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PRELIMINARY STUDIES OF IODINE METABOLISM IN PATIENTS FROM AN AREA OF ENDEMIC GOITRE *

JOHN B. STANBURY, M.D.

Associate in Medicine, Department of Medicine, Harvard Medical School
Assistant Physician, Medical Service, Massachusetts General Hospital, Boston, Mass., USA

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SYNOPSIS

Patients chosen for study from an area of endemic goitre in Argentina were remarkable in that they had high retentions and high turnover-rates of iodide. In spite of this, their glands were capable of increased activity as a result of an administration of exogenous thyrotropic hormone. When dietary iodide was supplemented with additional iodide there was a slow fall in the radioiodine retention as a new equilibrium state was approached. One patient who received 1,500 μg of iodide daily developed thyrotoxicosis after 32 days. The proportion of a single dose of iodide which is retained is constant below about 2 mg, but a decreasing proportion of the dose is retained when higher doses are given.

Much remains to be learned by taking advantage of the unique opportunities for study offered by patients who manifest the consequences of iodide deficiency.

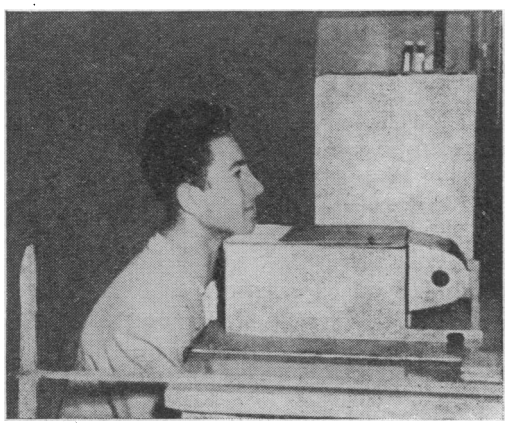
The studies reported here are based on observations of iodide metabolism which were conducted in Mendoza, Argentina, during the months of June, July, and August 1951. The project was conceived by Dr. James Howard Means when, in the course of a visit to the Thyroid Clinic of the Massachusetts General Hospital, Dr. Hector Perinetti of Mendoza described the nature and extent of the goitre endemic in western Argentina. It seemed possible that information of value might result from the application of the newer techniques of thyroid study in such an area to patients in their native environment who manifested endemic goitre. The expedition was generously financed by the Rockfeller Foundation, Parke-Davis and Co., Detroit, and the Loomis Institute for Scientific Research, Inc. The members of the team were Dr. Gordon Brownell of the Massachusetts General Hospital, Dr. Douglas S. Riggs of the Harvard Medical School, Dr. Hector Perinetti

* These observations have been in part reported in *J. clin. Endocrin. Metab.* 1952, **12**, 191 and ,together with further related studies, will shortly be published as a monograph.

and Dr. Juan Itoiz of Mendoza, Dr. Enrique del Castillo of Buenos Aires, and the author. Through the generous co-operation of the Universidad Nacional de Cuyo of Mendoza and the Argentine Federal Government, ample facilities were available for such studies as were carried out. Mendoza is a city lying a few kilometres east of the Andes. Endemic goitre has long been recognized as a major health problem of the area. The terrain is a desert, irrigated since pre-Columbian times by the channelling of water from rivers fed by glacial snows from the mountains near the city.

Laboratories for the determination of radioactive iodide in vivo and in biological fluids, and for the determination of the protein-bound iodine (PBI) of the serum and of the inert iodide (^{127}I) of the urine, were established. An ample number of patients was available. In general, younger patients with diffusely hyperplastic glands were chosen rather than older patients whose glands often showed considerable nodularity. Observations were made on a total of 126 patients. The studies described here are only those which seem more nearly germane to the problems of goitre prophylaxis.

FIG. 1. TECHNIQUE FOR COUNTING ^{131}I LEVELS *



The patient is seated with the anterior surface of the neck 40 cm (about 16 inches) from the Geiger-Müller tube which is housed in the lead casing at the right.

