyrotoxicosis may be explained in two ways. Firstly, in thyrotoxicosis the gland is not subject to any regulation by TSH, and thus there is no physiological "brake" on thyroxine production. Secondly the time interval between trapping of iodide and thyroxine release is decreased in thyrotoxicosis and so the AIU and PBI would be expected to correlate better. Riggs (1952) and Berson and Yalow (1954) found a relationship between thyroid hormone production and the square of the PBI.

The total amount of hormonal iodine produced daily in thyrotoxicosis would be expected to vary with the severity of the cases studied. It was found to be 890 µg/day on the average by Ingbar and Freinkel(1955) and of this 359 µg were degraded; this compares with their figures in normal subjects of 58 and 54 µg for production and degradation respectively Berson and Yalow (1954) found that the amount of hormonal iodine secreted daily in thyrotoxicosis was on the average 671 µg/day when they used a method based on the kinetics of a tracer dose, or 597 µg/day using a method based on methimazole ("tapazole") block. These figures of iodine secretion are not very different from our mean AIU value of 20.7 µg/hr (506.8 µg/day) and suggest that in thyrotoxicosis, as well as in normal subjects, most of the iodide taken up is converted to thyroid hormone. We know, however, that a small fraction must be secreted as iodotyrosines and a more significant amount as iodide (Slingerland et al 1962).

ABSOLUTE IODINE UPTAKE AND PROTEIN-BOUND IODINE IN THYROTOXICOSIS

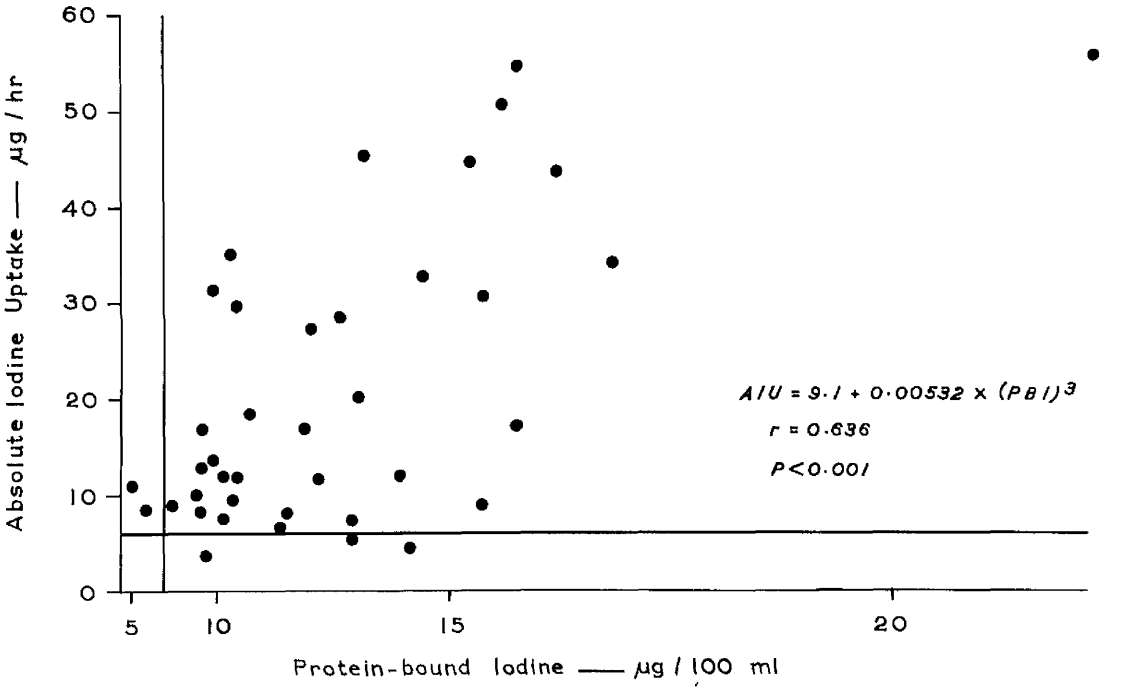

Figure 4.3

Absolute iodine uptake and protein-bound iodine in thyrotoxicosis

Two thyrotoxic patients have a normal PBI and three a normal AIU, but in no patient are both parameters normal. There is a good correlation ($r = 0.636$, $p<0.001$), but it is not a straight-line one.

Radiothyroxine turnover studies in thyrotoxicosis have consistently shown a decreased half-life of the hormone which is attributed to an increased rate of degradation (Ingbar and Freinkel 1955.; Sterling and Chodos 1956). The metabolism of T_3 in thyrotoxicosis hasbeen investigated by Hales and Dobyns (1960) who found that less than normal was taken up by the liver, and more remained in the plasma and was deiodinated or excreted in the urine. More T_3 is present in the serum in thyrotoxic subjects than in normals (Vannotti et al 1961) and cases have been reported where it was the major constituent of the PBI (Rupp and Paschkis 1961; Shimaoka 1963). Because of the greater metabolic activity of T_3 the PBI would not correlate with the clinical severity in such cases.

Farran et al (1959) have demonstrated iodotyrosines in the peripheral blood in thyrotoxicosis. This finding can be interpreted as indicating that the deiodinase system cannot keep pace with the increased amounts of iodotyrosines continuously released from the thyrotoxic gland. The presence of iodotyrosines in the peripheral blood also explains their presence in the urine of many thyrotoxic patients. In our thyrotoxic group 15% of the urinary iodine was found to be in organic form by the resin column method (p22). Since the urinary iodine is used in the estimation of the PII without correction for organic iodine, the true PII level in our thyrotoxic group would be 0.13 µg/100 ml instead of 0.15 µg/100 ml. In other words these patients are even more iodine deficient than appears from Table 4.4. Though only a small proportion of the urinary iodine is accounted for by organic compounds they nevertheless cumulatively represent a significant loss.

In conclusion, the thyroid radioiodine clearance and absolute iodine uptake are greatly increased in thyrotoxicosis. The plasma inorganic iodine is slightly diminished, probably owing to increased loss of iodine in the faeces and increased renal clearance.

Quantitative studies of iodine metabolism are not necessary for diagnosis in the majority of suspected cases of thyrotoxicosis. But in problem cases measurement of the PBI and AIU can indicate the true level of thyroid activity when standard radioiodine tests (thyroid uptake and PBI^{131}) are frankly misleading because the iodine pools of the body are increased or decreased (see also p 261 and p 253).

PRIMARY HYPOTHYROIDISM

Primary hypothyroidism is due to lack of sufficient functional thyroid tissue. Rarely this may be a congenital abnormality in which case the clinical picture of sporadic cretinism without goitre is seen but more often it appears later in life and affects particularly middle aged females. In many of these patients, thyroid specific auto-antibodies can be detected and this points to a causal association with auto-immune thyroiditis (Doniach et al 1961; Hall 1962). In fact the cases of auto-immune thyroiditis with a small goitre, hypothyroidism and low thyroid uptake may be considered as forms intermediate between primary hypothyroidism and the classical case of auto-immune thyroiditis.

Surgical excision of a toxic or non-toxic goitre or over-treatment with radioiodine may leave too small a portion of active thyroid tissue to prevent hypothyroidism. In such cases, the pattern of iodine metabolism is similar to that found in primary hypothyroidism.

In primary hypothyroidism all the stages of iodine metabolism are quantitatively diminished. Very little iodine goes into the thyroid gland and very little thyroid hormone is produced. Iodide trapping by the thyroid is markedly diminished as is shown by a low thyroid clearance, a low thyroid uptake and a low absolute iodine uptake (AIU). In six consecutive cases (Table 4.2), the mean thyroid clearance was 3.7 $\pm$ 1.3 ml/min, the thyroid uptake at 2$\frac{1}{2}$ hr 8.2 $\pm$ 1.8% and the AIU 0.3 $\pm$ 0.2 μg/hr. These results do not differ in any

important respect from those reported in the literature. For example, Reilly et al (1958) found a mean AIU of 11.8 ± 3.6 μg/day or 0.5 μg/hr.

The radioiodine uptake in hypothyroidism, although decreased on the average, nevertheless shows a considerable overlap with the normal range. The overlap is partly due to technical factors since the extrathyroidal neck radioactivity interferes with the estimation of the thyroid radioiodine uptake (p15). This extrathyroidal radioactivity decreases with time both absolutely and relatively to the thyroid uptake, and for this reason late uptake measurements (24 or 48 hr) are preferable for the diagnosis of primary hypothyroidism. When the radioiodine uptake is borderline, diagnostic help can be obtained from the TSH stimulation test. The uptake rises in a normal individual but not in a hypothyroid patient in whom the thyroid cannot function more efficiently than it is already doing i.e. the thyroid has no reserve.

The plasma inorganic iodine (PII) in primary hypothyroidism is not significantly different from that in normal subjects either in our own series or in that of Reilly et al(1958). Since the amount of iodide released by degradation of thyroid hormone is small, the PII consists almost entirely of iodide recently ingested with the food and would therefore be expected to fluctuate more than in normal subjects in whom some iodide is continuously released by breakdown of thyroid hormones.

The renal clearance is low, averaging 19.2 ± 3.9 ml/min in our

cases, which is significantly different from our normal controls ($p < 0.02$). Lowvalues for the renal clearance in hypothyroidism have also been reported by McCanahey et al (1951), Berson et al (1952) and Cassano et al (1959). The decrease in renal iodide clearance may be causally associated with the decreased glomerular filtration rate present in hypothyroidism.

The peripheral degradation of radiothyroxine proceeds at a reduced rate in hypothyroidism (Ingbar and Freinkel 1955; Sterling and Chodos 1956; Ingbar 1960). Thus the PBI concentration in hypothyroidism is not decreased as much as the thyroid hormone secretion rate. Nevertheless the PBI provides a very useful index, and lies below 3.5 µg/100 ml in the great majority of cases.

In conclusion, the diagnosis of primary hypothyroidism can nearly always be established using the clinical and other criteria described by Wayne (1960). Stable iodine studies may, however, explain unexpected findings, such as a low thyroid uptake in a euthyroid person or a high PBI level in a hypothyroid subject, sometimes seen after administration of iodine-containing drugs.

NON-TOXIC GOITRE : AETIOLOGY

Classification of non-toxic goitre

It is clear that non-toxic goitre is not a disease entity but simply a clinical sign, and there are many aetiological factors. Figure 4.4 shows the classification we adopt. Iodine deficiency is the most widely recognised cause of non-toxic goitre and many reports have established its existence in areas where the majority of the population has enlargement of the thyroid. There has been much debate as to whether iodine deficiency alone is responsible for the goitre or whether additional factors must act synergistically with iodine deficiency before thyroid enlargement ensues. Most probably both types of goitre exist, some due to a severe degree of iodine deficiency alone, others due to a mild iodine deficiency acting on a constitutionally predisposed individual. This is further discussed below.

Goitrogenic substances are by definition capable of producing thyroid enlargement. They may affect the individual either because they are present in his usual diet or because they are taken as a drug. If goitrogens are present in the food many persons in the same community are affected, and there is evidence that this happens in Tasmania, but their possible role in other countries has not yet been clearly defined.

An inherited metabolic abnormality in thyroid hormone synthesis may give rise to non-toxic goitre with or without associated hypothyroidism. The term dyshormonogenesis is used for this condition.

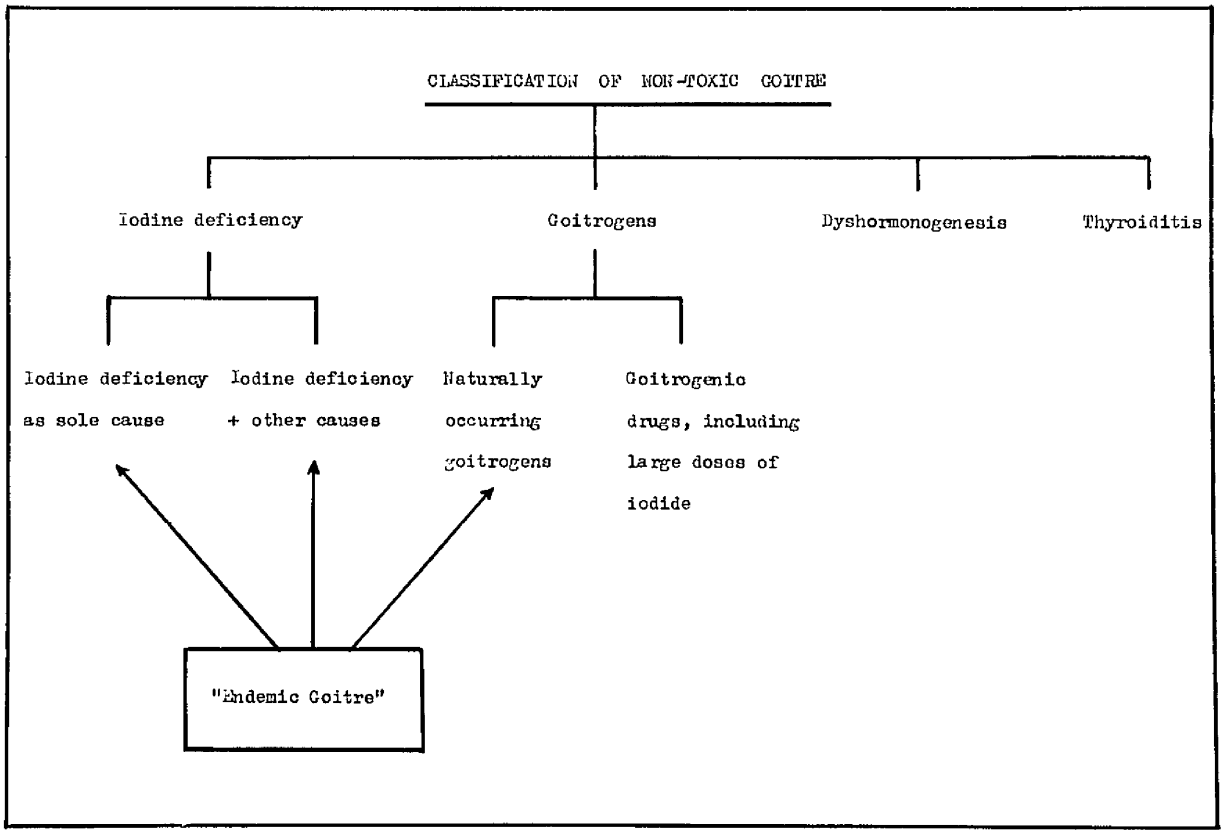
CLASSIFICATION OF NON-TOXIC GOITRE
Iodine deficiency
Goitrogens
Dyshormonogenesis
Thyroiditis
Iodine deficiency as sole cause
Iodine deficiency + other causes
Naturally occurring goitrogens
Goitrogenic drugs, including large doses of iodide
"Endemic Goitre"

Figure 4.4

Autoimmune thyroiditis may also affect the individual and produce thyroid enlargement. There is some evidence that a predisposition to autoimmune disease may be inherited, but the familial incidence is not nearly so striking as in the previous type.

EPIDEMIOLOGY OF NON-TOXIC GOITRE

It is an old observation that non-toxic goitre tends to be frequent in some areas, affecting almost the entire population, and yet is extremely rare in others. The terms endemic and sporadic goitre are time honoured. They have been used differently by different writers and the prevalence above which goitre has been considered to be endemic varies from 10% (Stanbury 1959) to 50% (Trotter 1959). Table4.5 shows that there is a continuous variation in prevalence and that it is impossible to find a point at which an obvious separation into two groups occurs. Thus the terms endemic and sporadic, though useful, are entirely arbitrary.Although there is good evidence that iodine deficiency is the major factor in most areas in which the prevalence of goitre is high we do not know at what point it ceases to be of major importance. Beckers (1962) in a recent extensive and thorough study of non-toxic goitre also points out that endemic and sporadic goitre form a continuous spectrum, and lists many clinical and metabolic features which these two supposedly different types have in common.

Table 4.5

Goitre prevalence in different parts of the world

(Kelly and Snedden, 1960)

Kashmir (Karakoram mountains)	90%
Bihar, Ranchi district	70%
West Bengal, Darjeeling	67%
Central Brazil	53.8%
Bihar, Purnea district	50%
Mordos, Mexico	46%
East Punjab, Shivolsk Hills	37%
Hidalgo, Mexico	35%
Mexico, Mexico	30%
South East Brazil	27%
Puebla, Mexico	24%
Faticeni, Romania	20.2%
Chad, Africa	13.4%
N.E. Brazil	11.8%
Distrito Federale, Mexico	5%
Vorn, Nigeria	3%
East Brazil	0.9%
Gabon, Africa	0.4%

It seems fair to conclude that goitre will be endemic if there is a serious deficiency of iodine or a high concentration of goitrogens in the diet. But less severe abnormalities in the diet may well affect only individuals especially predisposed either because of their dietary preferences, or because of their hereditary constitution, and the goitres will be termed "sporadic". On the other hand, persons living in endemic areas are not protected from inherited abnormalities of iodine metabolism, and cases of dyshormonogenesis will presumably be seen as commonly as in non-endemic areas.

EVIDENCE OF IODINE DEFICIENCY IN AREAS WITH A LOW GOITRE PREVALENCE

If the majority of persons in a community have a goitre, the aetiology is either iodine deficiency or naturally occurring goitrogens. Iodine deficiency is a much more common cause and it is generally agreed that it is the important factor in most places where the majority of the inhabitants are affected. On the other hand in areas where large quantities of fish are consumed, or where household salt is generally iodised, non-toxic goitre is almost always a rare condition, and the few cases found are almost certainly not due to iodine deficiency. The aetiology of non-toxic goitre is more difficult to establish in a country like Great Britain, where iodised salt is rarely used and where non-toxic goitre affects only a minority of the inhabitants. Nevertheless as many as 26% of women had enlarged thyroid glands in

Sheffield, a city in the Derbyshire goitre area (Kilpatrick et al 1963). Our experience in Glasgow suggests that in such areas the iodine intake is neither uniformly adequate nor uniformly deficient, and only a proportion of the inhabitants will develop iodine-deficiency goitre. This is not only because some persons take more iodine-containing foods than others, but also because individual requirements vary.

