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PUBLICAÇÃO IEA N.º 177
Dezembro — 1968

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SÃO PAULO — BRASIL

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* Reprinted from The Journal of Clinical Endocrinology and Metabolism, Vol. 28 - Nº 8 , August 1968, pp. 1205-1213.

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Thyroidal Iodoproteins in Pendred's Syndrome

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ABSTRACT. The distribution of ^{127}I, ^{129}I, or ^{131}I, and protein was studied in thyroid tissue from 3 patients with Pendred's syndrome. In each of these patients a significant amount of trapped iodide was dischargeable after administration of perchlorate. Two specimens (nodular and paranodular tissue) were studied from each patient. Iodinated insoluble protein comprised 6.4–33.1% of the total radioactive iodine in the homogenates. More particulate labeled iodine was present in the nodular tissue, per g of tissue, as compared to paranodular tissue. Nearly ⅓–½ of the total ^{127}I was incorporated into the particulate protein. The pattern of protein distribution followed closely that of stable iodine. In the nodular tissue it was found that the insoluble protein had more labeled iodine per μg of ^{127}I than in the soluble fraction. After 3 weeks of a tracer dose the particulate protein had more labeled iodine per g than after 24 hr of labeling. The particulate iodoprotein was solubilized with trypsin and could be separated from normal thyroglobulin by gel filtration. It also behaved differently from thyroglobulin in agar plates when tested again antisera. In both specimens of thyroid tissue (nodular and paranodular) less than 15% of total soluble protein was in the 19S peak; in one specimen of nodular tissue no detectable 19S protein could be found in the supernatant. It is suggested that patients with Pendred's syndrome may have iodide organification and an inherited disorder affecting normal thyroglobulin synthesis. (*J Clin Endocr* **28:** 1205, 1968)

THE SYNDROME of goiter and congenital deafness (Pendred's syndrome) is transmitted as a single recessive trait (1) and is grouped with the dishormonogenetic diseases of the thyroid gland. Patients with this disorder often show a significant discharge of iodide from their thyroids after a dose of perchlorate. They are usually euthyroid but some have varying degrees of hypothyroidism.

Nonthyroglobulin iodoproteins may be found in congenital goiter (2–5) and in other pathological human thyroid tissue (4, 7). One of the patients with congenital goiter reported by Michel *et al.* (2) was a deaf-mute but a thiocyanate test was negative; in this patient 22% of the total ^{131}I was particulate and a large amount of a nonthyroglobulin iodoprotein was found at the soluble fraction. Recently, Lizarralde *et al.* (5) reported a patient with congenital goiter in whom thyroglobulin was virtually absent from the thyroid tissue.

The present report concerns studies on the thyroidal iodoproteins from three patients with Pendred's syndrome. It seems possible that the presence of abnormal iodoproteins might have been the consequence of a collateral pathway when synthesis of thyroglobulin was reduced because of an inherited defect.

Received October 16, 1967; accepted May 2, 1968.

Materials and Methods

A. *Clinical histories*

1. *Patient ERC*, a 27-yr-old female, was admitted to the Surgical Service for thyroidectomy of a large multinodular goiter. She had been a deaf-mute since birth. No reliable data could be obtained due to poor information from relatives. She was mentally retarded and was brought up in a small village in an endemic goiter area. It was not possible to confirm the existence of goiter in the family. On physical examination she was a cooperative patient with unintelligible speech. Her height was 1.53 m and weight 40.9 kg. The skin was dry, the hair brittle and coarse, and the tongue en-

TABLE 1. Distribution of radioactive iodine, stable iodine and protein in the particulate fraction of nodular (N) and paranodular (PN) tissue (results expressed as per cent of total present in the whole homogenate)