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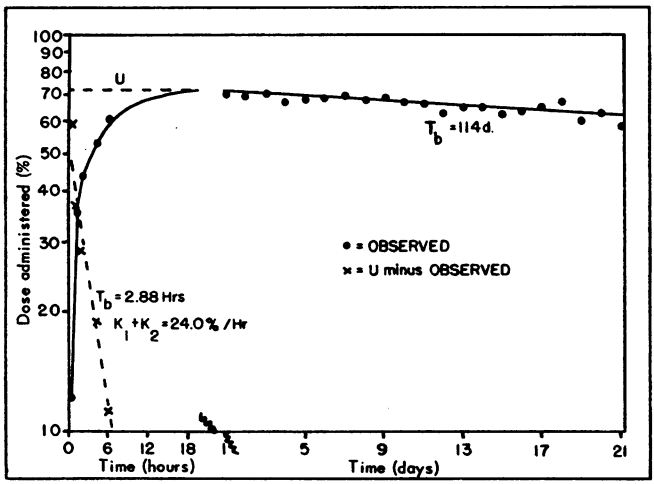
The in vivo measurement of radio-iodine (^{131}I) was carried out as illustrated in fig. 1. The Geiger-Müller tube was placed 40 cm (about 16 inches) from the patient's neck and was housed in a lead casing. It was necessary to standardize the observed readings because of radiation back-scatter. This was done in several ways. The in vivo measurement was compared with the 48-hour excretion of ^{131}I in the urine. Another technique was to measure known amounts of radioactive iodide contained in glass capsules when these were immersed in water in beakers of varying dimensions. A third method was to sow in the thyroid gland of a cadaver a known amount of radioactive iodide contained in a glass capsule, and to compare the residue with that from the same capsule suspended in air. A correction factor of 0.85 for the in vivo uptake measurements was obtained by these three methods.

Uptake and decay pattern

The first striking finding was the rapidity with which ^{131}I was removed from the blood and appeared in the thyroid gland (fig. 2). The peak concentration of ^{131}I in the thyroid was often reached within six hours or less, whereas the normal individual from an area of iodide abundance may not reach his peak uptake in the thyroid gland before 24 hours or even longer. The pattern most commonly observed after the peak uptake had been reached is also illustrated in fig. 2. If the quantity of ^{131}I remaining in the thyroid each day is plotted on a logarithmic scale, the slope of decay is a straight line. The rate at which the activity is disappearing from the gland, therefore, can be expressed most simply as the half-period of disappearance, or biological half-time (T_b in fig. 2). The rate at which the total iodide space of the body is cleared of ^{131}I can be derived by the graph technique of Brownell.[1] In this case (fig. 2) the iodide space was

FIG. 2. UPTAKE AND RELEASE OF RADIOACTIVE IODIDE FROM THE THYROID GLAND *



Note that maximal counts were very nearly reached within six hours. The biological half-time (T_b) is 114 days.

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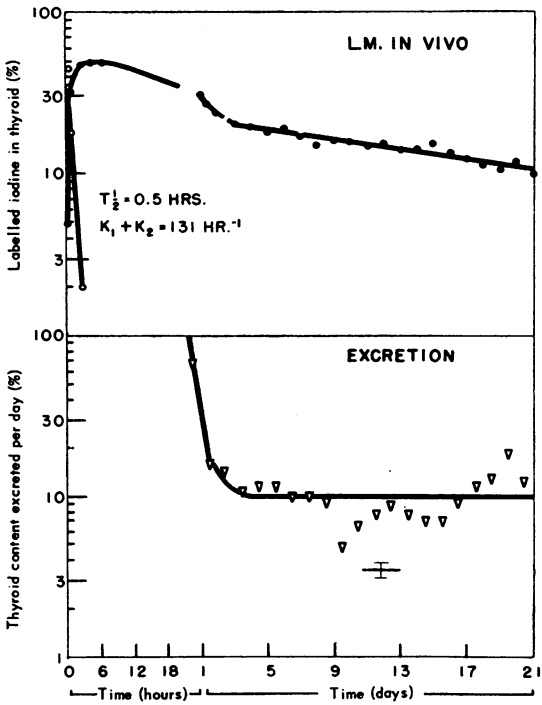
being cleared of iodide by the thyroid at the high rate of 24% per hour. The usual value for a normal individual is probably of the order of 7%. The thyroids of some of the patients studied in Mendoza were clearing over 100% of the iodide space per hour.