In practice, it is difficult to decide whether a particular goitre is due to iodine deficiency or not, because firstly, some persons can adjust to mild iodine deficiency without the formation of a palpable goitre, and secondly because an established iodine-deficiency goitre does not necessarily diminish in size following iodine administration, in spite of correction of the biochemical abnormality. Hence, one may meet patients with goitre who have been iodine deficient at some time in the past, but who at the time of investigation show no biochemical abnormality. In other words an iodine deficiency state and an iodine-deficiency goitre do not necessarily coexist, and this leads to further confusion.

In Glasgow we see more patients with non-toxic goitre than with thyrotoxicosis. Some non-toxic goitres are examples of frank dyshormonogenesis, autoimmune thyroiditis, or are due to goitrogenic drugs. However, in more than 90% of our cases of non-toxic goitre, we could not find evidence of any of the above factors and these are the cases we propose to call "simple goitre". Measurements of the plasma inorganic iodine (PII), 24-hr urinary excretion of iodine and diet

histories all suggest that the great majority of these simple goitres are the result of present or past iodine deficiency. Table4.6 shows that our patients with "simple goitre" are as a group iodine deficient, irrespective of whether the thyroid radioiodine uptake is high or normal. However, the sub-group with a high radioiodine uptake had more severe iodine deficiency, and their plasma inorganic iodine values suggested that almost every patient in this group had iodine deficiency at the time of examination. The sub-group with a normal radioiodine uptake on the other hand was not as homogeneous and consisted of patients with a lesser degree of iodine deficiency, with previous iodine deficiency, and possibly some cases not due to iodine deficiency at all.

The importance of iodine deficiency as a cause of non-toxic goitre in other areas where goitrous patients constitute only a small minority of the population, has also been established by workers in Belgium (Beckers 1962; de Crombrugghe et al 1963), and in the north east of Scotland (Crooks, personal communication). Beckers found a plasma inorganic iodine of 0.134 $\pm$ 0.035 µg/100 ml in his cases of non-toxic goitre as compared with a value of 0.256 $\pm$ 0.028 µg/100 ml in non-goitrous persons living in the same district. Estimates of the 24 hr urinary iodine also showed a significantly lower iodine content in the goitrous cases.

THE CONSTITUTIONAL FACTOR IN NON-TOXIC GOITRE

There is no doubt that a sufficiently severe inherited

Table 4.6

Evidence of iodine deficiency in the cases of "simple goitre"

	Simple goitre with high radioiodine uptake	t and p values	Control cases	t and p values	Simple goitre with normal radioiodine uptake
Dietary iodine intake (µg/day)	79 ± 20.2 (5)	t = 5.82 p < 0.001	273 ± 26.6 (43)	t = 3.09 p < 0.01	164 ± 23.3 (12)
Plasma inorganic iodine (µg/100 ml)	0.05 ± 0.01 (21)	t = 5.86 p < 0.001	0.18 ± 0.02 (24)	t = 3.60 p < 0.001	0.10 ± 0.01 (28)
Urinary iodine excretion (µg/day)	44 ± 5.5 (9)	t = 2.76 p < 0.02	81 ± 12.2 (12)	t = 2.18 p < 0.05	45 ± 11.2 (8)

All the figures (mean ± S.E.) refer to female persons, to allow valid comparison between the goitrous cases (predominantly females) and the controls. The number of persons in each group is shown in brackets. Individual values obtained in the goitrous patients are shown in Tables 4.3a and 4.3b.

metabolic abnormality can give rise to a non-toxic goitre, even if the iodine intake of the individual is high. In such cases a clear family history is usually apparent and these abnormalities are described in the chapter on dyshormonogenesis. On the other hand, there is also no doubt that a severe iodine deficiency is in itself an adequate cause of goitre (p214). In between, however, come the great bulk of cases of non-toxic goitre seen in many parts of the world, in which both iodine deficiency and constitutional factors are implicated. In such cases, it is clear that a mild degree of iodine deficiency induces goitre formation in certain individuals predisposed to it by constitutional make-up, and not in others. This concept that some individuals are more susceptible than others was well recognised many years ago. Thus Curtis and Fertman (1943, 1949) reported that susceptible (i.e. a few) individuals can develop thyroid enlargement after six months residence in a goitrous district.

There is no precise information about the nature of the constitutional factor which predisposes some individuals and not others to goitre, and little evidence that mild degrees of the same abnormalities which produce the clear-cut picture of dyshormonogenesis in some individuals are widely distributed through the population. However, McGirr (1960) has described ten young patients with sporadic goitres who showed biochemical abnormalities similar to those described in sporadic goitrous cretinism. We ourselves have observed a family,

some members of which had goitrous cretinism due to impaired organic binding of iodine as shown by a positive perchlorate discharge test. Some other members of the family had non-toxic goitres, but in these the perchlorate discharge test was negative. It nevertheless seems likely that they represent a lesser degree of the same biochemical abnormality. If so, degrees of dyshormonogenesis not detectable by a routine test may be responsible for some cases of non-toxic goitre. On the whole, however, the fact that there is a strong sex incidence in simple goitre, but not in the cases of non-toxic goitre associated with sporadic goitrous cretinism, and also the lack of evidence of faulty utilization of iodine in simple goitre (p198), makes it improbable that the constitutional factor operating in most cases of simple goitre is qualitatively similar to the abnormalities described in the section on dyshormonogenesis and differs from them only in degree.

The sex factor in simple goitre is striking. Of course when almost everybody in a community has an iodine deficiency goitre the sex ratio must necessarily approach unity, but with decreasing prevalence, females appear to be more and more affected than males, though this may not be true for children before puberty. This sex difference is difficult to explain. Normal females have the same PII level as normal males, but in contrast to them they show an age relation (PII increasing with age) and their thyroid clearance adjusts much more readily to alterations in PII level (p71). Possibly increased losses of iodine during pregnancy and lactation (slight losses also occur during

menstruation) may in part be responsible. As noted in Chapter 3, an increased renal clearance at puberty and during pregnancy has been reported by Cassano et al (1957a,b). However, stilboestrol has been shown not to affect the thyroid uptake of radioiodine or the renal clearance (Dowling et al 1959). In rats, faecal excretion of thyroxine is increased during lactation or by estrogen administration (Grosvenor 1962a,b) but there is no evidence that this is true of humans. Crooks et al. (1963) noted an increase in renal iodide clearance in pregnancy associated with low PII values. This is consistent with the clinical observation that the thyroid gland in women may enlarge during pregnancy. There is also considerable variation in pituitary activity during the reproductive life of the female, and it is possible that intermittent stimulation by TSH may account for the greater liability of the female gland to undergo cycles of hyperplasia and involution.

A <u>genetic factor</u> operating in all forms of thyroid disease has been suggested by Bartels (1953), and Stanbury (1960b) has pointed out that endemic goitre might, in certain instances, be the result of a mild environmental deficiency of iodide playing upon a constitutional defect.

It is perhaps relevant that some strains of rats and mice have a more efficient iodide-trapping mechanism than others, as revealed by the thyroid/serum (T/S) iodide concentration gradient (Silverstein et al 1960; Silverstein and Lee 1961). The thyroid in the animals with the higher T/S ratio was smaller than in the other strains. This suggests

that in mice and rats some strains have a smaller but more efficient (per unit of weight) thyroid gland than others. It would be interesting to compare the effects of mild iodine deficiency in such different strains.

It is reasonable to suppose that the enzyme systems in some glands are more effective than in others when called upon to work under adverse conditions. It should be remembered that the same degree of vitamin deficiency may produce clinical symptoms in some subjects and not in others, and the minimum effective doses of many drugs varies from individual to individual. Similarly iodine deficiency of the same degree or goitrogens in the same amount may give rise to goitre in some individuals and not in others, but in this instance additional factors must make the female thyroid more sensitive than the male.

Additional evidence that constitutional factors may predispose some persons to the effect of iodine lack is shown by the fact that a mild degree of iodine deficiency may exist in persons not having an obvious goitre. This subject is discussed in more detail on p 211.

IODINE-DEFICIENCY GOITRE.

The diagnosis of iodine-deficiency goitre is difficult to establish in the individual case. This is because an iodine-deficiency goitre and an iodine-deficiency state do not necessarily coexist: the same degree of iodine deficiency may give rise to goitre in some individuals and not in others. On the other hand, a goitre produced by iodine deficiency may persist even after the deficiency has been made good. For these reasons it is more satisfactory to draw conclusions from groups of patients rather than from single cases. Thus in the classical studies of Stanbury and his colleagues in Argentina, iodine deficiency was established for the group studied as a whole; this does not, however, preclude the possibility that a few persons in the group had other types of non-toxic goitre. These occasional cases, however, would not affect the validity of conclusions derived from the study of the group as a whole, but their existence illustrates the difficulties with which investigators in this field are faced. It is for this reason that in Glasgow we have preferred to study a group of patients with what we term "simple goitre", that is to say patients with goitres not due to auto-immune thyroiditis, frank dyshormonogenesis or goitrogenic drug administration. Patients with "simple goitre" constitute more than 90% of the cases of non-toxic goitre seen at my clinic. The evidence shows that as a group they are iodine deficient (p183), but it is, of course, quite probable that some individual cases are not. About half of these

patients had a raised uptake of radioiodine and in this group the plasma inorganic iodine (PII) was uniformly low so that there is clear evidence of iodine deficiency. The other half with a normal uptake are iodine deficient when considered as a group, but as individuals several were not iodine deficient at the time of investigation.

IODINE METABOLISM.

The basic abnormality in iodine deficiency goitre is a low plasma inorganic iodine (PII) concentration, and this is reflected in a low urinary excretion of iodine. The thyroid gland attempts to compensate for the low PII by increased thyroid clearance (Fig 4.5 p191) and this is reflected in a high thyroid uptake of radioiodine, which is the most easily recorded abnormality in iodine deficiency, although it is non-specific.

We owe much of our knowledge on this subject to the classic studies of Stanbury et al (1952, 1954) in the endemic iodine deficiency areas of Mendoza, Argentina. These workers established the main features of iodine metabolism in iodine deficiency, namely a high thyroid uptake of radioiodine, and a reduced 24 hr excretion of chemical iodine. Their patients had a variable thyroid radioiodine uptake, but on the average it was raised. There was an inverse relation between the chemical iodine excretion and the thyroid radioiodine uptake, which showed that the more severe the iodine deficiency the higher the radioiodine uptake

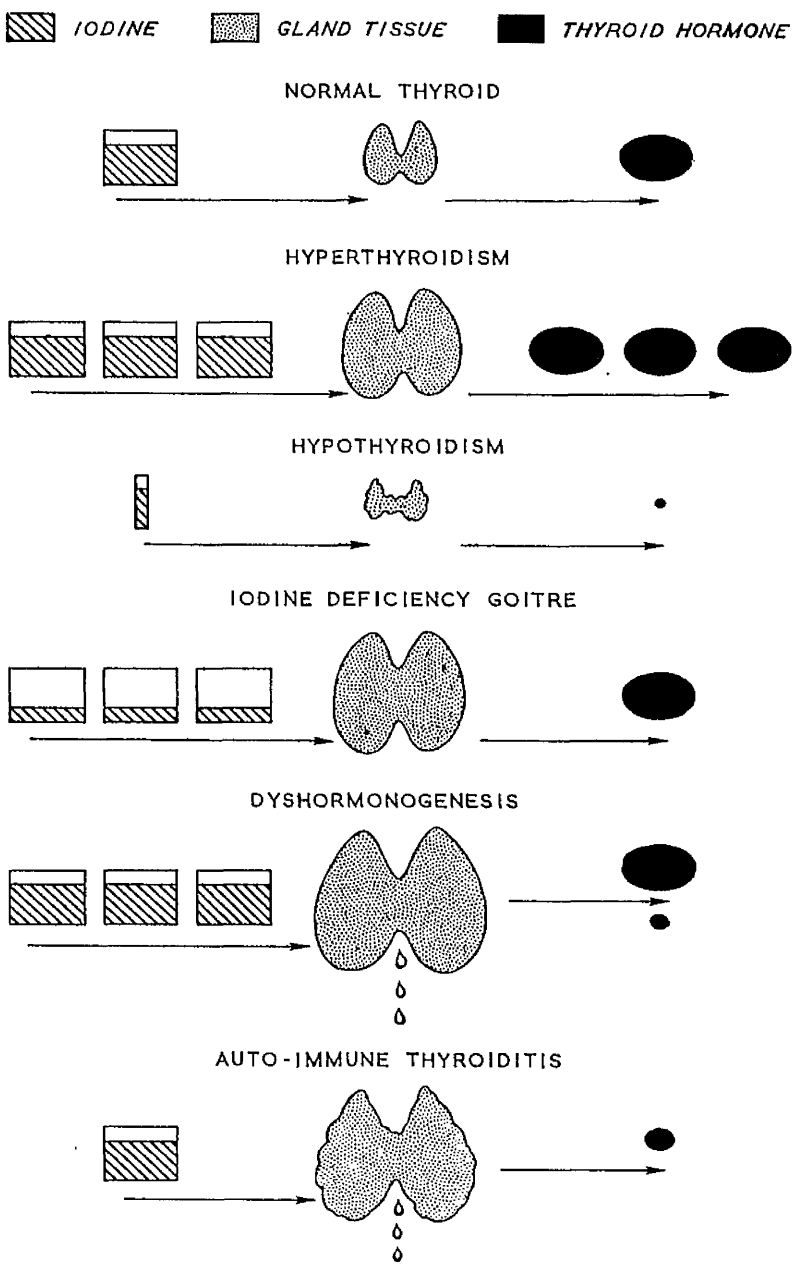

FIG. 6. Quantitative aspects of iodine metabolism in thyroid disease.

The blocks on the left of the figure indicate the volume of plasma cleared of its iodide content by the thyroid (thyroid clearance), and the concentration of the plasma inorganic iodine (PII) is indicated by cross hatching. On the right of the figure the amount of thyroid hormone produced is shown in black. In hyperthyroidism the thyroid has a larger absolute iodine uptake (AIU), and forms a correspondingly larger amount of thyroid hormone. In hypothyroidism both the AIU and the production of thyroid hormone are reduced. In iodine-deficiency goitre the thyroid clears a larger volume of plasma than normal, thus compensating for the low PII concentration, and resulting in a normal AIU; the iodide taken up is efficiently utilized, and a normal amount of thyroid hormone is produced. In dyshormonogenesis the AIU is high, as in thyrotoxicosis, but the iodide taken up is not efficiently utilized. Thus the amount of thyroid hormone produced is normal or subnormal, and some of the trapped iodide leaks from the gland in inactive form, either as abnormal iodinated compounds or as iodide. The dissociation between iodide uptake and hormone output is also found in auto-immune thyroiditis, but the AIU is less and most patients are hypothyroid.

Figure 4.5

becomes. Some patients, however, had a low urinary iodine excretion and a normal thyroid uptake and this finding was interpreted as the one "expected if the patient had taken iodine medication in the recent past but had discontinued it." That is to say, it is suggested that these patients had at one time been iodine deficient, had then had the deficiency relieved by the administration of iodine, and after its withdrawal had become deficient again. The thyroid clearance, however, had not had time to adjust again to the newly decreased PII. In theory, at least, this is quite possible since the thyroid clearance adjusts to the PII level only after a considerable delay (p84). The mean PBI in Stanbury's series was normal, but there was a wider scatter of individual values; that is to say many patients had high-normal or slightly high values, and some had low ones.

Other studies of endemic goitre have also shown a high thyroid uptake and this has usually been considered as evidence of iodine deficiency (Ghalloungui and Shawarby 1958; Kao et al 1958). Fuller studies have been conducted in Venezuela by Roche et al (1957) and in Finland by Lamberg et al (1958, 1962), who in addition measured the urinary iodine excretion by chemical methods, and found it low. As already mentioned, measurements of stable iodine either as the plasma inorganic iodine or as the urinary iodine are the only direct proof of iodine deficiency.

An extensive study of endemic iodine-deficiency goitre has been

carried out in the Republic of the Congo by De Smet and De Visscher (1960), De Visscher et al (1961) and Ermans et al (1961). This group of workers also found a high thyroid radioiodine uptake and a low 24-hr urinary iodine excretion, but the mean PBI was lower than normal and indeed many patients were clinically hypothyroid. This type of iodine deficiency may be described as uncompensated (p214), since presumably it was so severe that the rise in thyroid clearance was not enough to keep the AIU within the normal range. Hypothyroidism which is clinically obvious is however so rare in iodine deficiency that it is possible that there were contributory factors. These primitive people had a low standard of nutrition and it may be that deficiency of other essential dietary constituents such as protein played a part.* Racial predisposition is possible but unlikely.

Abnormally low PBI values have also been reported in India (Raman and Beierwaltes 1959) and in goitrous patients in Salvador and Guatemala (Scrimshaw et al 1953). In the latter study the PBI reverted to normal after the administration of iodine supplements. These studies show that iodine deficiency may, rarely, be so severe that the thyroid is

* Plotnikova (1959) concluded that in iodine-deficient rats, both lack and excess of protein may lead to enlargement of the gland. On the other hand, Aschkenasy (1961a,b) found that in rats on a protein-deficient diet the thyroid was smaller than in controls, but could still enlarge in response to iodine deficiency or hemithyroidectomy.

not capable of producing enough hormone to keep the individual euthyroid, and also that even this degree of deficiency is reversible if iodine is given.

The PBI^{131} is usually normal in iodine-deficiency goitre and this is in keeping with the normal amounts of intrathyroidal exchangeable iodine usually found (p200). In fact the combination of a high radioiodine uptake and a normal PBI^{131} is usually referred to as an "iodine deficiency pattern". However, some of the Congolese patients studied by the Belgian workers had high PBI^{131} values as well as high thyroid uptake, and high PBI^{131} values in endemic goitre have also been found in Venezuela by Roche et al (1957). Reduced intrathyroidal iodine stores would explain these findings (p253). Furthermore, 5 of 9 Congolese patients had considerable amounts of T_3 in their plasma.

Glasgow study.