Parameter	Tissue	Patients		
		ERC	ES	IF
^{125}I	N	6.4	21.5	33.1
	PN	26.9	13.4	23.8
^{127}I	N	26.4	30.7	41.3
	PN	54.9	24.5	21.3
Protein	N	63.2	54.0	42.0
	PN	59.7	45.8	57.9

larged. The deep tendon reflexes were active. The thyroid was enlarged, and a large nodule was present at the left lobe. The 2 hr RAI uptake was 33.0% and the 24 hr was 68.5%; a scintiscan revealed a "cold" nodule at the left lobe. The PBI was 3.9 μg 100 ml and the BMR +16%. A perchlorate test was done according to the method previously described (8), and 40% of the RAI accumulated at 1 hr was discharged. She received a tracer dose of ^{125}I and several chromatograms of plasma were performed on the following days by the Blanquet-Meyniel method (9); these were considered within the normal limits for the method. The total iodoprotein relative proportion did not exceed the usual 15% of the total iodine value in any of the samples. There were no circulating iodotyrosines and the relative proportion of iodothyronines (T_3+T_4) was in the lower limit of the normal. Thirteen days after the tracer dose of $RA^{125}I$ a subtotal thyroidectomy was performed. The pathologic diagnosis for the nodule was fetal adenoma; the paranodular tissue was a hyperplastic colloid goiter with several hemorrhagic areas. Both tissues were processed separately.

2. *Patient ES*, a 15-yr-old female, was admitted to the Endocrine Service for evaluation of a congenital goiter. She had been a deaf-mute since birth but otherwise she was a normal, cooperative, adolescent girl. Sexual development was normal and menses were regular. There were no physical signs of hypothyroidism. The thyroid was enlarged, mainly due to the right lobe, which was quite firm. A sister had thyroid enlargement and was also a deaf-mute; she was later examined and was classified as having the Pendred syndrome. No other reliable family tree could be obtained. The PBI was 3.8 μg/100 ml, the BMR +2%, and the photomotogram (Achilles tendon reflex relaxation time) was 370 msec (normal). The 2 hr RAI uptake was 50.5% and the 24 hr uptake 62.0%. A dose of perchlorate discharged 36.0% of the total tracer dose of $RA^{131}I$ accumulated at 1 hr. Daily chromatograms were done for several days after a tracer dose of ^{125}I. There was no evidence for circulating iodotyrosines, but a rising abnormal proportion of an iodinated protein or polypeptide was observed which reached a peak of 25.9% of the total circulating iodine by the end of the third day. This component was later identified as albumin both in paper and starch-gel electrophoresis. Fourteen days after the tracer dose of ^{125}I the patient underwent subtotal thyroidectomy. A large nodular fetal adenoma was found in the right lobe. The remaining glandular tissue was very vascular and was microfollicular, with scant colloid.

3. *Patient IF*, a 20-yr-old female of short stature with a large goiter and deaf-mutism since birth, was admitted to the Endocrine Clinic for evaluation. The goiter had been increasing in size, mostly on the right side. She had had a normal childhood and had menstruated for the first time when she was 12 yr old. At that time she ceased growing.

Although she was brought up in an endemic goiter area there was no goiter in the family. Her height was 1.42 m and weight 49.0 kg. The skin was dry and the deep tendon reflexes were slow. The thyroid was enlarged, mainly due to the right lobe, which seemed to contain a large cyst or nodule.

The PBI was 4.1 μg/100 ml, and the photomotogram (Achilles tendon reflex relaxation time) was 350 msec (normal). The RAI uptake was 19.5% at 2 hr and 51.5% at 24 hr. Of the total iodide accumulated at 1 hr 54% was discharged by perchlorate. Several daily plasma chromatograms for iodinated compounds were done after a tracer dose of ^{125}I. The total iodoprotein value did not exceed 16% in any of the several samples collected after the tracer dose. Thus, it was concluded that circulating iodoproteins or polypeptides were not present in this case. Iodothyronines were considered within the limits of normal and no iodotyrosines could be detected in any of the plasma samples.

Twenty-three days after the tracer dose a subtotal thyroidectomy was done. The nodule in the right lobe proved to be a fetal adenoma. The paranodular tissue was microfollicular and virtually no colloid was found.