[1] Brownell, G. L. (1951) *J. clin. Endocrin.* **11**, 1095

FIG. 3. UPTAKE AND DECAY PATTERN OF ^{131}I

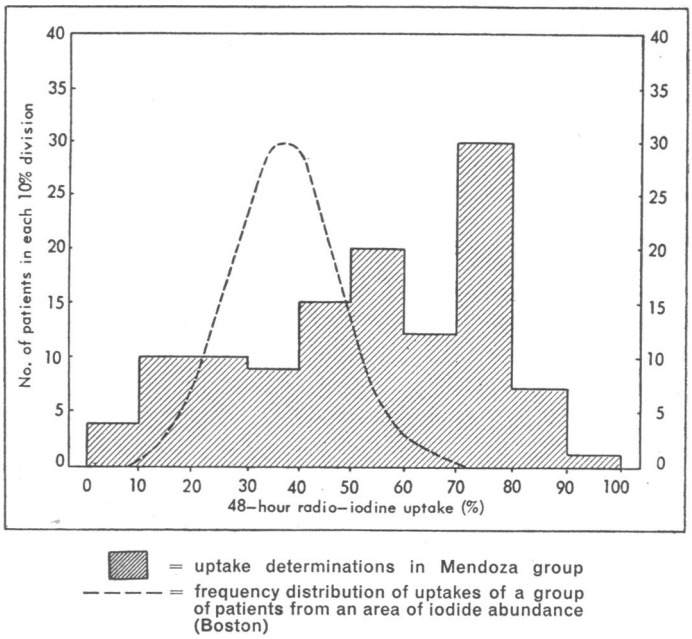


The upper figure shows the rapid uptake of ^{131}I during the first six hours, and the biophasic nature of the decay slope.
The lower figure shows the high level of urinary excretion. Approximately 10% of the thyroid content of iodide was being excreted daily.

Occasionally a somewhat different pattern was observed. This is illustrated in fig. 3. Two things are particularly noteworthy. When the peak uptake is reached it is seen that the initial portion of the curve does not form a straight line until after a sharp dip downward has occurred. In addition, the biological half-time of disappearance of ^{131}I from the gland was surprisingly rapid. One can only speculate on the nature of these findings. If one assumes that these patients had unusually small amounts of bound iodine in their glands, then it might follow that they would have unusually rapid turnover rates of hormone, and consequently a very large proportion of the bound iodine would be secreted daily, broken down into iodide, and made available for differential clearance between kidney and thyroid. Consequently, one might with reason expect a more rapid biological half-time than in a patient where the specific activity of the ^{131}I in the gland was relatively low. Actually, a calculation of the quantity of hormonally bound stable iodine in the glands of patients who demonstrated these rapid decay rates showed that they had relatively minute quantities of ^{127}I in their glands.

It is somewhat more difficult to account for the biphasic nature of the early portion of the curve (fig. 3). One might speculate that there are two phases in the secretion of thyroid hormone, one a cellular phase and one a colloid phase, the cellular phase having a particularly rapid turnover. During the cellular phase there would be rapid trapping, rapid formation of hormone, and rapid secretion into the blood, without this portion of the ^{131}I ever becoming incorporated into the colloid of the gland. The second phase would be that involving mobilization of bound iodine from the colloid stores. Of course, other and perhaps better explanations for the biphasic nature of this curve are possible. As is seen in fig. 3, the determination of the quantity of iodine leaving the gland per 24 hours in this patient was very high. The triangles in the figure are measurements of the percentage per day of thyroid content leaving the gland. All the patients who demonstrated the steep slope and the biphasic initial curve were secreting between 3% and 10% of the gland content of thyroid hormone per day, whereas patients who did not demonstrate the steep slope and who did not show the biphasic curve were, in general, excreting only approximately 0.3% of the thyroid content of stable iodide per day.

FIG. 4. DISTRIBUTION OF RADIOACTIVE IODIDE UPTAKE DETERMINATIONS IN TWO GROUPS OF PATIENTS *



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The lesson to be derived from these studies is that when working with glands that have a high avidity for iodide, one must be careful to take into account the biphasic nature of the uptake curve which may occur. The peak uptake value may have been passed well before the usual 24- or 48-hour uptake is measured. Actually, it would probably be preferable to obtain in vivo values at 6, 12, 24, and 48 hours, particularly in patients extremely depleted of iodide, or with severe Graves' disease.

^{131}I uptake

Fig. 4 shows the distribution of ^{131}I uptakes by the patients studied in Mendoza. The dotted line is a frequency distribution of a large group of normal individuals studied several years ago by Skanse [2] in Boston—an area of iodide abundance. It can be seen from this figure that a large proportion of the Mendoza subjects had ^{131}I uptakes which are above the upper limits of normal for patients from an area of iodide abundance.