The observations made on patients who attended the thyroid clinic at the Western Infirmary are summarised in Table4.7and Figs 4.1,4.2 and 4.6. Fifty-three cases of simple goitre, 48 females and 5 males were studied (Table 4.3)and Fig 4.6 shows the thyroid clearance and the PII values in this group. The patients can be divided into those with a high thyroid clearance (> 40.0 ml/min) and those with a normal clearance (≤ 40.0 ml/min). The first group had, in addition to the high clearance and uptake, a uniformly low PII, the highest value found being 0.08 µg/100 ml. These patients were clearly iodine-deficient as shown by the markedly low PII

Table 4.7

Iodine metabolism in simple (iodine-deficiency) goitre

	High Th. Cl. (24 cases)	Normal Th. Cl. (29 cases)	Total (53 cases)	Normal Range
Th.Upt.at 2½ hr (%)	42.6±2.7 (25.8-74.1)	24.6±1.7 (7.0-51.0)	32.8±1.95 (7.0-74.1)	10.0-35.0
Th.Cl. (ml/min)	79.7±7.9 (40.6-179.7)	25.7±1.6 (7.3-39.6)	50.2±5.2 (7.3-179.7)	8.0-40.0
PII (µg/100 ml)	0.05±0.004 (0.01-0.08)	0.10±0.012 (0.02-0.35)	0.08±0.008 (0.01-0.35)	0.08-0.60
AIU (µg/hr)	2.2±0.2 (0.5-5.7)	1.5±0.22 (0.4-6.2)	1.8±0.16 (0.4-6.2)	0.5-6.0
PBI (µg/100 ml)	5.0±0.25 (2.7-7.5)	5.1±0.23 (2.5-6.9)	5.1±0.17 (2.5-7.5)	3.0-7.5
R.Cl.(ml/min)	34.9±2.5 (15.4-63.4)	35.9±2.6 (14.1-81.0)	35.5±1.5 (14.1-81.0)	15.0-55.0

The individual results are shown in Table 4.3.

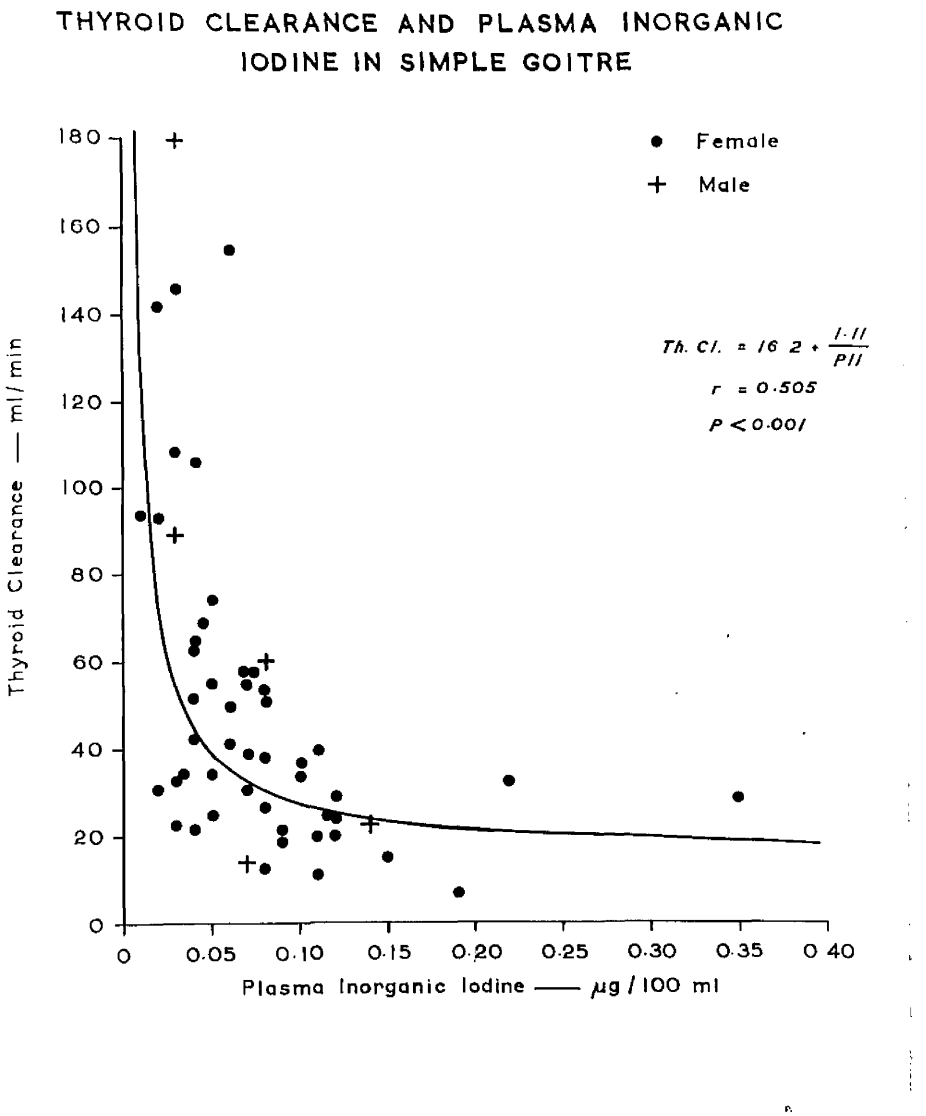

Figure 4.6

Relation between thyroid radioiodine clearance and plasma inorganic iodine (PII) in simple goitre

There is an inverse relation ($r = 0.505$, $p < 0.001$) similar to that found in normal females.

(mean 0.05 μg/100 ml), the 24 hr urinary iodine excretion (mean 44 μg/day) and the dietary intake (mean 79 μg/day). As shown previously (Table 4.6) all these values differ significantly or highly significantly from the control values. These patients were well compensated as shown by normal AIU and PBI values.

The second group with simple goitre had thyroid clearance rates within the normal range. Some of these cases had a low PII and in some it was normal. On the whole this group is also iodine deficient, as is shown by significantly low PII values, by the 24 hr urinary iodine excretion, and by the diet histories (Table4.6), but it is less homogeneous than the previous one. Probably some cases had been iodine deficient previously, but not when studied by us. The AIU was not significantly different from that found in normal females and the PBI was well within normal limits.

The difference in the AIU in our two sub-groups is worthy of comment. Taken as a whole our goitrous patients had the same AIU as our control female cases, but the subgroup with a high thyroid clearance had a slightly higher AIU, and that with a normal thyroid clearance a slightly lower AIU. Neither of these subgroups differed significantly from the controls, but there was a significant difference ($p < 0.02$) between the subgroups themselves. That is, the first goitrous subgroup had a higher AIU than the other, yet they both produced similar amounts of thyroid hormone as shown by the PBI levels. Our patients with a low PII and a normal thyroid clearance are comparable with those of Stanbury and his

colleagues, who, in spite of a low urinary iodine excretion had a normal radioiodine uptake. The explanation may be as suggested by Stanbury et al, that in these patients iodine deficiency is of recent origin. If the low PII were to persist, either the thyroid clearance (and the AIU) would rise or the PBI level drop. The alternative explanation is that the goitrous patients with a normal thyroid clearance are able to utilize iodide trapped by the gland more efficiently than those with a high thyroid clearance, and perhaps even better than the normal controls.

The overall quantitative relations between the thyroid clearance and PII in our goitrous patients are shown in Fig 4.6. There is obviously a highly significant inverse relation:

$$\text{Thyroid clearance} = 16.2 + \frac{1.11}{\text{PII}}, \quad r = 0.505, \; p < 0.001.$$

The correlation coefficient between thyroid clearance and PII in goitrous females was not significantly different (after z transformation) from the same coefficient in normal females, and this implies that the thyroid glands of these patients on the average responded normally to the decreased PII levels. The cases with normal PII values also had normal thyroid clearances. Presumably if these patients had had iodine deficiency in the past, it was now no longer present but the goitre had persisted. In general, all patients from both groups had a normal AIU and a normal PBI/AIU ratio (iodine utilization index, p222) and this is strong evidence against any significant defect of thyroid hormone synthesis, either congenital or goitrogen-induced. However, although iodine utilization was always within the normal range, it was better in some

cases than in others, and this suggests that there may be individual variations in iodine utilization in the normal population. Both the mean AIU and the PBI in our goitrous cases was exactly the same as in normal females, suggesting that the goitrous patients did not differ on the average from the normal population, except in so far as they had a reduced concentration of plasma inorganic iodine available for synthetic purposes. In general our findings in these cases of simple goitre in Glasgow are similar to those reported by Stanbury et al in endemic goitre in Argentina and this reinforces our view that the disease in the two countries is essentially similar, although milder in Glasgow.

The diagnostic value of the AIU is shown in Figs 4.2 and 4.1. The first of these shows that the AIU gives a better separation of thyrotoxicosis from simple goitre than does the 2½ hr uptake of radioiodine. Figure4.1shows that the AIU and the PBI are of approximately equal value in the differentiation of thyrotoxicosis from simple goitre. The mechanism responsible for the highradioiodine uptake when the PII is low is shown in Fig 5.2.

Other aspects of organic iodine metabolism.

Emmans et al (1961) have made direct measurements of the iodine content of excised glands in cases of severe iodine-deficiency goitre from the Congo. The total iodine content was in the normal range but the concentration per gram of tissue was reduced to about 25 per cent of normal. Hence the finding of a normal value for total intrathyroidal exchangeable iodine in no way excludes the diagnosis of iodine deficiency. Iodine deficiency is characterised by a low PII and not by a low intra-

thyroidal exchangeable iodine or a low AIU, except in some extreme cases of uncompensated iodine deficiency. In fact, our patients had normal or slightly elevated values of intrathyroidal exchangeable iodine, the figures in 6 cases being 29.6, 15.4, 14.6, 6.3, 10.0, and 6.2 mg respectively (mean 13.7 mg). If expressed, however as µg iodine/g of tissue, there is an inverse relation between iodine concentration and gland size. It is only in very severe or acute iodine deficiency that the intrathyroidal exchangeable iodine may be decreased, and this explains the occasional high PBI^{131} values recorded.

Chromatographic studies in the endemic area of the Congo (Ermens et al 1961) showed an increased ratio of labelled MIT to DIT and also of labelled iodotyrosines to iodothyronines. These authors postulated that the low concentration of iodine in the gland resulted in a slower transfer of I^{131} from MIT into the more heavily iodinated compounds (DIT and iodothyronines). A high MIT/DIT ratio has also been found in experimental iodine deficiency in animals (Leloup and Lechivor 1955; Querido et al 1957; Bois and Larsson 1958). This increased MIT/DIT ratio is not specific for iodine deficiency, since it has been found in many other thyroid disorders. Probably it is associated with a primitive form of iodine metabolism (Pitt-Rivers et al 1958) and may therefore be found in almost any thyroid disorder except iodide induced goitre .

The high MIT/DIT ratio is probably not due to increased TSH stimulation, since the reverse relation, decreased ratio of MIT to DIT has been found in animals after partial thyroidectomy or exogenous TSH

administration (Cukier and Triantaphyllidis 1959; Triantaphyllidis and Cukier 1959). The finding of an increased MIT/DIT ratio in human goitres (Pitt-Rivers et al 1957; Dimitriadou et al 1960b, 1961) is therefore in no way indicative of their etiology.

Increased concentration of radio-T_3 in the plasma of some iodine-deficient Congolese patients has been noted by de Visscher et al (1961). In iodine-deficient rats, on the other hand, the plasma concentration of T_3 was not abnormal (Querido et al 1957), but there was an increased T_3/T_4 ratio in the thyroid gland (Leloup and Lachiver 1955).

Beckers and De Visscher (1961a) found decreased tissue deiodinase activity in endemic iodine-deficiency goitre in the Congo, as revealed by a slight increase in the proportion of radioactive DIT excreted in the urine after a tracer dose of this compound. Since these patients were slightly hypothyroid (mean PBI 3.53 µg/100 ml) this finding is probably comparable to the similar observation made in hypothyroidism by Stanbury and Litvak (1957); that is to say, it is associated with the hypothyroidism and not with iodine deficiency as such.

Regulation of iodine metabolism.

The thyroid radioiodine uptake in iodine-deficiency goitre can be increased after administration of exogenous TSH (Stanbury et al 1952). The response to exogenous TSH has also been fully confirmed in our series. This means that these patients are not under maximal endogenous TSH stimulation, which is not surprising in view of their

euthyroid state.

The high thyroid uptake and clearance of radioiodine is suppressed by administration of exogenous T_3 or T_4, and this may serve to differentiate iodine deficiency from thyrotoxicosis (p261).

In summary, in iodine deficiency goitre the low plasma inorganic iodine (PII) level is compensated by an increased thyroid clearance. In this way the absolute iodine uptake (AIU) by the thyroid is normal. The iodide taken up is efficiently utilized, and a normal amount of thyroid hormone is produced. These concepts are illustrated in Fig 4.5(p191) which compares the patterns of iodine metabolism in different types of non-toxic goitre.

AETIOLOGY OF IODINE DEFICIENCY

Good evidence of iodine deficiency is provided by either a low plasma inorganic iodine (PII) or a low urinary excretion of iodine. The normal PII range in our series was 0.08 to 0.60 µg/100 ml and values below the lower figure indicate iodine deficiency. For the results to be significant in a single case, however, either repeated measurements or a PII value below 0.04 µg/100 ml is required since the S.E. of a single measurement is ±0.02 µg/100 ml. Stanbury (1953) considered a 24 hour urinary excretion of iodine below 40 µg as indicative of iodine deficiency, since most patients with such a low excretion had a high thyroid uptake. A PII of 0.08 µg/100 ml would correspond to 40 µg of urinary iodine/24 hr, assuming an average renal clearance rate of iodide (34 ml/min). Thus the findings in Mendoza and Glasgow are in complete agreement. On the whole, however, we prefer the PII to the 24 hr urinary excretion as evidence of iodine deficiency, since in some rare cases with an increased renal iodide clearance iodine deficiency may be present in spite of a normal or low normal 24 hr urinary excretion of iodine. Furthermore the PII can be estimated in out-patients with greater accuracy than the 24 hr urinary excretion of iodine, because of the difficulties associated with 24 hr collections.

Deficient dietary intake

Deficient dietary intake is the most important single cause of iodine deficiency, and its role is especially important in districts with a

high prevalence of simple goitre. The best known areas of high prevalence are mountainous, e.g. the Alps, the Himalayas and the Andes, but high prevalence was also found in certain low-lying areas such as those around the Great Lakesin North America. It has been suggested that all these areas as either high or low altitude have been subjected to flooding after the last ice-age, and that most of the iodine in the soil has been washed away into the sea. The decreased concentration of iodine in the soil leads to a correspondingly decreased concentration of iodine in the drinking water, in plants growing in the soil, and in dairy produce. An inverse relation has been found in many areas between the iodine content of soil or water and the prevalence of goitre (Kelly and Snedden 1960), but other sources of iodine have not usually been adequately considered. Fish and other seafood is much richer in iodine than any other foodstuffs and in mountainous areas not only is the iodine in the drinking water frequently low but little sea fish is usually eaten. The spontaneous decrease in goitre prevalence observed over recent years in several mountainous regions (Kelly and Snedden, p. 113) is probably the result of better communications, with a greater availability of both sea food and other food items produced in relatively iodine-rich areas. The increased prevalence of non-toxic goitre in Germany during the Second World War and immediately after it has been attributed, probably correctly, to decreased fish consumption (Ligdas 1953).

One must distinguish between the average intake of iodine in a community and the individual intake of its members. Since sea products

are the richest source of iodine (Richmond 1962) and since many persons dislike the taste of fish, individual variations in iodine intake within the same community would be expected to be large. Individual variations in fish consumption between goitrous patients and normal subjects in the same community have been noted by Ligdas (1953) in Germany, and by Trotter et al (1962) in the Vale of Glamorgan. In Glasgow, using diet histories, we found the mean dietary intake of iodine to be 273 ± 26.6 µg/day in randomly selected female subjects without clinical thyroid disease, whereas that of patients with simple goitre was 130 ± 19.6 µg/day (p184). The intake was lower in the group with a high thyroid clearance (79 ± 20 µg/day) than in that with a normal clearance (164 ± 23 µg/day), but in both groups the intake was significantly less than in the normal controls ($p < 0.001$, and $p < 0.01$ respectively). However in places where the iodine content of the soil is relatively rich, sufficient iodine may be present in the food items produced. In such places the importance of sea fish is obviously smaller. For instance in some remote parts of Africa goitre is not prevalent although the great distance from the sea makes regular consumption of sea fish highly improbable.

Absorption of iodine.

Decreased absorption of iodine is difficult to evaluate as an aetiological factor in simple goitre. Iodide is readily absorbed from the gastro-intestinal tract especially in the fasting state (Keating and

Albert 1949), but very little is known about the availability and absorption of iodine present in organic form in the food. However, there is no evidence that malabsorption plays a part in the aetiology of iodine deficiency. It has been suggested that excess calcium in the water interferes with absorption of iodine but Taylor (1954) did not find any evidence of this in rats.

Renal loss of iodine.

Increased renal excretion of iodine has recently been suggested as a cause of iodine deficiency, and in particular Cassano et al. (1959, 1961) have stressed the importance of an increased renal clearance of iodide in the pathogenesis of simple goitre. They have reported several cases of simple goitre with a renal clearance of more than 41.0 ml/min, that is to say one S.D. above the mean clearance in their normal series. Our evidence, however, suggests that with few exceptions the renal clearance is an important factor only when it is associated with a low dietary intake. The range in our series of normal persons extends to 55.0 ml/min and even Cassano et al (1959) have noted values of more than 41.0 ml/min in a variety of disorders not associated with disturbances of thyroid function. It is only when the renal clearance is well above the normal range (more than 70.0 or 80.0 ml/min) that it can be considered as the main cause of iodine deficiency and only then can the goitre be labelled "renal goitre". In Glasgow we have seen only one such case, with a renal clearance of 81.0 ml/min

but several others have been reported by Cassano et al.

Although a high renal clearance is rarely the sole cause of iodine deficiency, it may potentiate the effects of low dietary intake. Since iodine requirements are influenced by the renal clearance one would expect to find an increased renal clearance among patients with simple goitre. That such is the case is shown in Table 4.7. The goitrous patients show a slight increase over the normal controls: 35.5 ± 1.5 as compared with 31.1 ± 1.66 ml/min ($p < 0.1$). Since females have a smaller renal clearance than males this must be taken into account and if female subjects only are considered, we have values for goitrous patients of 35.2 ± 1.65, normals 25.3 ± 1.8 ml/min. The difference is statistically highly significant ($p < 0.001$), but less striking than the difference in dietary intake. In fact, an increase of 10.0 ml/min in the renal clearance would lead to an increase in the daily iodine loss of 14.4 µg at a mean PII level of 0.10 µg/100 ml or of 21.6 µg/day at a PII of 0.15 µg/100 ml.