B. *Tissue preparation*. The patients were each given 200 400 μc of ^{125}I 13 25 days before re-

moval of the goiter. A second tracer dose of ^{131}I (200–400 μc) was given 12–24 hr before the operation. After thyroidectomy the individual tissues were immediately collected in ice, rinsed free of blood, and homogenized at 4 C in 0.25M sucrose, as described before (7). Preparative centrifugation, at different speed, separated 3 main fractions: nuclear, mitochondrial and soluble protein fractions (7). Aliquots of the nuclear, mitochondrial and soluble fractions were taken for ^{127}I, ^{131}I, ^{125}I and protein determinations as indicated.

C. *Analytical methods.* Chromatography of most samples was done after applications of pancreatic (0.9%) hydrolysates of the whole homogenate, particulate and soluble proteins to Whatman 3 or 3MM paper for descending resolution in a butanol-2N acetic acid (v/v) solvent system. The chromatograms were sprayed with diazotized sulfanilic acid and palladium choride for detection of the carriers. Column chromatography in Dowex resins was also done according to the Blanquet-Meyniel technique (3) as follows: 2 ml of plasma was gently poured over a small column (1.5 × 3.0 cm) of Dowex 50W-X4; the effluent of this first column was directed to a second column (1.5 × 3.0 cm) of Dowex 1-X10. The final effluent was collected in a plastic tube until the final volume reached 15 ml. Both columns were eluted with 10–15 ml of a 0.15M solution of NaCl and taken directly to the well scintillation counter. Five ml of the final effluent was similarly counted. The first column (Dowex 50W-X4) was then washed with a 30% sodium formate solution to remove iodothyronines, and the column again counted directly in the well scintillation counter. Iodotyrosine relative value is found by difference. The relative proportion of iodide was given by the Dowex 1-X10 column and the relative proportion of iodoprotein or polypeptides was given by the final effluent value.

Stable iodine determinations were made by the Benotti and Benotti modification of Zak's method (10). Samples containing $^{125}I/^{131}I$ were measured in a well-type scintillation detector with pulse height analyzer. Protein was determined by the method of Lowry *et al.* (11). Gel filtration was done according to the technique of Perelmutter *et al.* (12). Protein was eluted from the gel with 0.15M NaCl solution, at a rate of 3 ml/10 min, each fraction containing 3 ml. Pancreatin digestion and solubilization of the particulate iodoprotein was done according to previously reported methods (7). Ultracentrifugal studies were conducted in the Spinco Model E analytic centrifuge, the extracts being diluted to a protein concentration of 0.5%, with 0.1M NaCl solution.

TABLE 2. Ratio of ^{131}I and ^{125}I in relation to particulate and soluble iodoprotein. The ^{131}I was administered 24 hours and ^{125}I two to three weeks before surgery. Results expressed as per cent of the administered dose per g of particulate or soluble protein.

Patient	Isotope	Particulate iodoprotein	Soluble iodoprotein
ES	^{131}I	0.0455	1.6963
	^{125}I	0.1528	1.0774
IF	^{131}I	0.0448	0.9766
	^{125}I	0.5768	0.9527

Results

1. *Distribution of ^{127}I, ^{125}I and protein in nodular and paranodular tissue* (Table 1). Labeled iodinated insoluble protein comprised 6.4 to 33.1% of the total radioactive iodine present in the whole nodular homogenate. When the paranodular tissue was examined it was found that 13.4 to 25.9% of the total radioactive iodine was particulate. In one patient (ERC) there was more labeled insoluble protein in the paranodular tissue than in the adenoma.

The distribution of ^{127}I was also measured in the nodular and paranodular tissue, both in the particulate and in the soluble fraction. It was observed that an abnormally small amount of ^{127}I was present at the soluble fraction; in patient ERC, for example, only 43.5% of the total iodine (^{127}I) was recovered in the 105,00 × *g* soluble fraction. As can be seen in Table 1, nearly one third to one half of the total ^{127}I was incorporated into an insoluble iodoprotein which precipitated with the 700 × *g* fraction. In only one instance (ERC) did the paranodular tissue have a larger amount of this particulate iodoprotein than the nodular tissue. In the tissue from the two other patients the amount of insoluble material was higher in the nodule than in the remaining glandular tissue.