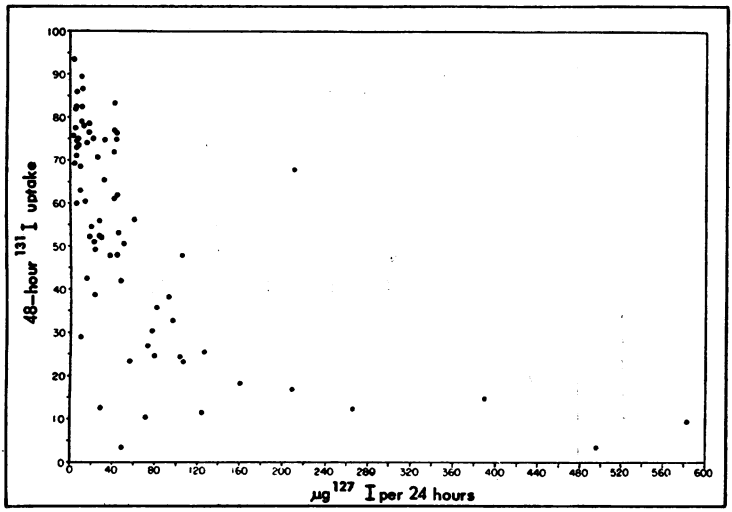
Relation between ^{127}I excretion and ^{131}I uptake

Fig. 5 shows the relation between the ^{127}I excretion of these patients and their ^{131}I uptakes. These patients were on their normal diets when measured, and the assumption is made that the daily excretion of ^{127}I was identical with their ^{127}I intake. This is not strictly true, because a very small proportion of the ^{127}I which is ingested is excreted in the faeces, sweat, and expired air in extremely minute amounts. However, urinary excretion accounts for between 90% and 95% of the total. It can be seen from the figure that, in general, patients with low excretions (and accordingly low intakes) of ^{127}I tend to have high retentions of ^{131}I and, vice versa, patients with high intakes of ^{127}I tend to have lower retentions of ^{131}I. It can also be seen from this figure that a large proportion of the patients were excreting less than 40 μg of ^{127}I daily, and many were excreting less than 15 μg. By contrast, patients living in an area of iodide abundance, such as Boston, will excrete between 100 μg and 200 μg of iodide daily, and more if they are ingesting iodinated salt. There seems, therefore, to be a good reciprocal correlation between the intake of iodide and the uptake of ^{131}I. There are, however, certain discrepancies which are in need of explanation. For instance, occasionally a patient showed not only a high uptake of radioactive iodide but also a high excretion of ^{127}I. Since, as will be shown later, it takes many days for the ^{131}I uptake to be depressed by relatively large daily quantities of ^{127}I, the most reasonable explanation for this discrepancy would seem to be that these patients were ingesting larger amounts of iodide daily, but that this had not been occurring

[2] Skanse, B. (1949) *Acta med. scand.*, Suppl. No. 235

for a sufficiently long time to depress their ^{131}I retentions. On the other hand, certain patients demonstrated a low excretion of ^{127}I and a depressed uptake of ^{131}I. The simplest explanation for this discrepancy is that in the recent past the glands of these patients had been saturated by ^{127}I, but at the time of the ^{131}I measurement their daily intake of ^{127}I was low.

FIG. 5. RELATION BETWEEN ^{127}I EXCRETION AND ^{131}I UPTAKE OF MENDOZA PATIENTS *



Note that the lower the iodide in the urine, the higher the radioactive iodide uptake, and vice versa.

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Effects of a thyroid-blocking agent and of thyrotropic hormone