The role of an increased renal iodide clearance as a cause of iodine deficiency seems to be especially important during pregnancy. Work now in progress in Aberdeen has confirmed the view that the prevalence of simple goitre increases markedly in pregnant women (Crooks et al 1963 and personal communication). These workers have found a higher goitre prevalence in pregnancy as compared with matched controls. The renal iodide clearance was, on average, doubled throughout pregnancy.

This increase had returned to normal levels six weeks postpartum. During pregnancy the plasma inorganic iodine (PII) was markedly decreased, whereas the thyroid radioiodine clearance was increased to between two and three times the normal levels. Consequently the absolute iodine uptake (AIU) remained within normal limits.

A massive loss of organic iodine compounds in the urine occurs in congenital deiodinase deficiency, and so this type of dyshormonogenesis may be associated with a conditioned iodine deficiency. Such cases, however, are rare, and loss of organic iodine compounds in the urine is not a feature of the usual type of simple goitre.

Faecal excretion of iodine.

Increased excretion of iodine in the faeces has also been suggested as a cause of goitre. According to Van Middlesworth (1960) rats receiving diets relatively low in iodine do not develop goitres unless there is also an increased faecal excretion of iodine, and this worker suggests that increased faecal excretion of iodine may be an important aetiological factor in human goitre. Hydovitz (1960) reported a single case of goitre in an infant on a soya bean diet which he attributed to an increased faecal excretion of iodine induced by the soya bean diet, although he did not make any measurement of the faecal iodine. Shepard et al (1960) have also reported goitres in infants receiving soya bean milk, but they assume that it is the low iodine content of the diet which is reponsible. There is as yet no evidence that soya increases

faecal loss of iodine in humans and even in rats the evidence on this point is conflicting (Van Middlesworth 1957; McPherson and Albert 1961).

In general, faecal excretion in man accounts for a relatively small proportion of the daily iodine loss, but there are variations of sufficient degree to influence the iodine requirements of the individual. In theory it is quite possible that excessive faecal excretion of iodine may lead to iodine deficiency.

In summary, deficient dietary intake of iodine is usually the major cause of iodine deficiency. Particularly affected are regions where the iodine content of the soil is low and where sea fish or iodised salt are not usually consumed. Individual food preferences lead to large individual variations in iodine intake within the same locality. Abnormally high levels of renal, and possibly of faecal, excretion of iodine are sometimes encountered and may be sufficiently severe in themselves to produce iodine deficiency, although this is rare. More usually they act as additional factors in persons on a marginal dietary intake of iodine.

PATHOGENESIS OF IODINE DEFICIENCY GOITRE.

As already mentioned, in the case of most ions essential for the body economy, adaptation to deficient intake is brought about by an adjustment of the renal clearance so that the plasma level is kept within the normal range. Such a renal mechanism does not exist for the conservation of the iodide ion (Fig 3.2). Thus Stanbury et al (1952) found no decrease in renal clearance in 3 subjects with endemic goitre in Argentina and we have found normal or elevated values in the Glasgow group. It is by increasing the thyroid clearance of iodine that adaptation to iodine deficiency takes place. In this way the gland clears a greater volume of plasma and so preserves a normal absolute iodine uptake in spite of the lower PII concentration.

The sequence of events leading to the appearance of an iodine-deficiency goitre is not fully established but the following account is consistent with the known facts. After a reduction in iodine intake there is a fall in PII which does not however fully reflect the reduction in iodine intake, because the iodine resulting from the breakdown of the thyroid hormones is still available in the plasma. At this stage there is a progressive diminution in the iodine content of the thyroid gland. Eventually the drop in the intrathyroidal iodine results in diminished hormone synthesis, slightly decreased PBI levels, and decreased available thyroid hormone for the tissues. This transient

fall in circulating thyroid hormone (or alternatively the decrease in the intrathyroidal iodine stores) results in increased TSH production which raises the thyroidal iodide clearance. Thus the absolute iodine uptake returns to the normal range. This functional overactivity of the thyroid is accompanied by an increase in the gland size. When final equilibrium occurs, the PII is even lower than in the initial stage, since the decrease of the thyroidal iodine stores has stopped, and intake and output of iodine equal each other both in the thyroid and in the body. At this stage the PII is proportional to the iodine intake*. The intrathyroidal iodine is normal and so is the circulating PBI. Since the PBI level is normal the TSH output also returns towards normal values, and this is consistent with the fact that an iodine-deficiency goitre will increase its output of hormone in response to exogenous TSH. The level of endogenous TSH, however, although not increased to the point of producing further progression in goitre size, is enough to maintain the thyroid gland at its present size.

Iodine deficiency without goitre.

When iodine deficiency is not severe, the compensatory increase in thyroid clearance may not necessarily be accompanied by an iodine deficiency goitre. Thus Bishopric et al (1955) observed an increased

* More accurately the PII is proportional to absorbed iodine minus faecal excretion and is inversely related to the renal clearance rate.

uptake of radio-iodine in a group of non-goitrous patients who had been taking for long periods a "rice diet" with a content of iodine roughly estimated at 25 μg a day or less. High values of thyroid uptake reverting to normal after administration of iodine have also been reported in apparently healthy euthyroid Egyptian children (Divany et al 1960). Even in areas of endemic goitre some persons may have a high thyroid uptake but no goitre (Roche et al 1957; Querido et al 1957). Thus Roche (1959) and Roche et al (1961) observed a South American tribe with impalpable or just palpable thyroids and a high thyroid uptake together with a low urinary iodine excretion (21 μg/day).* In such cases adaptation to moderate iodine deficiency occurs without the development of an obvious goitre. Lamberg et al (1958) concluded that the endemic goitre in the Aland Islands (Finland) was due to iodine deficiency. Their goitrous patients excreted a mean of 41.2 μg of iodine per 48 hr, and non-goitrous subjects 49.1 μg per 48 hr which is also low. This suggests that almost everybody in the Aland Islands is iodine-deficient but that some of the less severely affected manage to adapt without the formation of an obvious goitre.

In Glasgow we have studied two euthyroid patients without goitre but with a high radioiodine uptake and high PBI^{131} (p253). These patients had a low PII and a normal absolute iodine uptake. The

* However, even a just palpable thyroid is a sign of thyroid enlargement, at least in males.

intrathyroidal iodine stores were however low in both cases. These patients are, therefore, examples of a different type of adaptation to iodine deficiency. Perhaps the most likely explanation is that adaptation without goitre may be associated with low intrathyroidal stores and hence a high PBI^{131}. In this respect adaptation to iodine deficiency without a goitre may be regarded metabolically as less complete than adaptation with goitre formation.

Can iodine deficiency alone produce non-toxic goitre?

There is no doubt that evidence of iodine deficiency has been found in most places with a high prevalence of non-toxic goitre, and even in areas where the prevalence is not high the evidence suggests that many patients with simple goitre are iodine deficient when compared with normal controls. In most communities in which it has been used iodised salt has greatly reduced the incidence of goitre and some goitres in iodine-deficient persons diminish in size when treated with small doses of iodine. All these facts point to iodine deficiency as the essential factor in the production of simple goitre. On the other hand as we have seen it is sometimes possible to demonstrate biochemical abnormalities suggestive of iodine deficiency in persons who have no goitre. For these reasons some workers have suggested that iodine deficiency per se cannot lead to goitre formation, and that additional factors must exist before a goitre develops. However, some simple considerations of the physiology of iodine metabolism leave no doubt that, in the presence

of severe iodine deficiency, goitre is inevitable. Thus when the PII falls to 0.01 µg/100 ml the thyroid clearance must rise to 300.0 ml/min in order to assure an absolute iodine uptake of 1.8 µg/hr, and such a degree of functional overactivity of the gland must necessarily be accompanied by an increase in size as well. As Riggs (1952) has pointed out in forceful terms "The only alternative would be to assume that a gland of normal size could accommodate a litre and a half of blood per minute and could extract the iodide from this torrent with normal efficiency. Since this alternative is obviously ridiculous, the recurring argument that iodine deficiency is not a sufficient cause of endemic goitre is finally and utterly demolished. In euthyroid persons with normal renal function, goitre is an obligatory response to prolonged and severe iodine deficiency".

Nevertheless when iodine deficiency is not severe, some individuals will develop a non-toxic goitre and some will not. Thus different persons display a different sensitivity to the effects of iodine deficiency. For instance when iodine deficiency in only mild some persons will readily develop a goitre, whereas others will increase their thyroid clearance rate without the formation of a palpable goitre. Furthermore some persons may produce more T_3 than T_4 and thus make a more potent hormone with a smaller quantity of iodine. Lastly some persons may not be able to compensate for iodine deficiency and, if this is severe, may become hypothyroid more easily than others (p193). It seems therefore that there is a spectrum of responses to iodine deficiency,

although the most typical response is the development of an iodine-deficiency goitre and the preservation of euthyroidism.

One can therefore conclude that although severe iodine deficiency inevitably leads to goitre, a mild iodine-deficiency state may or may not do so according to the individual sensitivity of the person.

Differences between naturally occurring and goitrogen-induced iodine deficiency.

It is reasonable to consider whether iodine deficiency, often found in patients with simple goitre (p183), may be the result of prolonged administration of goitrogens. Present evidence favours the view that this is not the case. Goitrogen-induced iodine deficiency presupposes a former stage during which radioiodine uptake and binding by the thyroid is reduced, thus leading to depletion of the intrathyroidal iodine stores. Such a stage, however, has never been described in simple goitre, and the radioiodine uptake has been found to be either normal or elevated, but never low. Since the uptake is not low the intrathyroidal stores cannot be depleted. This is borne out by actual measurements of the intra-thyroidal iodine stores in simple goitre, which have been found to be normal (p200).

In summary goitrogen-induced iodine deficiency shows basic differences from the common type of naturally occurring iodine deficiency. During goitrogen administration the organic iodine pools, both intra- and extra-thyroidal are the first to be decreased, and the decrease in PII is a secondary phenomenon, occurring after the goitrogen is discontinued.

In natural iodine-deficiency goitre the primary change is the decrease in PII, and the organic iodine pools are usually in no way diminished. It may perhaps be possible to mimic natural iodine deficiency at a certain specific time after discontinuing goitrogens, but it seems extremely unlikely that all cases with iodine-deficiency goitre studied by different workers were exactly at that phase. If goitrogens were responsible, they would presumably still be acting in some patients, in which case the pattern of iodine metabolism would be entirely different.

DYSHORMONOGENESIS

(INBORN DEFECTS OF THYROID HORMONE SYNTHESIS)

The thyroid gland may fail to produce a normal amount of thyroid hormone even though it is presented with an adequate supply of iodine. When this is due to an inborn defect in hormone synthesis, McGirr (1960) uses the term dyshormonogenesis. Strictly speaking, the description could apply to other states in which defective synthesis occurs such as follow the use of goitrogens, or it could even be applied to glands other than the thyroid. Nevertheless, if it is agreed to use the term in McGirr's sense it is a most useful addition to our vocabulary. The alternative description "inborn errors of thyroid hormone synthesis" is more cumbersome. Defects in hormone synthesis are not always sufficiently severe to lead to frank hypothyroidism, but many patients are hypothyroid and since the condition dates from birth they are usually cretins. Indeed it is probable that most cases of the condition originally described as "sporadic goitrous cretinism" were the result of dyshormonogenesis.

In this section quantitative studies of iodine metabolism are described in four proven cases of dyshormonogenesis. The pattern of iodine metabolism was quite different from that found in other cases of non-toxic goitre. This dissimilarity may provide the basis of a screening procedure, simpler than others at present available, for the detection of cases of dyshormonogenesis.

Materials and methods

Four patients were studied. Three of the cases had impaired ability to utilize trapped iodide (peroxidase deficiency) and the fourth was of the type associated with the production of an abnormal iodinated protein (McGirr 1960, Stanbury 1960). In the first three cases, all siblings, the diagnosis was based on the family history of goitre with deaf-mutism, and the discharge of radioiodine from the thyroid gland, either by potassium perchlorate or spontaneously. In the fourth case the diagnosis was based on the presence of goitrous cretinism together with the finding of a high proportion of butanol-inextractable protein-bound iodine in the plasma. Immunological tests for thyroid auto-antibodies (precipitin and complement fixation) were negative. In all cases the uptake of radioiodine by the thyroid gland, the 48-hour plasma protein-bound radioiodine (Wayne 1960) and the stable protein-bound iodine were estimated. The potassium perchlorate discharge test was carried out by measuring the thyroid gland uptake 60 minutes after an

oral dose of 25 μc I^{132}. Immediately thereafter 0.5 g potassium perchlorate was given by mouth and 40 minutes later the thyroid uptake was again measured. The result was expressed as a percentage of the initial reading: a value of less than 90 per cent was considered positive.

The thyroid and renal radioiodine clearance rates, the plasma inorganic iodine, the absolute iodine uptake and the intrathyroidal exchangeable iodine were measured as described in chapter 1. In two patients (cases 2 and 3 below) the I^{131} tracer dose was administered intravenously and the thyroid and renal clearance estimated over the following 90 minutes. This was necessary because of the spontaneous discharge of radioiodine from the thyroid 2 hours after the tracer dose was administered, which prevented the estimation of the thyroid clearance rate in the usual way between 1 and 2½ hours. Total and organic urinary iodine were estimated by the resin column method. The difference was taken as the inorganic iodine fraction and was expressed as a percentage of the total urinary iodine. The butanol-inextractable radioactive iodine was estimated by butanol extraction of the plasma PBI^{131}, and subsequent assay of radioactivity in the remaining precipitate.

Results

Brief summaries of the four cases are given below, and laboratory findings are summarized in Table 4.8.

Case 1. A woman of 53 years, had been born a deaf-mute. She was referred because of a goitre of several years duration. She appeared otherwise normal and was the mother of two normal children. There was a family history of congenital deaf-mutism and goitre. One

Table 4.8

Laboratory findings in four cases of dyshormonogenesis

Table I. Laboratory findings.

	Case 1	Case 2	Case 3	Case 4	Normal range
Thyroid uptake at 4 hrs. (% of dose)	60.6	—	25.6	58.8	15—40
Thyroid uptake at 48 hrs. (% of dose)	61.5	76.2	19.6	62.6	20—60
Thyroid clearance (ml./min.)	55.4	346.0	85.0	113.0	6—40
Radioactive protein-bound iodine (P.B.^{131}I.) at 48 hrs. (% /l.)	0.29	0.09	0.08	0.21	0.0—0.4
Plasma inorganic iodine (P.I.I.) (μg./100 ml.)	0.85	0.10	0.46	0.32	0.10—1.00
Absolute iodine uptake (A.I.U.) (μg./hr.)	28.2	21.4	23.5	21.5	1—6
Protein-bound iodine (P.B.I.) (μg./100 ml.)	3.8	3.1	7.0	2.9	3.5—7.5
Intrathyroid exchangeable iodine (I.E.I.) (mg.)	6.0	12.4	—	1.0	5—20
Renal clearance of radioiodine (ml./min.)	32.2	53.8	39.3	17.4	15—50
Urinary organic iodine (% of total iodine)	6	—	6	5	< 20 %
P.B. ^{131}I. at 9 days (before T.S.H.)	0.53	0.22	0.07	0.29	—
P.B.^{131}I. at 10 days (after 10 units T.S.H.)	0.72	0.34	0.09	0.37	—
P.B.^{131}I. % rise after T.S.H.	36	55	—	41	—

Note: It should be noted that in Case 3 the rise in P.B.^{131}I. after T.S.H. administration was small; therefore the value of I.E.I. calculated in this case (11.3 mg.) is subject to considerable error.

of her four brothers (case 2) and one of her three sisters (case 3) showed the association of congenital deaf-mutism with goitre. On examination a large, firm nodular goitre was present. She was clinically euthyroid and of normal intelligence. The potassium perchlorate discharge test was positive, showing a fall in thyroid uptake of 45 per cent of the initial value.

Case 2. A man, aged 48 years, was a deaf-mute and had had a goitre for many years. He was married and worked as a woodman. On examination a large, firm, nodular goitre was found. Clinically he was euthyroid, but the PBI was 3.1 μg per cent. A potassium perchlorate discharge test was not carried out because his thyroid spontaneously discharged radioactive iodine.

Case 3. A female, 45 years old, was a deaf-mute, and has had a goitre since childhood. The goitre was moderately large and soft. Clinically she was euthyroid and of normal intelligence. A potassium perchlorate discharge test was not carried out for the same reason as in Case 2.

Case 4. A female, 54 years old, was reported in detail by Buchanan and Crooks (1959; Case 2). This patient had goitrous cretinism and the potassium perchlorate discharge test was negative. Fifty-seven per cent of the PBI^{131} was butanol-inextractable.

It can be seen from Table 4.8 that in all four cases, the most striking abnormality is the high AIU and thyroid clearance, both of which lie well within the thyrotoxic range. However, the PBI values are

either normal or low. In contrast to iodine-deficiency goitre (p190) the PII is normal. In the three cases tested there was no abnormal concentration of organic iodine in the urine.

In cases 1, 2 and 4 an increase in plasma protein-bound radioiodine was observed after administration of thyrotrophin (TSH). In these cases, therefore, it appears that the thyroid glands were not under maximal endogenous TSH stimulation.

Discussion

Our results show a marked difference in iodine metabolism between known cases of dyshormonogenesis and cases of high-uptake iodine-deficiency goitre. These two types of goitre have in common a high radioiodine uptake by the thyroid and a high radio-iodine thyroid clearance. In the iodine-deficiency cases, however, the high radio-iodine uptake is associated with a low plasma inorganic iodine (PII) and a normal absolute iodine uptake (AIU) whereas in goitres due to dyshormonogenesis the PII is normal, thus excluding iodine deficiency. The absolute uptake of stable iodine (AIU) is raised and lies within the thyrotoxic range. The combination of an abnormally high AIU with a normal PBI reflects the faulty utilization of iodine by the thyroid gland, and is entirely consistent with the enzyme defects known to be present in this condition. This can best be demonstrated by using an index which gives a measure of the capacity of the thyroid gland to utilize iodine presented to it. We define the iodine utilization index as the ratio of PBI to AIU. In normal cases it has always exceeded 0.6

whereas in the cases of dyshormonogenesis the figures are 0.13, 0.13, 0.14 and 0.30 (mean 0.17). This illustrates in a striking way the inability of the gland to utilize available iodine. When interpreting the iodine utilization index it must be remembered that circulating butanol-insoluble iodoproteins, or abnormal rates of peripheral thyroid hormone metabolism may influence the serum PBI level.