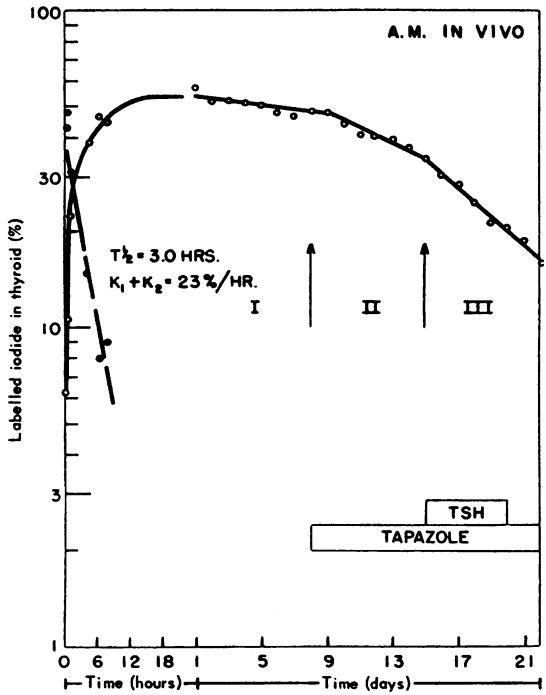
Six patients were studied for the effects, first of a thyroid-blocking agent, 1-methyl-2-mercaptoimidazole,[3] and then of the additional effects of thyrotropic hormone. After control, daily measurements of ^{127}I excretion and ^{131}I retention were made for seven or eight days following a tracer dose, and each patient was given 30 mg of the antithyroid drug three times daily. Immediately there was a sharp inflexion downward of the decay curve of the radioactive iodide in the gland, and a sharp increase in the quantity of excreted ^{127}I and ^{131}I. The drug, by preventing the re-utilization of iodide, made whatever iodide was available from the periphery available only for renal excretion.

After this phase of the curve had been observed long enough to establish its slope, each patient was given two daily injections of a potent

[3] Tapazole, produced by Eli Lilly & Co.

preparation of thyrotropic hormone. In every case there was a further change downward in the slope of the decay curve, which indicated that thyrotropin, even in these iodide-deficient patients, was still capable of stimulating further increased secretion of hormone (fig. 6).

FIG. 6. EFFECT OF 1-METHYL-2-MERCAPTOIMIDAZOLE AND OF THYROTROPIC HORMONE ON THE RELEASE OF LABELLED HORMONE FROM THE THYROID GLAND



The first portion of the curve (I) is the control period ; the second portion (II) represents the period during which the patient was receiving 1-methyl-2-mercaptoimidazole (Tapazole) ; and the third portion (III) the period during which the patient was receiving both thyrotropic hormone (TSH) and Tapazole.
—o— = % labelled iodine in thyroid
—●— = difference between maximal uptake and that observed at indicated time

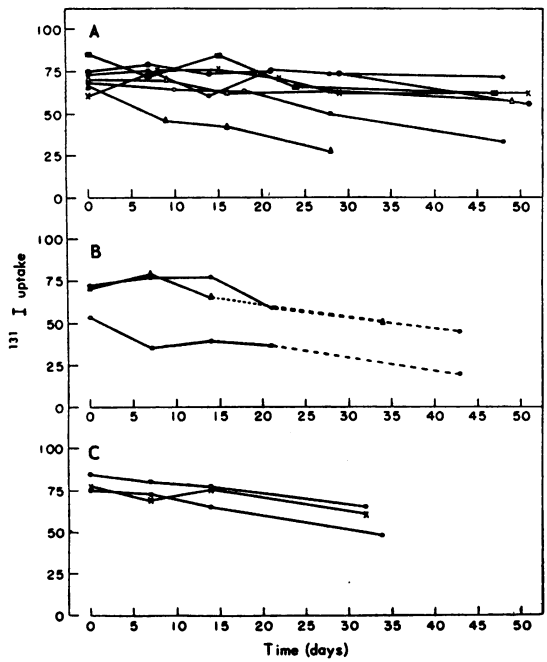
An interesting sidelight on this study was that all six of the patients who received thyrotropic hormone developed acute thyroiditis. In each case there was tenderness when the gland was palpated and slight to moderate enlargement of the gland, and, in one case, fever and nausea.

Effects of supplementary dietary iodide

The observations which are of most practical interest in the prophylaxis of endemic goitre derived from a study of the effects of various doses of potassium iodide given daily to patients deficient in dietary iodide.

Thirteen patients who had high uptakes of ^{131}I and low excretions of ^{127}I were chosen for this study. Seven received 150 μg of iodide daily, three received 500-600 μg, and three received 1,500 μg. Fig. 7 illustrates the drop in ^{131}I uptakes demonstrated by the three different groups.