I have not yet seen patients with other types of dyshormonogenesis. Theoretically one would expect a low PII in the deiodinase deficiency type because of urinary loss of iodotyrosines, but in the single case reported by Gardner et al (1959) it was normal. The pattern of iodine metabolism we have found (high AIU with normal PBI) differs from that observed in a patient with defective iodide trapping (Stanbury and Chapman 1960): this case would be expected to show a low AIU.

In all types of dyshormonogenesis the PBI is normal or low, in spite of the high AIU usually present. As shown in Fig 4.5 this discrepancy between the high AIU and the normal or decreased hormone synthesis must be explained on the basis of iodine leaking from the thyroid in an inactive form, either as iodide or as abnormal iodinated compounds.

The cases we have studied had PBI^{131} values which were normal or slightly increased (up to 0.29%/litre), but others have reported values in the thyrotoxic range, that is above 0.40%/litre (McGirr 1960). It may be that the difference in PBI^{131} levels is related to the thyroid

status of the patients: euthyroid patients have normal stores of intrathyroidal exchangeable iodine, and hence a normal PBI^{131}, whereas when the defect is uncompensated (goitrous cretinism) the intrathyroid iodine stores are depleted, thus leading to a high PBI^{131} (p250). Two of our cases were euthyroid and had normal intrathyroid iodine values whereas a third, which was hypothyroid, had an intrathyroid pool of only 1 mg.

Summary

Studies of stable iodine metabolism have been carried out in four cases of thyroid dyshormonogenesis (three due to peroxidase deficiency and one associated with an abnormal iodoprotein). A characteristic pattern of stable iodine metabolism has been found, consisting of a high thyroid clearance of radioiodine, a normal plasma inorganic iodine, a high absolute iodine uptake, and a normal or low plasma protein-bound iodine. This picture differs from that seen in other types of simple goitre. The iodine-utilization index, defined as the ratio of the protein-bound iodine to the absolute iodine uptake was abnormally low in every case. These studies have enabled differentiation of high-uptake iodine-deficiency goitres from four goitres due to dyshormonogenesis when this was impossible by the use of standard radioiodine tests and protein-bound iodine determinations. Such studies may provide help in the differential diagnosis of non-toxic goitre.

IODINE AS A GOITROGEN.

Iodine deficiency is the single most important cause of goitre (p181). However, in exceptional instances iodine in excess can also cause goitre and hypothyroidism (Morgans and Trotter 1953; Turner and Howard 1956; Rubenstein and Oliner 1957; Paley et al 1958; Morgans and Trotter 1959; Laroche and Hirsch 1960; Paris et al 1960; Mornex et al 1960; Ezrin et al 1961; Dimitriadou and Fraser 1961; Oppenheimer and McPherson 1961). Galina et al (1962) have described congenital iodide goitre in two newborn infants whose mothers had taken an iodide-containing proprietary mixture during pregnancy. Both infants died shortly after birth, and the large goitres were considered responsible for tracheal compression. Congenital iodide goitre has also been described in binovular twins whose mother was taking the iodine-containing drug Felsol during pregnancy (Anderson and Bird 1961).

That iodide may act as an antithyroid drug in thyrotoxicosis is well-known, but it is most unusual for a thyrotoxic patient to become hypothyroid even with large doses or after prolonged treatment. Indeed this wide safety margin has permitted the use of doses of iodine far in excess of the minimal effective amounts (Friend 1960). However, a few thyrotoxic patients seem to react in an unusual way to iodine and become hypothyroid. It seems that these thyrotoxic patients have a particular sensitivity to the antithyroid action of iodide. A similar special sensitivity must also be implicated in the development of goitre

and hypothyroidism in previously euthyroid persons, since out of a large number of persons receiving large doses of iodides only a very small minority develop iodide goitre. Indeed iodine and its compounds have been used in large doses in euthyroid persons for centuries in the treatment of a wide variety of conditions including teriary syphilis but goitre and hypothyroidism is rarely seen. Relatively high doses over long periods are still used in cough mixtures and remedies for asthma. Many of these mixtures are proprietary remedies sold direct to the public and their total consumption must be very large indeed. Thus the development of goitre is an exceptional occurrence.

In this section quantitative studies of iodine metabolism are described in four cases of iodine-induced goitre and hypothyroidism. The pattern of iodine metabolism proved to be characteristic, and was associated with an abnormality of the pituitary-thyroid relationship.

Methods

All four patients had thyroid enlargement estimated at 50 to 75 g, and showed clinical features of hypothyroidism (Wayne 1960). Other clinical details are shown in Table 4.9. The marked variation in the total quantity of iodine ingested by these patients before a goitre developed is shown in Fig 4.7.

Thyroid clearance of radioiodine, PII, AIU, PBI, and renal radioiodine clearance were measured as previously described (p12). These measurements were made serially in three of the four patients. In two of them studies were begun at or near the end of a period of

Table 4.9

Details of four patients with iodine-induced goitre and hypothyroidism

Age	Sex	Drug	Iodine per day	Past history of thyroid disease
45	M	'Pelsol'	48 mg	None
28	F	'Brovonex'	190 mg	None
52	F	'Pelsol'	24 mg	Thyrotoxicosis 8 years before
33	F	'Coffedrin'	1270 mg	None

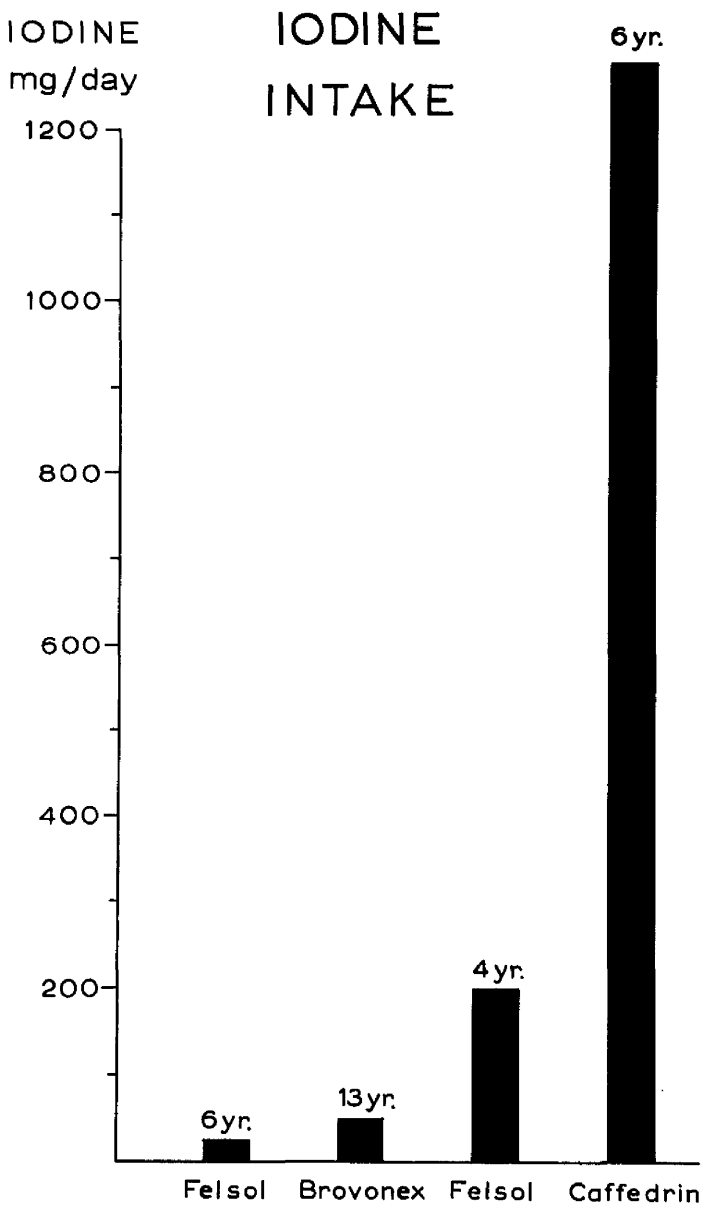

Figure 4.7

Quantity of iodine ingested prior to development of iodine-induced goitre

Both the total amount of iodine ingested and the duration of therapy before a goitre developed were very variable.

chronic iodine ingestion, while in the other patient studies were made before, during and after iodine ingestion. The remaining patient (Case 4) was found to be in the first trimester of pregnancy, and iodide ingestion was immediately stopped. No investigations were carried out until 4 months after parturition, which was uneventful.

In one patient (case 3) thyroxine in the serum was measured after separation from other iodine-containing compounds on a resin column as described by Piloggi et al (1961).

Tri-iodothyronine (T_3) suppression test. This was carried out after withdrawing iodine from patients for periods of 4 months to 1 year. After preliminary measurement of thyroid uptake of radioiodine at 48 hours, the patients were given T_3 in a dose of 40 µg three times daily for 9 days. On the 7th day a second tracer dose of I^{131} was given, and the thyroid uptake was again measured. In normal subjects the uptake after T_3 is reduced by at least 50% of the initial value (Trotter 1962).

Results

Serial data in cases 1, 2 and 3 are shown in Table 4.10 and Fig 4.8. The renal iodide clearance was within the normal range throughout, and does not merit further description.

In each patient the PII was very high while iodine was being

Table 4.10

Iodine-induced goitre

Plasma inorganic iodine, thyroid radioiodine clearance, and absolute iodine uptake, during, and after discontinuing, iodine administration

Time* days	PII µg/100 ml	Th.Cl. ml/min	AIU µg/hr
Case 1			
-300	.08	59.6	2.8
-1	350	57.9	12,159
8	12.04	156.0	1,127
38	4.48	37.0	99
41	5.10	49.2	150
44	4.10	145.9	359
46	1.03	100.0	61
53	0.54	38.6	12
60	0.27	29.1	4.7
74	0.09	25.4	1.4
Case 2			
-24	263	7.2	1139
-1	143	9.6	822
7	.66	263.6	104
28	.12	40.0	2.9
32	.13	50.7	4.0
60	.10	36.8	2.2
Case 3			
-36	53.4	44.5	1426
-28	53.3	7.2	230
-1	48.6	12.4	361
1	15.0	14.8	133
2	9.22	18.7	103
3	3.83	7.9	18
10	1.00	132.7	79
17	0.12	95.1	6.8
31	0.06	34.4	1.2
59	0.05	30.1	0.9

* Measured from day iodine administration was discontinued.

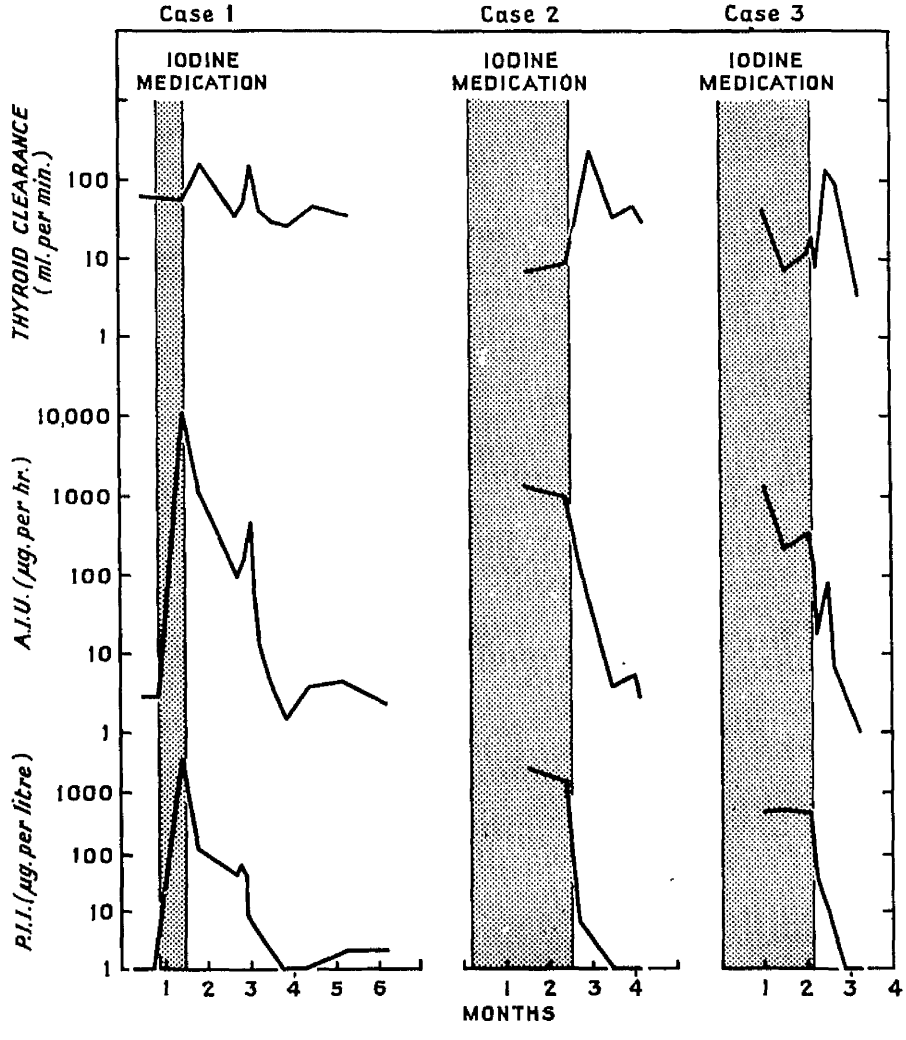

Figure 4.8

Thyroid radioiodine clearance, absolute iodine uptake and plasma inorganic iodine in iodine-induced goitre

In spite of the very large amounts of iodine taken up by the thyroid gland (AIU) all three patients were clinically hypothyroid.

ingested, but the thyroid radioiodine clearance was abnormally high in two patients, and within the normal range in the third. This resulted in large amounts of iodine being taken up by the thyroid, and the AIU exceeded 1000 μg/hr in every case. While the patients were taking iodine the levels of PBI in the serum were greater than normal although there was clinical evidence of hypothyroidism. However, thyroxine was present in less than normal amounts in the serum of case 3, showing that much of the iodine measured as PBI was not thyroid hormone.

When the administration of iodine was stopped the PII level fell rapidly, but there was a marked temporary increase in the rate of clearance of iodine by the thyroid gland. A rapid disappearance of the features of hypothyroidism was noted, and the patients became euthyroid without the administration of thyroxine. The PBI and serum thyroxine values returned to normal.

The results of the T_3 suppression tests are shown in Table 4.11. In all four patients an abnormal result was obtained, with failure of the radioiodine uptake after administration of T_3.

Discussion

These patients with iodine-induced goitre and hypothyroidism showed a similar abnormal pattern of iodine metabolism and of thyroid function. While they were receiving iodine there was a large absolute iodine uptake by the thyroid gland - several hundred times normal. This was due to high levels of thyroid clearance and of PII, and it

Table 4.11

Thyroid uptake of I^{131} before and after administration of triiodothyronine

Patient	I^{131} uptake at 48 hr (% dose)	
	Before T_3	After T_3
1	59	43
2	56	38
3	46	61
4	46	49

persisted as long as the patients took iodine. In contrast, the most conspicuous finding in normal persons taking iodides is a low thyroid uptake and clearance (p 74).

It is believed that, because large amounts of iodine in the thyroid gland prevent organic binding of iodine to tyrosine, synthesis of thyroid hormone is inhibited (Wolff and Chaikoff 1948; Stanley 1949). Although in patients with iodine-induced goitre and hypothyroidism large amounts of iodine are taken up by the thyroid gland little of it is converted to thyroid hormone, and therefore, the gland becomes depleted of thyroglobulin. A large proportion of radioiodine taken up is discharged by thiocyanate or perchlorate (Paley et al 1958; Oppenheimer and McPherson 1961), indicating that organic binding is defective. Auto-radiography of the thyroid in one case showed that iodine was present only as inorganic iodide (Paris et al 1960). A proportion of the large amount of iodine taken up is probably released again spontaneously without undergoing any change inside the gland. This sequence of events is similar to that when antithyroid drugs, such as carbimazole, are given. When iodine is withdrawn the concentration inside the thyroid falls sufficiently to allow organic binding to occur normally, and synthesis of thyroxine then proceeds at a rapid rate. The thyroid, being depleted of thyroglobulin, isvery avid for iodine, and this is rapidly converted to thyroid hormone and stored by the gland until its normal thyroglobulin content is restored. Iodine now taken up by the thyroid can no longer be discharged by perchlorate or thiocyanate

(Paley et al 1958; Oppenheimer and McPherson 1961) indicating that it is now organically bound.

In all four of our patients another abnormality was discovered - namely, the absence of suppression of I^{131} uptake by the thyroid after administration of T_3. This is evidence of a disturbance of the pituitary-thyroid axis which may be the basic abnormality in these cases: the thyroid may be unable to decrease its clearance rate in spite of the rise in PII so that iodide in excessive quantities accumulates within the thyroid and inhibits thyroid hormone synthesis. However in another case suppression after T_3 administration did occur (Dimitriadou and Fraser 1961), and I have also recently seen a case of this type. Thus failure of normal homeostatic control of the thyroid is certainly not the only mechanism which can lead to iodine-induced goitre and hypothyroidism.

If thyroid extract or thyroxine is given the goitre decreases in size, even if iodide administration continues (Paris et al 1960). This type of goitre is therefore probably the result of excessive amounts of endogenous TSH, as is the case with every other type of non-toxic goitre, so far as is known. However, this does not fit well with the lack of thyroid suppression after T_3 occurring in some of our cases, and it is possible that, at least in some instances, iodide goitre constitutes an exception to the rule.

Summary

Four patients with iodine-induced goitre and hypothyroidism

were studied. In all of them the uptake of I^{131} by the thyroid gland was not normally suppressed after tri-iodothyronine, indicating abnormal pituitary-thyroid control. In three of the patients serial measurements were made of thyroid clearance of iodine, plasma inorganic iodine, and absolute iodine uptake by the thyroid, both during and after the administration of iodine. In each case the absolute uptake of iodine was very high during the period of ingestion, owing to an abnormally high thyroid clearance and to high levels of plasma inorganic iodine. When iodine was discontinued, the iodine uptake and plasma inorganic iodine fell rapidly, but the thyroid clearance temporarily increased still further.

The basic abnormality in some patients with iodine-induced goitre may be an inability of the thyroid to stop taking up iodine when large amounts are available to it.

Chapter 5 - VALUE OF QUANTITATIVE STUDIES IN THE DIAGNOSIS OF THYROID DISEASE

VALUE OF QUANTITATIVE STUDIESOF IODINE METABOLISM IN THE DIAGNOSIS OF THYROID DISEASE

Quantitative measurements of the type described in this thesis are valuable in clinical diagnosis in two ways. Firstly, they provide information of great assistance in the correct interpretation of the standard radioiodine tests of thyroid function. These tests are dependent not only on the level of thyroid activity, but also on the size of the iodine pools in which the radioiodine is diluted. The significance of the pool size is analysed in the first part of this chapter.

Secondly, quantitative measurements may give valuable information about the level of thyroid activity in the individual case. The range in health and disease has been defined in Chapters 2 and 4, and the circumstances in which the measurements may be of value in clinical diagnosis are described in the latter half of this chapter.

STUDIES OF STABLE IODINE METABOLISM AS A GUIDE TO THE INTERPRETATION OF RADIOIODINE TESTS

Radioiodine tests are generally interpreted as if they reflected only the level of thyroid function and it is not usually appreciated that they are also influenced by the amount of iodine in the body with which the tracer dose in diluted. This section illustrates with examples the importance of this second factor.

The standard radioiodine tests give information about two different aspects of iodine metabolism and so fall into two main groups. Tests of the first type measure either directly or indirectly the capacity of the thyroid gland to accumulate radioiodine. In the second group of tests an attempt is made to measure the output of thyroid hormone into the circulation. Better correlation with the final clinical diagnosis have been reported when measurements of both phases of iodine metabolism are taken into consideration (Macgregor and Wayne 1958). Discrepancies, however, are not infrequent and it has not been possible to account for them satisfactorily until methods for the quantitative study of stable iodine metabolism became available. We shall consider separately the tests used to measure each of the main phases of iodine metabolism in the light of studies of stable iodine metabolism.

ACCUMULATION OF IODINE BY THE THYROID

Tests available for the study of this important step in iodine metabolism include estimations of: (a) the percentage uptake of radioiodine by the thyroid at various times after its administration, (b) the volume of plasma cleared of iodide by the thyroid per unit of time, that is the plasma clearance rate (Myant et al 1949; Berson et al 1952), (c) the percentage excretion of radioiodine in the urine during a fixed time interval (Skanse 1949; Fraser et al 1953), (d) several modifications, such as the neck-thigh ratio (Pochin 1950). These tests all measure essentially the same parameter, and the choice is based chiefly on practical and technical considerations.

The plasma clearance rate gives a direct quantitative estimate of this phase of iodine metabolism, and the other tests are used because they correlate with it. Thus the radioiodine-uptake tests depend on the competition between the thyroidal and the renal clearance of iodide, and can be predicted if both these clearance rates are known (p 53). Therefore from the biological point of view the thyroid clearance is a better measurement of this step in iodine metabolism than the radioiodine uptake, since it is not influenced by alterations in renal clearance. Even in normal subjects the renal clearance of iodide has a wide range, varying from 15 to 55 ml/min.

The results of radioiodine tests are dependent not only on thyroid function but also on the size of the iodine pools in which the radioiodine is diluted. The uptake of I^{131} is inversely related to the extrathyroidal inorganic iodine pool and the PBI^{131} is inversely related to the intrathyroidal iodine pool. Both these pools may be diminished in euthyroid persons and thus a high uptake of I^{131} may be associated with a high PBT^{131} and so lead to false diagnostic conclusions.

The range is considerably wider if cases with renal abnormalities are also included. In practice, however, the radioiodine uptake is more commonly used than the thyroid clearance rate since it is more easily performed and hence has a smaller technical error. If a single measurement of the radioiodine uptake is to be carried out, it is best to make it not more than 6 hours after the administration of the tracer dose. These early uptake measurements not only correlate better with the thyroid clearance rate (p54), but also are unaffected by the discharge of radioiodine from the thyroid which commonly occurs in thyrotoxicosis after that time. Wayne (1954) concluded that the 4-hour uptake was a good parameter of this aspect of iodine metabolism, and he and his collaborators preferred it in practice to the thyroid clearance rate.

The urinary excretion of radioiodine also measures the same fundamental process, since the larger the quantity of iodide concentrated by the thyroid, the smaller the amount available for

excretion by the kidney. Tests based on this fact have been used especially in the diagnosis of hypothyroidism. Fraser et al (1953) have devised a T index which gives a greater numerical difference between hypothyroid and euthyroid patients than an estimation of the total 48-hour excretion of radioiodine, but in practice it is more liable to inaccuracy from faulty collections of urine.

It is clear that all the tests in this group give an estimate of the volume of plasma cleared of its iodide content by the thyroid, whereas the information we really require is the absolute amount of iodine retained by the thyroid per unit of time. In order to obtain an estimate of this we must have information about the concentration of stable inorganic iodine in the plasma cleared by the thyroid. The radioiodine clearance rate (and therefore the radioiodine uptake) is a good index of the absolute iodine uptake when the concentration of stable plasma inorganic iodine (PII) is normal, but this does not hold when the PII is either unusually low or high.

Figure 5.1 shows the relation between the AIU and the 2½ hr uptake of I^{132} in 37 thyrotoxic patients, including seven who had been receiving iodine in some form, and in 45 patients with simple goitre. Nineteen patients with simple goitre had a high radioiodine uptake, whereas six thyrotoxic patients had normal or low values. The AIU gave much more reliable results, since there were no abnormally high values in the group with simple goitre, and only three normal values in the thyrotoxic group. Thus the so-called "avidity for iodine"

RADIOIODINE UPTAKE (2½ hr) AND ABSOLUTE IODINE UPTAKE IN THYROTOXICOSIS AND SIMPLE GOITRE

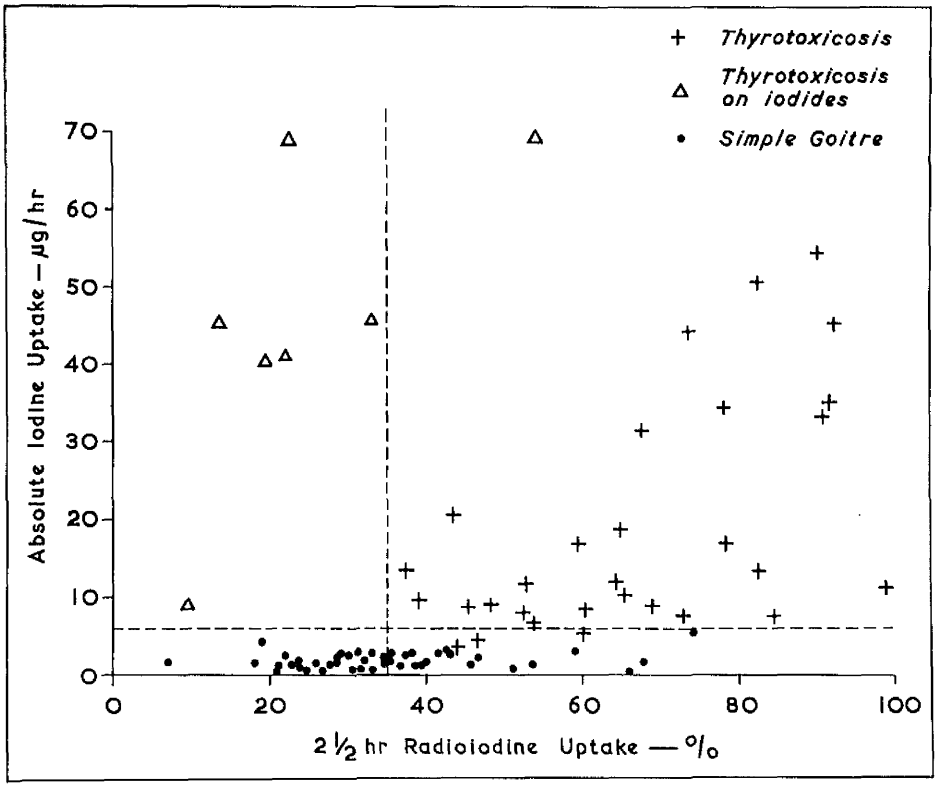

Figure 5.1 (same as Fig 4.2)

Radioiodine uptake and absolute iodine uptake (AIU) in simple goitre and thyrotoxicosis

The AIU gives a good separation of patients with simple goitre from those with thyrotoxicosis. In contrast, a good separation is not obtained with the 2½ hr I^{132} uptake because a large proportion of patients with simple goitre show increased values, whereas thyrotoxic patients receiving iodides usually show normal or low values.

of the iodine-deficient goitre is true only in a special sense. The high uptake of radioiodine does not reflect a high uptake of stable iodine, but an increased volume of plasma cleared of its iodine content in unit time (Fig 5.2).

The converse is seen when the PII is raised. Thus an unexpectedly low uptake of radioiodine may be found in thyrotoxic patients who have previously received iodine in any form. This relatively low uptake of radioiodine by the thyroid reflects a diminution in the volume of plasma cleared of iodide, but because the PII is increased, the AIU may be similar to or higher than that before the administration of iodine (Fig 5.1). Therefore the so-called "saturation" of the thyroid gland with iodine is a misnomer, since this phenomenon is accounted for by the increase in the extra-thyroidal inorganic iodine pool. The low uptake of radioiodine in those who have a large iodine pool has been misleading in other circumstances. D-thyroxine in large doses has been shown to reduce the uptake of I^{131} and this has been interpreted as evidence of suppression of thyroid function (Starr and Liebold-Schueck 1953; Greene and Farran 1958). The doses used, however, contain a large quantity of iodine which is liberated within the body, and Alexander et al (1961) have shown that, at least in thyrotoxic patients, the decreased radioiodine uptake is a consequence of the elevation of PII - indeed in such circumstances the AIU is increased (Fig 5.3).

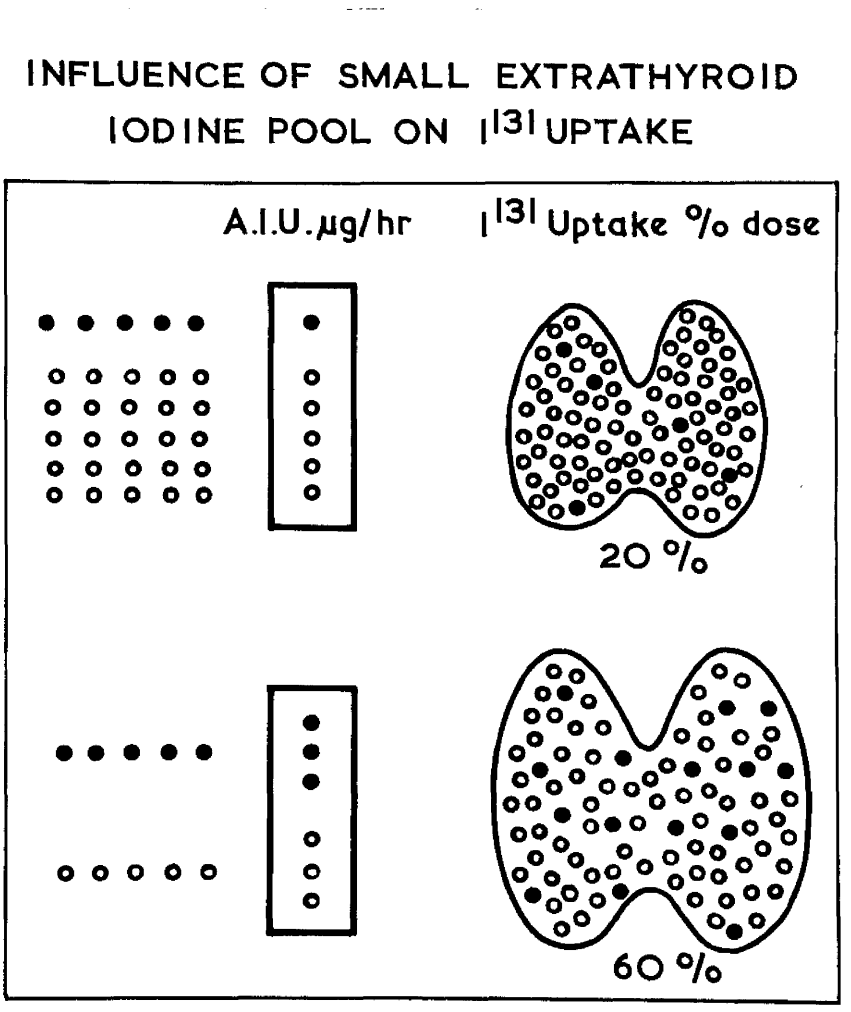

Figure 5.2

Influence of a low plasma inorganic iodine (PII) concentration on radioiodine uptake

The normal gland is shown above, and the gland with iodine deficiency goitre below. Atoms of radioiodine are indicated by solid dots, atoms of stable iodine by circles. If both glands take up the same absolute number of iodine atoms, the proportion of radioactive atoms is greater in the iodine-deficiency goitre because the plasma inorganic iodine (PII) is decreased. Although the absolute iodine uptake (AIU) expressed in µg/hr is the same in both cases, the radioiodine uptake expressed in % dose is 20% in the normal gland, but 60% in the one with iodine deficiency goitre.

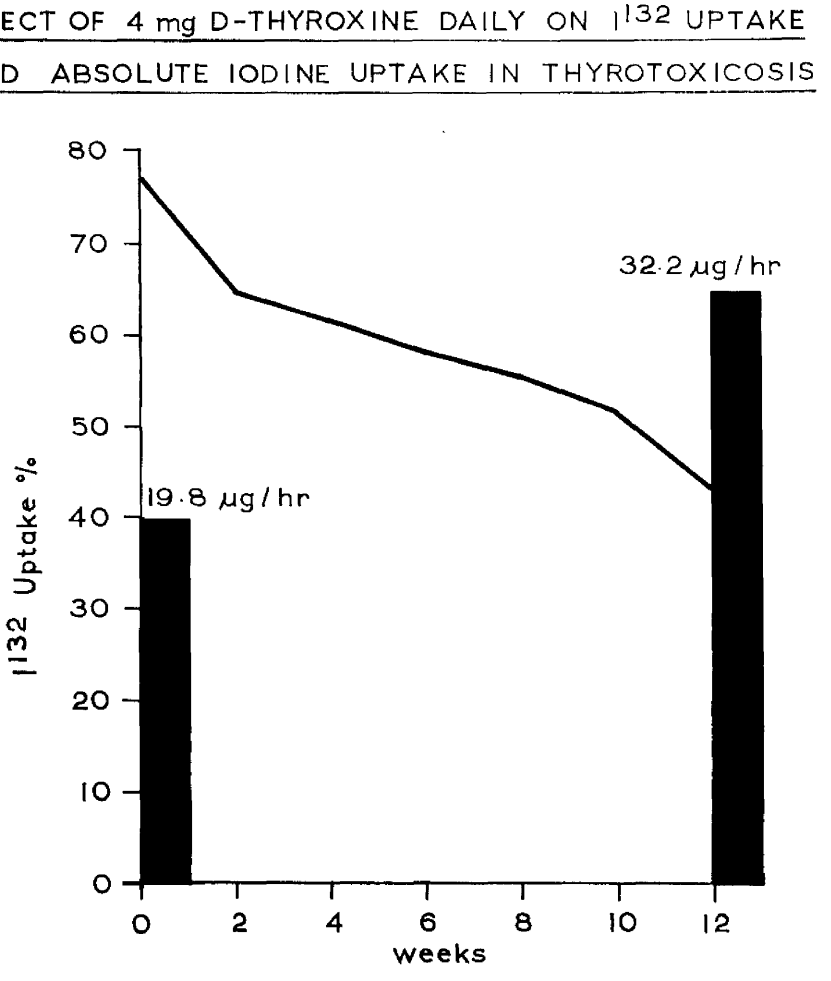

Figure 5.3

Radioiodine uptake and absolute iodine uptake(AIU) during administration of d-thyroxine

Response to 4 mg d-thyroxine daily in thyrotoxic patients (mean of 3 cases). Although the thyroid radioiodine clearance and uptake fell, the latter from 77% to 44% at 2½ hr, the absolute iodine uptake increased from 19.8 µg/hr to 32.2 µg/hr.

RELEASE OF THYROID HORMONE INTO THE CIRCULATION

The basic measurement of this phase of thyroid function is the plasma protein-bound radioactivity (PBI^{131}) measured 48 or 72 hours after administration of a tracer dose (Wayne 1954, 1960; Macgregor and Wayne 1958).

Essentially the same parameter is measured by the "conversion ratio" (Clark et al 1949), by the ratio of plasma to red cell radioactivity, or by the ratio of the 48 hour to 2 hour plasma radioactivity (Blondal 1952). The direct estimation of PBI^{131} is preferable to the use of these ratios, which bear a complex relation to it without adequate compensating technical advantages. The separation of the protein-bound fraction of the plasma radioactivity has been made easier by the use of an ion exchange column (Zieve et al 1956).

Wayne (1954) found the PBI^{131} at 48 hours the best single radioiodine test for thyroid overactivity in untreated patients. Out of 342 untreated thyrotoxic cases only 13 had a value of less than 0.4% of dose/litre plasma and out of 352 untreated euthyroid patients only 4 had a value higher than 0.4% of dose/litre plasma.

However, although the PBI^{131} is usually a good index of thyroid hormone production, it must be realised that this, too, like the radioiodine uptake, is not an absolute measure, but a relative one. It does not depend solely on the amount of thyroid hormone produced, but also on the size of the intrathyroidal exchangeable iodine pool.