FIG. 7. INDIVIDUAL PLOTTINGS FOR ALL PATIENTS GIVEN SUPPLEMENTARY DIETARY IODIDE



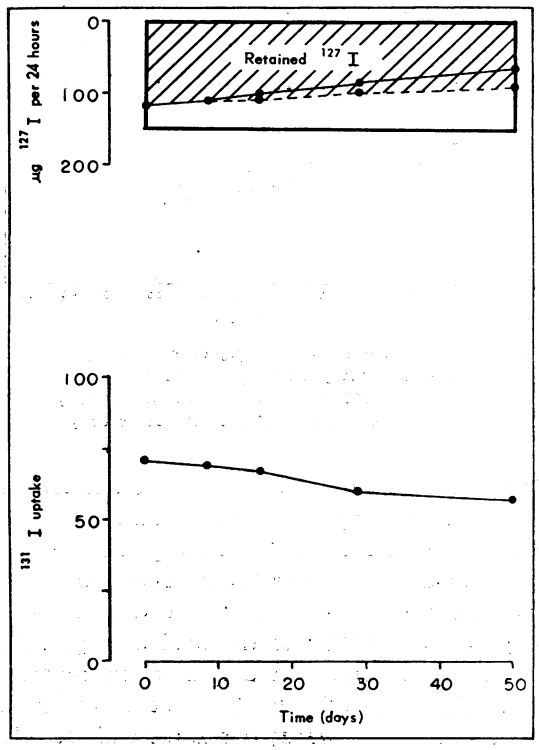
A = patients given 150 μg of iodide daily
B = patients given 500 μg (solid line) and 600 μg (broken line) of iodide daily
C = patients given 1,500 μg of iodide daily

From the data which were obtained it is possible to estimate the amount of iodide which was retained by these patients during the periods of observation. Fig. 8 shows a balance study on the group of seven patients who received 150 μg of iodide daily. The lower curve shows the fall in radioactive iodide uptake during the 48 days of observation. The initial average uptake for this group was 71% and the final average uptake was 56%. The upper portion of the curve is a diagrammatic representation of the iodide balance of this group of patients. The daily intake of iodide is plotted from the baseline downward; this is the daily supplement, 150 μg, plus the control average daily excretion of iodide by this group of patients, which was 12.3 μg. The area of the rectangle, therefore, represents the

total intake of iodide for the 48 days of observation. The balance of iodide can be estimated in two ways. From the daily intake one can subtract the daily excretion of ^{127}I; this gives the solid line. The balance can also be estimated from in vivo data by multiplying the daily intake of iodide by the ^{131}I uptake; this gives the dotted line. The agreement between the two methods of calculation seems to be fairly good. If the curve is extrapolated to the time when equilibrium would be restored, the not unreasonable figure of a little over 7 mg is obtained as the net quantity of retained iodide.

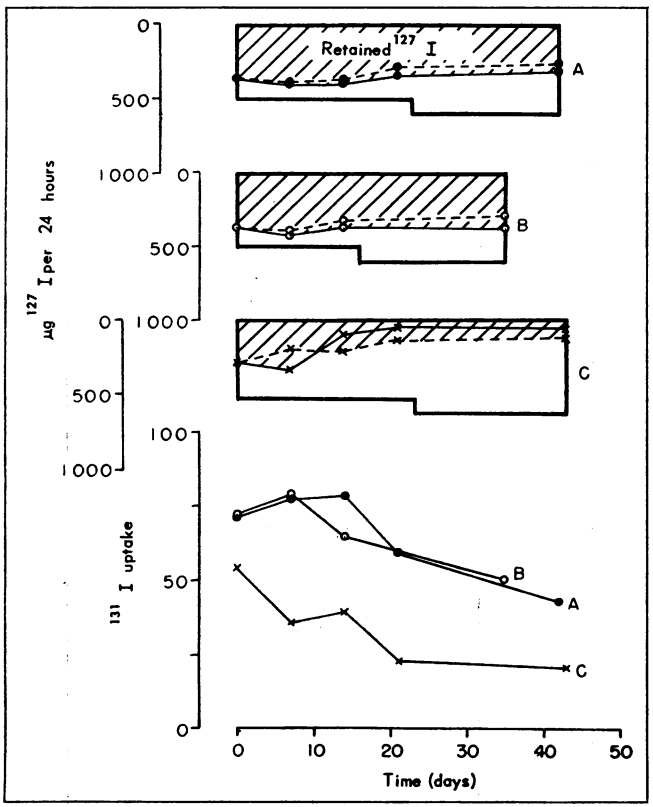
The findings in the group which received 500-600 μg of iodide daily are illustrated in fig. 9. The data were sufficiently diverse to obviate averaging. In this case, the balance of each patient is calculated individually. Again the slow return to equilibrium is illustrated, but in these patients calculation shows that each was retaining much more iodide than were the patients of the previous group.

FIG. 8. IODIDE BALANCE OF A GROUP OF SEVEN PATIENTS RECEIVING 150 μg OF SUPPLEMENTARY IODIDE DAILY



The lower curve indicates the average uptake of the seven patients. The upper curve is a balance diagram. The daily intake is plotted downward from the baseline. The solid line indicates the iodine balance, calculated from urinary excretion data; the broken line indicates iodine balance, calculated from in vivo ^{131}I data. The shaded portion indicates the net retention of iodine.

FIG. 9. IODIDE BALANCE OF THREE PATIENTS RECEIVING DAILY SUPPLEMENTARY DOSES OF 500-600 μg

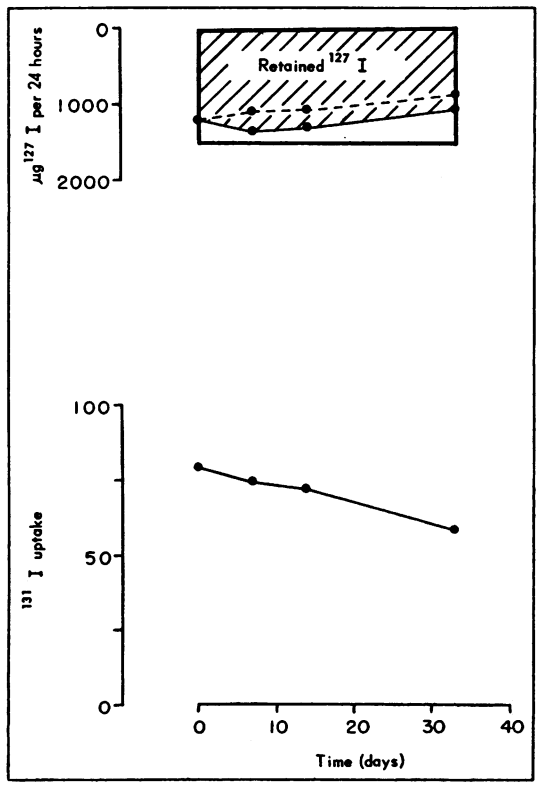


The charting of the data is identical with that for fig. 8.

The findings in the patients who received 1,500 μg of iodide daily are illustrated in fig. 10. Again there was a slow fall in the radioactive iodide retention, although the rate of return to balance appears to be about the same as it was for the group which received only one-tenth of this quantity of iodide daily. The actual net positive balance of iodide is much greater. An extrapolation of this curve gives a net positive balance of 60-75 mg of iodide at the time of restoration of equilibrium. This is far higher than the normal iodine content of the thyroid gland. What could be the consequences of such a positive balance ? Three possibilities may be mentioned : (1) a goitre extremely rich in iodide might be the result ; (2) the patient might go through a " rebound " phase of negative iodine balance at a later date in order to rid himself of the excess iodide; or (3) the patient might expand the extrathyroidal PBI pool—i.e., he might develop thyrotoxicosis. Indeed, this last possibility is exactly what happened to one of the patients.

This woman had a serum PBI of 3.5 μg%, and after 32 days of 1,500 μg daily of iodide (given as potassium iodide), her PBI was 13.5 μg% and she had the classical clinical signs of thyrotoxicosis.

FIG. 10. IODIDE BALANCE OF THREE PATIENTS RECEIVING 1,500 μg OF SUPPLEMENTARY IODIDE DAILY



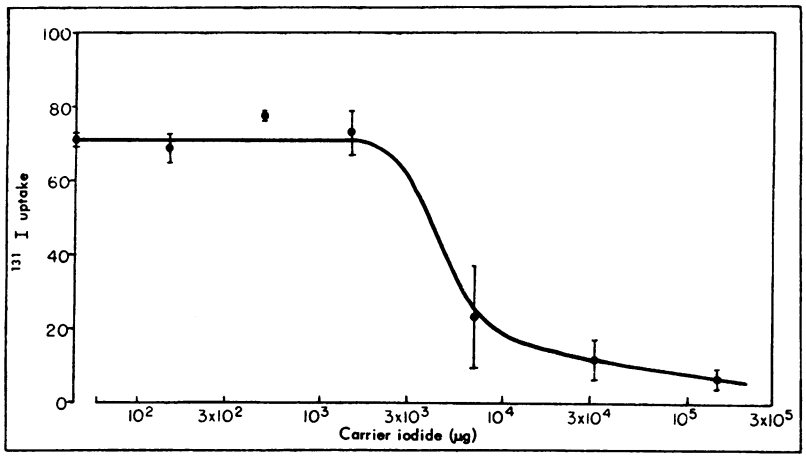
The charting of the data is identical with that for fig. 8 and 9.