Figure 5.4 shows the relation between the size of the intrathyroidal iodine pool and the PBI^{131} in 28 euthyroid patients, including those with normal thyroid function, with simple goitre, and with autoimmune thyroiditis. A highly significant inverse relation is observed ($r = 0.64$, $p < 0.001$). The PBI^{131} exceeded 0.2% of the dose per litre of plasma in 8 patients, and in all of these the intrathyroidal iodine pool was less than 4 mg. This implies that the relatively high PBI^{131} in these euthyroid patients is due to dilution of the radioactive atoms taken up by the thyroid in a smaller pool of intrathyroidal iodine than normal.

Thus the hormonal iodine released has a higher specific activity, although the total amount may be normal (Fig 5.5). This figure shows that the PBI^{131} is in fact related not only to the amount of thyroid hormone released, but also to its specific activity, which is inversely related to the intrathyroidal exchangeable iodine pool. For example after partial thyroidectomy, when this pool is reduced, the PBI^{131} may be above 0.4%/litre plasma even in euthyroid patients.

SUITABLE COMBINATIONS OF TESTS

From what has been said it is clear that tests which estimate the accumulation of radioiodine by the thyroid give figures which are not only proportional to the amount of thyroid hormone produced, but also

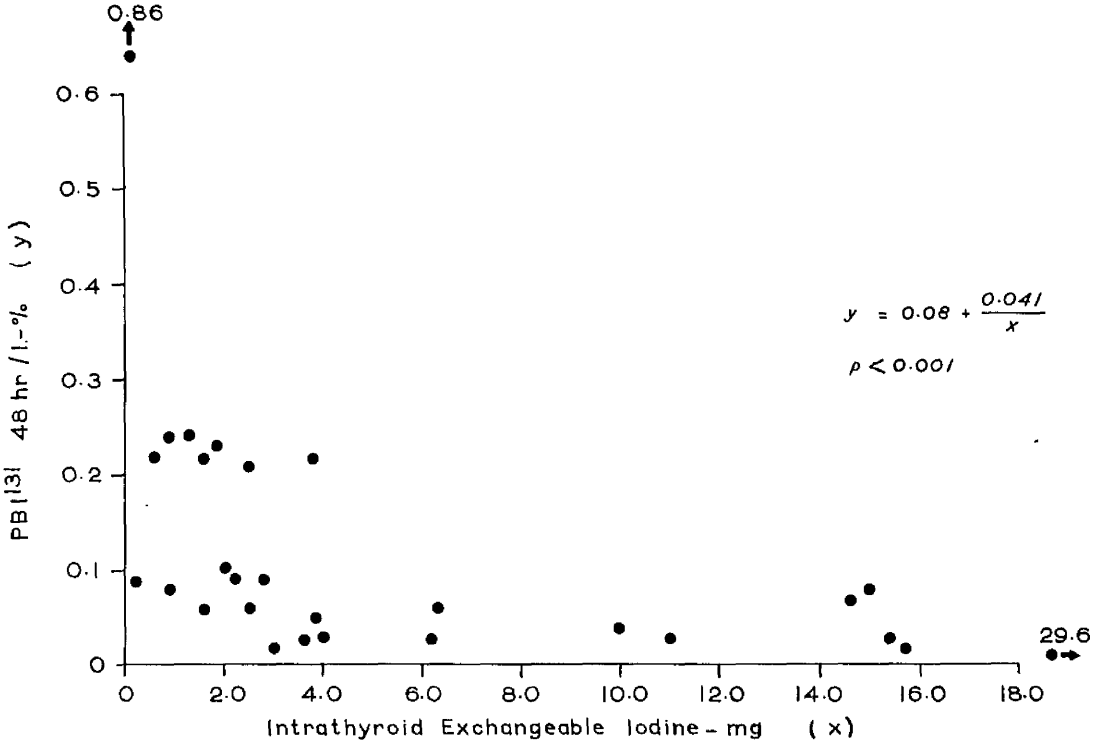

Figure 5.4

Relation between PBI^{131} and intrathyroidal exchangeable iodine.

There is a significant inverse relation between the PBI^{131} values and the intrathyroidal exchangeable iodine in 26 euthyroid individuals ($p<0.001$).

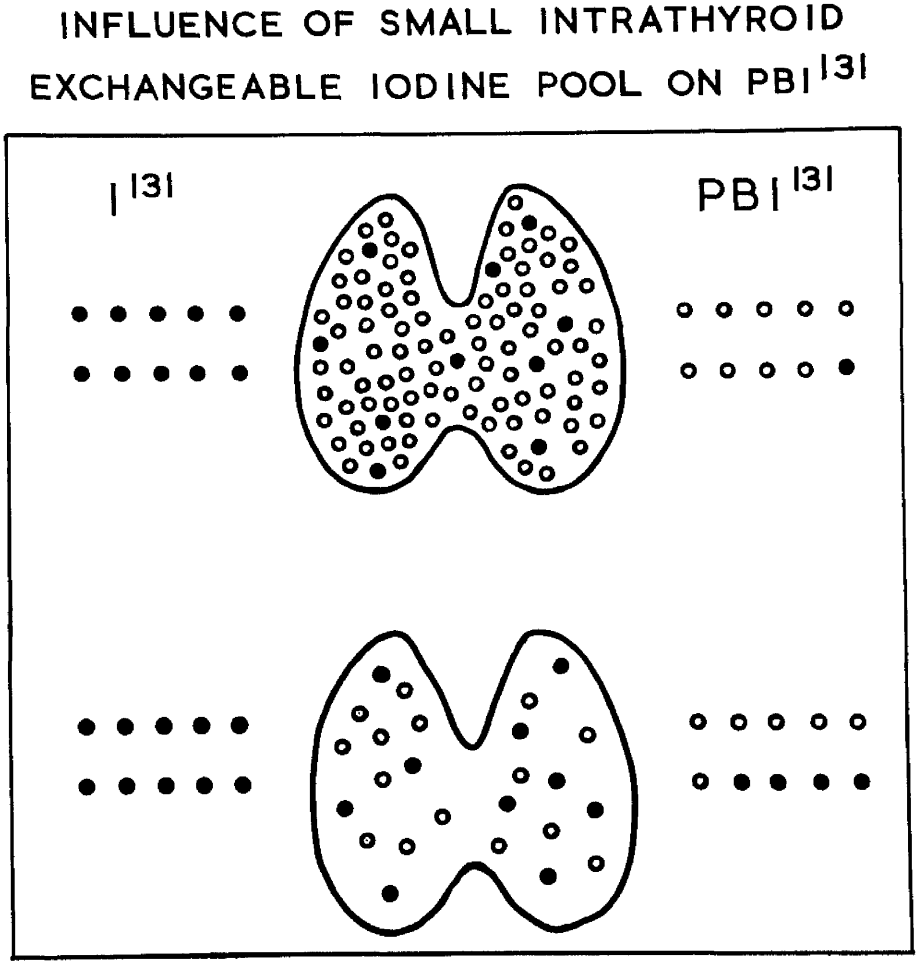

Figure 5.5

Influence of small intrathyroidal iodine pool on PBI^{131}

The normal gland is shown above, the gland with a small pool of intrathyroidal exchangeable iodine below. Atoms of radioiodine are indicated by solid dots, atoms of stable iodine by circles. Both glands take up the same amount of radioiodine, and produce the same quantity of thyroid hormone. In the gland below, the radioiodine atoms are diluted in a smaller pool of intrathyroidal iodine, and so the thyroid gland discharges hormone of a higher specific activity. This results in a higher PBI^{131}.

inversely related to the PII. Similarly radioiodine tests which measure the release of thyroid hormone give figures which are not only proportional to the amount of thyroid hormone produced, but are also inversely related to the iodine pool of the thyroid.

Neither the thyroid radioiodine uptake nor any other tests of this type will differentiate between the thyrotoxic gland and iodine deficiency goitre, since all of them reflect the thyroid clearance rate and not the AIU. In both conditions the thyroid clearance rate is high, but in iodine deficiency goitre this is simply a compensatory mechanism to maintain the AIU within the normal range.

Since the intrathyroidal exchangeable iodine pool is normal in simple goitre (Table 5 J) the PBI^{131} is also normal and thus simple goitre can be differentiated from thyrotoxicosis by using this estimation.

The PBI^{131} may be raised not only when increased quantities of thyroid hormone are being produced as in thyrotoxicosis, but also when the thyroidal iodine pool is decreased, for example, after thyroidectomy, I^{131} therapy or in auto-immune thyroiditis. In the last three conditions the iodine clearance, and therefore the radioiodine uptake, is usually normal and this permits their differentiation from thyrotoxicosis.

It follows that the combination of measurementsof both basic steps (iodine uptake and hormone release) should provide much better diagnostic help than either alone, and this has been long known in practice. Wayne (1960) found that the combination of the 4-hour

Table 5.1

Intrathyroidal exchangeable iodine and PBI^{131} in euthyroid patients

	No.	Name	Sex	Age	Diagnosis	IEI mg	PBI^{131} 48 hr %
Normal group							
	1	J.P.	M	53	Hypercalcaemia	11.0	0.03
	2	P.A.	M	58	Hemiparesis	0.9	0.08
	3	H.M.	M	72	Low back pain	4.0	0.03
	4	A.H.	F	63	Myocardial infarction	1.6	0.06
	5	A.G.	M	48	Myocardial infarction	15.7	0.02
	6	M.M.	F	22	Obesity	2.5	0.06
	7	W.F.	M	54	Mitral valve disease	3.8	0.05
	8	T.C.	M	54	Chronic bronchitis	15.0	0.08
	9	A.L.	M	36	Addison's disease	2.8	0.09
	10	E.B.	F	62	Myocardial infarction	0.9	0.24
Autoimmune thyroiditis							
	11	T.M.	F	44		3.8	0.22
	12	C.F.	F	51		1.3	0.24
	13	A.S.	F	62		0.1	0.09
	14	D.M.	F	30		0.1	0.86
	15	W.B.	M	56		1.9	0.23
	16	M.L.	F	62		1.6	0.22
	17	R.A.	M	71		2.2	0.09
	18	M.C.	F	64		2.0	0.10
	19	J.H.	F	45		2.5	0.21
	20	J.C.	F	61		0.6	0.22
	21	A.S.	M	37		2.5	0.02
	22	J.M.	M	46		3.6	0.03
Simple goitre							
	23	A.G.	F	32		14.6	0.07
	24	J.L.	F	59		10.0	0.04
	25	M.M.	F	45	All had	6.2	0.03
	26	E.F.	F	34	PII < 0.08	29.6	0.01
	27	J.W.	F	37		15.4	0.03
	28	G.M.	M	37		6.3	0.06

radioiodine uptake and the PBI^{131} carries, when the results are in agreement, a diagnostic error of about 2%. In this study patients who had received antithyroid or iodine-containing drugs were excluded as were those who had been treated by operation or radioiodine. Even so, the results in about 10% of many cases were "equivocal", that is to say, one of these two parameters was increased while the other was normal. When this happened almost equal numbers were toxic or euthyroid. Our results suggest that some of these anomalous results were due to the inclusion in the series of cases of iodine deficiency goitre and Hashimoto's thyroiditis.

When both the extrathyroidal inorganic iodine pool (as represented by the PII) and the intrathyroidal iodine pool are diminished, a high radioiodine uptake may be associated with a high PBI^{131} even in euthyroid patients. This association occurred in 4 euthyroid patients (Table 5.2), two of whom had auto-immune thyroiditis (Hashimoto's disease) and two of whom had no goitre or other clinical evidence of thyroid disease. These cases could have been mistaken for thyrotoxicosis if the diagnosis had been based solely on routine I^{131} tests. It is clear that a diagnosis should never be based on the result of standard radioiodine tests alone, without knowledge of the clinical findings. In practice, a suggestive clinical picture together with typical radioiodine tests should suffice for diagnosis, but when there is a discrepancy between the clinical findings and radioiodine tests, or when these tests are equivocal, further and more specific investigations are required, such as

Table 5.2

Iodine metabolism in euthyroid patients with a 4-hr I^{131} uptake greater than 45% and a 48-hr PBI^{131} greater than 0.4% dose/litre plasma

No.	Diagnosis	Thyroid uptake at 4-hr %	PBI^{131} % dose/ litre	PBI µg/100 ml	Absolute iodine uptake µg/hr	Intra-thyroidal iodine mg
1	No clinical thyroid abnormality	80.9	0.80	4.7	1.6	1.6
2	No clinical thyroid abnormality	49.4	0.67	5.0	2.4	3.9
3	Autoimmune thyroiditis	47.1	1.08	3.1	2.1	0.4
4	Autoimmune thyroiditis	47.0	0.86	4.8	2.9	0.1

Patients 1 and 2 both suffered from back pain due to osteoporosis.

the chemical determination of the PBI, the tri-iodothyronine suppression test and tests for thyroid auto-antibodies.

QUANTITATIVE STUDIES OF IODINE METABOLISM IN THYROID DISEASE : PLACE IN ROUTINE DIAGNOSIS

The results described in Chapters 2 and 4 permit definition of the range of a number of parameters of iodine metabolism in normal subjects, and in patients with a variety of thyroid diseases (Table 5.3). They also allow one to construct a model of the way in which the thyroid metabolises iodine in normal and pathological states, shown in Fig 5.6. This figure is over-simplified but it illustrates in a general way the alterations in thyroid function which may occur in disease, and the theoretical basis underlying the findings of diagnostic value presented in Table 5.4.

The normal values of the thyroid radioiodine uptake and clearance differ from place to place, varying with the usual plasma inorganic iodine (PII) level of the district, being lower in places where iodine intake and PII are high. Therefore each centre must establish its own normal range for the thyroid uptake and clearance, and the PII. The account which follows is based on the results obtained in Glasgow.

In normal subjects the thyroid gland clears about 23 ml of plasma per minute containing on an average 0.18 μg of iodide per 100 ml

Table 5.3

Summary of Results

	Normal (48 cases)	Thyrotoxicosis (40 cases)	Simple goitre with high thyroid clearance (24 cases)	Simple goitre with normal thyroid clearance (29 cases)	Autoimmune thyroiditis (15 cases)	Hypothyroidism (6 cases)
Radioiodine uptake at 2½ hr % dose	19.7 ± 1.3 (9.7 - 43.0)	69.4 ± 2.6 (37.6 - 99.9)	42.6 ± 2.7 (25.8 - 74.1)	24.6 ± 1.7 (7.0 - 51.0)	25.7 ± 2.4 (14.7 - 46.6)	8.2 ± 1.8 (3.6 - 13.0)
Thyroid clearance ml/min	22.6 ± 1.7 (2.9 - 57.8)	280.8 ± 34.0 (61.4 - 1054.0)	79.7 ± 7.9 (40.6 - 155.4)	25.7 ± 1.6 (7.3 - 38.8)	22.7 ± 3.7 (6.7 - 46.5)	3.7 ± 1.3 (0.0 - 8.0)
Plasma inorganic iodine g/100 ml	0.18 ± 0.015 (0.04 - 0.57)	0.15 ± 0.015 (0.02 - 0.57)	0.05 ± 0.004 (0.01 - 0.08)	0.10 ± 0.012 (0.02 - 0.35)	0.20 ± 0.04 (0.02 - 0.58)	0.14 ± 0.04 (0.01 - 0.26)
Absolute iodine uptake g/hr	2.2 ± 0.22 (0.1 - 8.2)	20.7 ± 2.39 (4.4 - 56.0)	2.2 ± 0.2 (0.5 - 5.7)	1.5 ± 0.22 (0.4 - 6.2)	2.0 ± 0.4 (0.4 - 5.9)	0.3 ± 0.2 (0.0 - 1.1)
Protein-bound iodine g/100 ml	4.9 ± 0.10* (3.0 - 9.3)	12.3 ± 0.52 (4.8 - 21.6)	5.0 ± 0.25 (2.7 - 7.5)	5.1 ± 0.23 (2.5 - 6.9)	2.7 ± 0.4 (0.5 - 4.9)	0.8 ± 0.2 (0.5 - 1.6)
Renal iodide clearance ml/min	31.1 ± 1.66 (11.7 - 61.8)	35.3 ± 2.59 (12.4 - 81.2)	34.9 ± 2.5 (16.0 - 63.4)	35.9 ± 2.6 (14.1 - 81.0)	28.1 ± 1.9 (20.3 - 43.6)	19.2 ± 3.9 (13.7 - 30.0)

The observed range is shown in parenthesis below the mean and standard error.

From Alexander et al (1962).

* 130 cases.

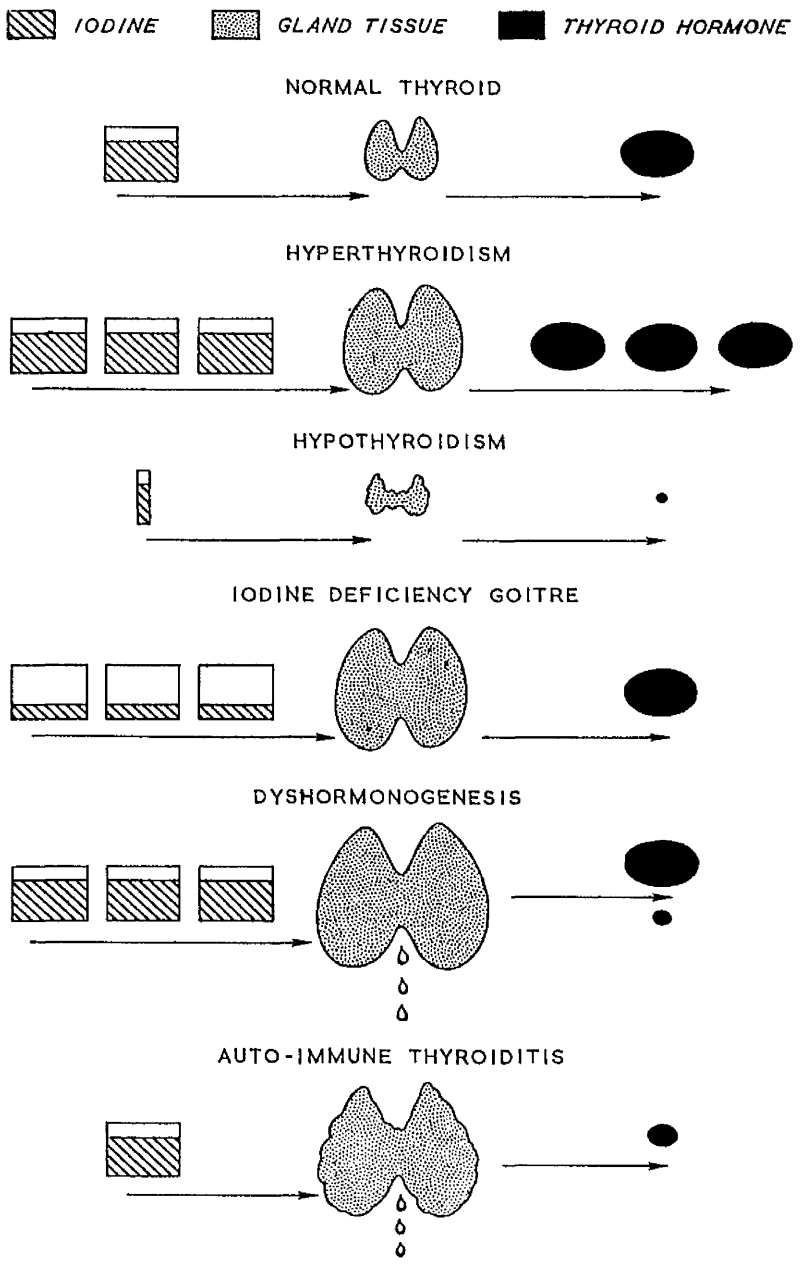

FIG. 6. Quantitative aspects of iodine metabolism in thyroid disease.

The blocks on the left of the figure indicate the volume of plasma cleared of its iodide content by the thyroid (thyroid clearance), and the concentration of the plasma inorganic iodine (PII) is indicated by cross hatching. On the right of the figure the amount of thyroid hormone produced is shown in black. In hyperthyroidism the thyroid has a larger absolute iodine uptake (AIU), and forms a correspondingly larger amount of thyroid hormone. In hypothyroidism both the AIU and the production of thyroid hormone are reduced. In iodine-deficiency goitre the thyroid clears a larger volume of plasma than normal, thus compensating for the low PII concentration, and resulting in a normal AIU; the iodide taken up is efficiently utilized, and a normal amount of thyroid hormone is produced. In dyshormonogenesis the AIU is high, as in thyrotoxicosis, but the iodide taken up is not efficiently utilized. Thus the amount of thyroid hormone produced is normal or subnormal, and some of the trapped iodide leaks from the gland in inactive form, either as abnormal iodinated compounds or as iodide. The dissociation between iodide uptake and hormone output is also found in auto-immune thyroiditis, but the AIU is less and most patients are hypothyroid.

Figure 5.6 (same as Fig 4.5)

Table 5.4

Diagnostic value of parameters commonly used to measure thyroid function

	Thyroid radioiodine uptake and clearance	AIU	PBI	PBI^{131}
Pregnancy	Normal	Normal	High-normal	Normal
Thyrotoxicosis	High	High	High	High
Hypothyroidism	Low	Low	Low	Normal
Iodine Deficiency	High	Normal	Normal	Normal
Dyshormonogenesis (most cases)	High	High	Low or normal	Variable
Autoimmune thyroiditis	Variable	Usually normal	Low-normal	High or normal
Goitrogens of the perchlorate type	Low	Low	Low-normal	Normal
Goitrogens of the thiouracil type	Variable	Variable	Low-normal	Normal
Iodine administration	Low	Normal or high	High	Normal
Thyroid neoplasm	Usually normal	Normal	Normal	Usually normal
Thyroidectomy (euthyroid when tested)	Normal	Normal	Normal	High-normal
I^{131} treatment (euthyroid when tested)	Normal	Normal	Normal	High or normal

and in this way takes up 2.2 μg of iodide per hour. This leads to a 24-hour accumulation of 53 μg of iodide, which is in keeping with the amount of thyroid hormone which has been calculated by Ingbar (1960) to be degraded daily. This finding suggests that normally almost all the iodine taken up by the gland is efficiently utilized to form hormone. The amount of thyroid hormone produced is reflected in the level of the serum protein-bound iodine, and is proportional to its square, (Riggs 1952; Berson and Yalow 1954). The serum protein-bound iodine in our series of euthyroid subjects was 4.9 ± 0.1 μg per 100 ml (mean ± SE).

In thyrotoxicosis an increased amount of iodide is taken up by the thyroid, and an increased amount of thyroid hormone is produced. In our thyrotoxic patients the thyroid clearance rate of the plasma iodide was 12 times greater than normal, but, since the concentration of iodide in the plasma (PII) was slightly diminished (p172), the absolute iodine uptake (AIU) was increased only nine times. The increased amounts of thyroid hormone produced in thyrotoxicosis are reflected in the high serum concentration of protein-bound iodine, although this increase is proportionately less than the rise in AIU because the peripheral metabolism of thyroxine is greatly accelerated (Ingbar and Freinkel 1955; Sterling and Chodos 1956).

For the routine diagnosis of thyrotoxicosis quantitative studies of iodine metabolism are not essential in the majority of suspected cases. When the four-hour radioiodine uptake and the protein-bound I^{131} at 48 hours are concordant, the likelihood of a correct diagnosis is high, provided that the patient has not received or is not receiving treatment (Wayne, 1954, 1960). In a significant number of cases of suspected thyrotoxicosis, however, these measurements are discordant, and the most valuable additional evidence is then afforded by the serum protein-bound iodine. The most common clinical problem is the differentiation between patients with mild thyrotoxicosis and those with nontoxic goitre and an anxiety state. The difficulty can usually be traced subsequently to the presence of iodine deficiency, although auto-immunizing thyroiditis may rarely be implicated. The simplest additional method of investigation is by the triiodothyronine suppression test (Werner and Spooner 1955; Werner 1962). There is, however, no agreement about the degree of suppression which may occur in mild cases of thyrotoxicosis, and thus the test may give equivocal results. For these reasons the quantitative studies of iodine metabolism which we have described, and which give an estimate of the absolute iodine uptake, are more specific, and increase the reliability of diagnosis in problem cases, as can be clearly seen from Figures 5.1 and 5.7. We have never met a case of thyrotoxicosis in which both the protein-bound iodine and the absolute iodine uptake were normal, and we have never seen a euthyroid subject in whom

ABSOLUTE IODINE UPTAKE AND PROTEIN-BOUND IODINE
IN THYROTOXICOSIS AND SIMPLE GOITRE

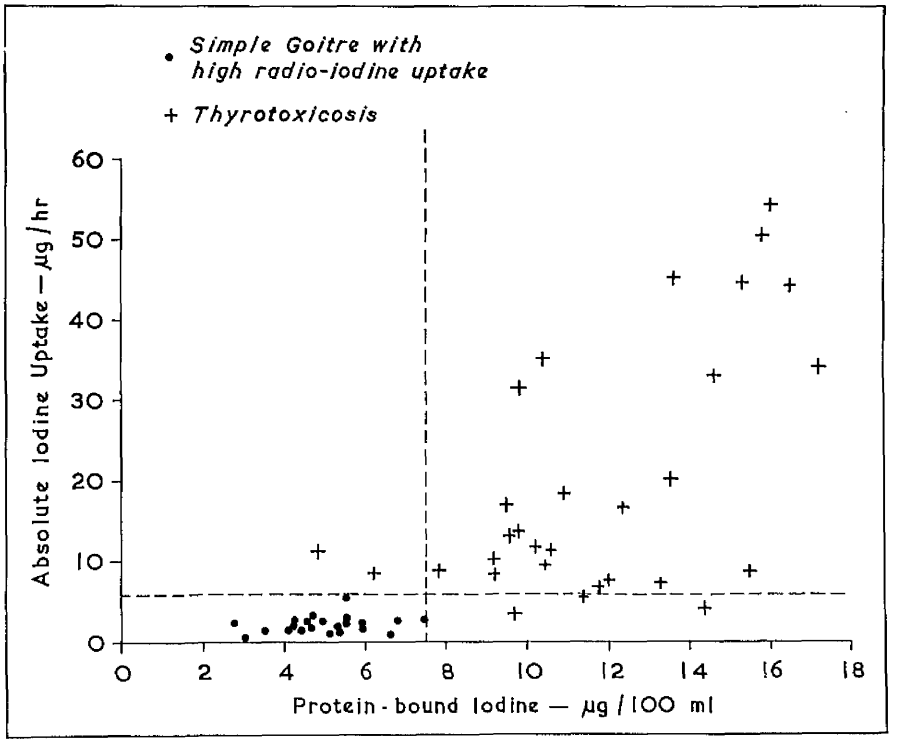

Figure 5.7 (same as Fig 4.1)

Absolute iodine uptake (AIU) and PBI in simple goitre and thyrotoxicosis

All the patients shown in this figure have a high radio-iodine uptake. Both the AIU and PBI give a good separation between patients with simple goitre and those with thyrotoxicosis. A small overlap occurs with either test, but when both are used the diagnostic accuracy is increased.

both these measurements were increased (Fig 5.7). Many asthma cures and cough medicines, and some "tonics", contain relatively large amounts of iodine; if a patient with suspected thyrotoxicosis is taking one of these remedies radioiodine tests are always, and the protein-bound iodine sometimes, misleading, and this is the case even if the patient is aware of the nature of the medicament he is receiving. Stable iodine studies, however, will show whether or not normal or low-normal radioiodine measurements are due to exogenous iodine. Furthermore, if such a patient is thyrotoxic, the absolute iodine uptake will be raised. For example, Alexander et al (1961) found that after administration of D-thyroxine to thyrotoxic patients the thyroid radioiodine uptake fell, but the absolute iodine uptake remained high and was in better agreement with the clinical status. Very rarely cases of thyrotoxicosis will be encountered in which, in spite of every test, doubt will remain, and the final court of appeal must be the response to specific therapy under controlled conditions.

In simple goitre quantitative studies of iodine metabolism usually reveal iodine deficiency, if we exclude frank cases of dyshormonogenesis, of autoimmune thyroiditis, and of goitrogen administration. Iodine deficiency is present almost without exception if the uptake of radioiodine is high, but even patients with a normal uptake, considered as a group, show evidence of iodine deficiency. This deficiency is shown by the markedly decreased plasma inorganic iodine, and also by studies of the 24-hour urinary excretion of iodine

and by our dietary survey (Table 4.6). In these circumstances the thyroid compensates for the low level of plasma inorganic iodine by clearing a large volume of plasma and so the absolute iodine uptake remains normal in spite of the decreased concentration in the plasma (Fig 5.6). The fact that these glands concentrate a normal amount of iodide, and use it to produce a normal amount of thyroid hormone, suggests that the available iodide is efficiently utilized, and this is evidence against the presence of enzyme defects, either inherited or induced by goitrogens.

From our studies we conclude that a plasma inorganic iodine concentration of less than 0.00 μg per 100 ml indicates iodine deficiency. Since, however, the standard error of a single measurement is 0.02 μg per 100 ml a value less than 0.04 μg per 100 ml is necessary before iodine deficiency can be identified in an individual case unless repeated measurements are carried out. We have had the opportunity of studying stable iodine metabolism in one patient with a goitre produced by the goitrogen resorcinol, which had been absorbed from an ulcer on the skin to which it had been regularly applied as an ointment. The plasma inorganic iodine was normal, the absolute iodine uptake high-normal, and the protein-bound iodine decreased (Table 5.5). In fact the picture was similar to that found in dyshormonogenesis of genetic origin, and unlike that seen in our cases of simple goitre.

In autoimmune thyroiditis the capacity of the gland to

Table 5.5

Studies of iodine metabolism in a case of resorcinol-induced goitre

	On resorcinol	11 months after discontinuing resorcinol	Normal range
2½ hr uptake (%)	39.1	12.4	10.0 - 35.0
Thyroid clearance (ml/min)	79.5	22.4	8.0 - 40.0
PII (µg/100 ml)	0.13	0.09	0.08- 0.60
AIU (µg/hr)	5.8	1.2	0.5 - 6.0
PBI (µg/100 ml)	1.2	7.1	3.0 - 7.5
PBI/AIU ratio	0.2	5.9	1.0 - 8.0
Renal Clearance (ml/min)	17.6	29.9	15.9 - 55.0

utilize iodine efficiently varies, but in general the gland retains a normal amount of iodine and produces a subnormal quantity of thyroid hormone. This is shown by a normal absolute iodine uptake and a low level of protein-bound iodine. The defects in hormone synthesis are multiple, since both abnormal butanol-insoluble iodoproteins and defective organic binding of trapped iodine may occur in the same case (Buchanan et al 1961b). The increased protein-bound I^{131} at 48 hours not infrequently found in patients with autoimmune thyroiditis is due to a low intrathyroidal exchangeable iodine pool (Table 5.1). In these cases the radioiodine atoms taken up by the thyroid mix in the gland with a smaller number of stable iodine atoms, and so the hormone produced has a higher specific activity, although its absolute amount is normal or even subnormal. The faulty utilization of iodine and the diminished intrathyroidal iodine pool make the standard radioiodine tests difficult to interpret in autoimmune thyroiditis. Confusion is likely to arise particularly in cases which may be suspected of thyrotoxicosis on clinical grounds (Buchanan et al 1961). Measurement of protein-bound iodine and absolute iodine uptake in such cases will suggest the correct diagnosis, but only exceptionally will it be necessary to carry out such studies to make the diagnosis of autoimmune thyroiditis; the essential confirmatory evidence is the demonstration of precipitating thyroid auto-antibodies and the characteristic histological changes in the gland.

There is evidence that many cases of primary hypothyroidism

are the end-result of autoimmune thyroiditis (Goudie et al 1957; Donlach et al 1961; Hall 1962). Our studies have confirmed the fact that an amount of iodide amounting to about one-eighth of the normal quantity is taken up by the gland, and that a diminished amount of thyroid hormone is produced. It is of interest that, although the plasma inorganic iodine is not significantly different from that of the normal control patients, the renal clearance of iodide is decreased in hypothyroidism (Table 5.3). The protein-bound iodine and the radio-iodine uptake nearly always fall below normal levels in primary hypothyroidism. Stable iodine studies may, however, explain unexpected findings such as a low thyroid uptake in a euthyroid person, or a high level of protein-bound iodine in a hypothyroid subject, such as is sometimes seen when medicinal iodine is being taken. In general, however, the clinical and other criteria described by Wayne (1960) are adequate for the diagnosis of primary hypothyroidism.

A number of inborn errors of iodine metabolism, leading to faulty hormone production or dyshormonogenesis, have been described. For full reviews see McGirr (1960) and Stanbury (1960). We have studied four such cases, three of Pendred's syndrome and one associated with an abnormal circulating iodoprotein (p218). In both these types the plasma inorganic iodine was normal and the absolute iodine uptake increased, but only a small proportion of the iodide taken up was being converted to thyroid hormone. The dissociation between the high

absolute uptake of iodine and decreased or normal protein-bound iodine in these cases reflects the faulty utilization of iodine characteristic of this condition (Fig 5.6). The diagnosis of inborn errors of iodine metabolism depends at present on chromatography of blood, urine, and thyroid tissue after the administration of radio-iodine or radio-iodinated tyrosines, and on the perchlorate discharge test. In the cases which we have studied, however, the diagnosis of dyshormonogenesis could have been suspected by the combination of an abnormally high absolute iodine uptake with a low or normal level of protein-bound iodine, and this finding differentiates them from simple goitre. Although we have not studied other cases of dyshormonogenesis in this way, it is probable that all types associated with faulty utilization of trapped iodine would show a similar pattern. In the type in which iodine uptake is impaired, however (Stanbury and Chapman 1960), we would expect the absolute iodine uptake to be low. Stable iodine studies are thus of some diagnostic value in cases of non-toxic goitre suspected of dyshormonogenesis, particularly in the selection of cases for more detailed investigation.

Finally, one should point out that these investigations do not involve difficult technical procedures, and that they are available to any observer who has access both to radioiodine techniques and to reliable methods of assaying small quantities of stable iodine. Although either the short-lived isotope I^{132} or the long-lived I^{131}

may be used, the radiation dosage to the thyroid and gonads is so much smaller with the former that it is greatly to be preferred (Halnan and Pochin 1958). The wider use of quantitative studies of the type described would increase the accuracy of diagnosis in difficult cases of thyroid disorder.

Summary

QUANTITATIVE STUDIES OF IODINE METABOLISM IN THYROID DISEASE

The only known function of iodine in the body is to take part in thyroid hormone synthesis, therefore iodine metabolism and thyroid function are inextricably linked. By combining radioisotopic and chemical iodine measurements a full picture of iodine metabolism can be obtained, including the plasma inorganic iodine concentration and the absolute uptake of stable iodine by the thyroid. Measurement of these parameters permits a much better estimate of thyroid function to be obtained than with radioisotopic methods alone.

The studies have provided new information about thyroid function in health, and the influence on iodine metabolism of age, sex and the level of the iodine stores of the body. Serial measurements, and extension of the studies to Icelanders, have resulted in a clearer understanding of the influence of varying levels of dietary iodine intake on the absolute iodine uptake by the thyroid, and on thyroid hormone production. A new assessment of the iodine requirements in man has been made, basing the estimate on quantitative measurements of iodine metabolism.

Investigation of patients with non-toxic goitre using these methods showed characteristic patterns of iodine metabolism indicative respectively of iodine-deficiency goitre, auto-immune

thyroiditis, dyshormonogenesis and iodine-induced goitre. The majority of cases of non-toxic goitre in the West of Scotland were found to have iodine deficiency.

Standard radioiodine tests (thyroid uptake and PBI^{131}) may give misleading results suggesting hyperthyroidism where it does not in fact exist. Thus a small extrathyroidal iodide pool raises the radioiodine uptake, and a small intrathyroid iodine pool raises the PBI^{131}. When both pools are small radioiodine tests are strongly suggestive of thyrotoxicosis, as has happened in several of our euthyroid patients. These conditions are readily detected and differentiated from thyrotoxicosis by stable iodine studies.

Estimations of the thyroid radioiodine clearance, the PII and the AIU can be made using I^{132}. In this way the patients receive very much less radiation than with the standard radioiodine tests, which require I^{131}. This is especially important when carrying out tests on young patients, and for repeated studies on the same patient. Reduction in radiation hazard is associated with increased diagnostic accuracy, and (in conjunction with PBI estimations) these stable iodine studies provide the best laboratory aid at present available for the investigation of problem cases of thyroid dysfunction.

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