One patient who develops thyrotoxicosis on supplementary iodide does not prove or disprove the controversial question of Jod-Basedow (iodine-induced hyperthyroidism). Our data, however, suggest that the phenomenon may be a real one and that its occurrence may depend on the *quantity* of supplementary iodide.

Acute effects of carrier ^{127}I on ^{131}I retention

Twenty-one patients who had high control ^{131}I uptakes were given second tracer doses of ^{131}I to which were added varying quantities of ^{127}I.

FIG. 11. EFFECT OF STABLE IODIDE ON UPTAKE OF RADIOACTIVE IODIDE IN 21 PATIENTS



The vertical lines are the standard deviations of the points. Each point indicates the mean uptake for patients who were given the tracer dose of radioactive iodide, together with carrier iodide in the amounts indicated by the abcissa.

The results are shown in fig. 11. It can be seen that supplementary doses of ^{127}I up to approximately 1,500 μg have very little, if any, effect on the ^{131}I uptake, whereas quantities above this value depress the uptake of radioactive iodide. To express it differently, the proportion of a dose of ^{127}I which is retained is dependent upon the quantity. It would seem from this curve that when more than 5 mg of iodine are given in a single dose, most of it is wasted.

RÉSUMÉ

L'auteur résume les résultats d'une étude du métabolisme de la thyroïde, effectuée sur des malades de la région de Mendoza, Argentine, en 1951. Cette région d'endémie goitreuse est irriguée depuis les temps pré-colombiens par des rivières alimentées par les neiges des montagnes environnantes.

On a déterminé au moyen d'iode marqué (^{131}I), l'iode présent dans la glande et dans les liquides biologiques, on a dosé l'iode lié aux protéines sériques ainsi que l'iode inerte excrété par l'urine. Les 126 malades choisis étaient jeunes pour la plupart et présentaient des glandes avec hyperplasies diffuses.

L'observation la plus frappante fut la rapidité avec laquelle ^{131}I administré aux malades carencés passe du sang dans la thyroïde: le maximum est atteint en 6 heures, parfois moins, tandis que chez l'individu non carencé il peut ne se manifester qu'au bout de 24 heures. Une proportion de 24% de la quantité d'iode disponible est fixée par la thyroïde des sujets carencés, ce chiffre étant de 7% en moyenne chez les sujets normaux. Divers schémas de rétention de l'iode par la thyroïde, du renouvellement de l'iode thyroïdien, de la mise en circulation de l'iode par l'hormone ont été observés chez différents malades. L'auteur analyse plusieurs cas.

Un rapport évident existe entre l'assimilation et l'excrétion de l'iode. Dans les régions carencées, l'excrétion rénale est de 15-40 μg par jour, alors que, là où l'iode est abondant, elle atteint 100-200 μg par jour. Le méthyl-1 mercaptoimidazole-2, qui bloque l'activité de la thyroïde en empêchant la réutilisation de l'iodure, provoque l'excrétion rénale de l'iode disponible. L'hormone thyréotrope est capable, même chez les malades carencés, de stimuler la sécrétion hormonale. Mais tous les malades ainsi traités ont développé une thyroïdite aiguë.

Les études les plus directement utiles à la prophylaxie du goitre sont celles qui ont trait à l'effet de diverses doses supplémentaires d'iode (0,150 mg, 0,5-0,6 mg, 1,15 mg) données chaque jour à des sujets carencés. On constate une lente diminution de l'avidité de la thyroïde pour l'iodure et l'apparition d'un bilan iodé positif. Un cas de thyréotoxicose a été observé après un traitement de 32 jours à 1,5 mg par jour. Ce cas unique ne permet pas de trancher la question controversée de l'hyperthyroïdisme induit par l'iode, mais on ne peut l'ignorer ; il est possible que cette affection dépende de la quantité d'iode supplémentaire administrée.

L'adjonction de diverses quantités d'iode stable (^{127}I) sous forme de doses uniques d'iodure, de 1,5 mg au maximum, a eu peu d'influence sur l'assimilation de l'iode radioactif (^{131}I). Mais si la dose dépasse 5 mg, la plus grande partie est excrétée par les reins.