The pattern of protein distribution followed closely that of stable iodine (Table

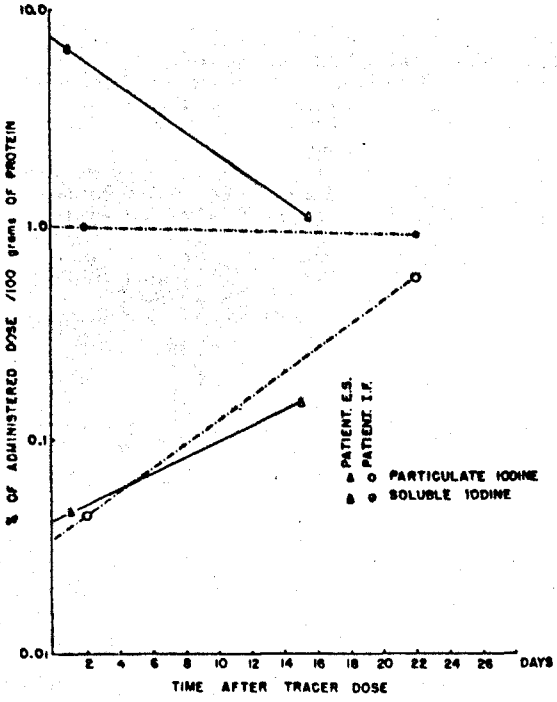


FIG. 1. Curves obtained plotting the % of the administered dose/100 g of particulate and of soluble protein, at both 24 hr and several days after the tracer dose. Note that the % of the administered dose as insoluble iodine increases over a period of 2–3 weeks (^{125}I), as compared with the same index at 24 hr (^{131}I). For the soluble iodine the value at 2–3 weeks after administration of the tracer dose (^{125}I) was decreased as compared with the 24 hr value (^{131}I).

1). In two instances (ERC, ES) only one third of the total protein content of the whole homogenate was present in the soluble fraction. In all cases nearly half of the total glandular protein was particulate, in both the nodular and paranodular tissues.

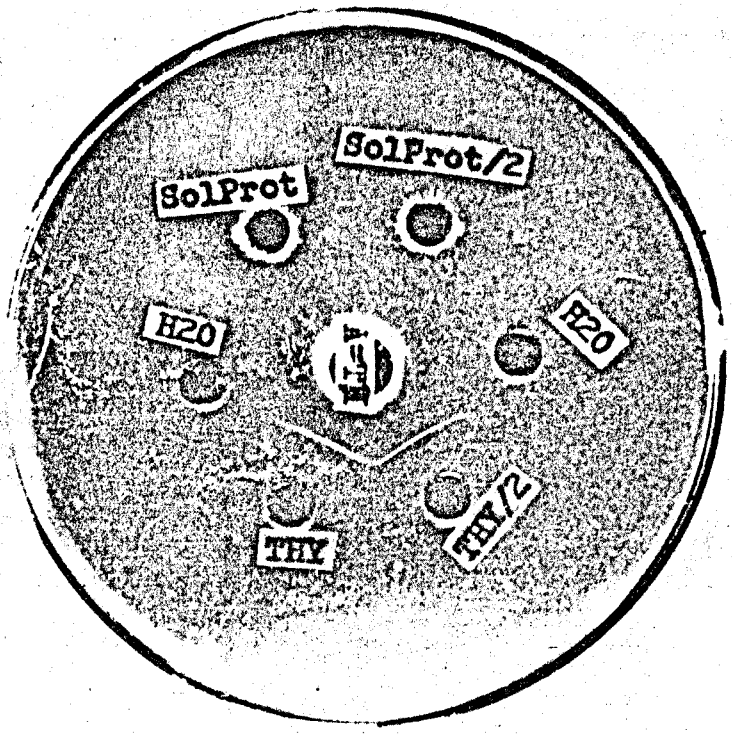
2. *Specfic activity of particulate and of soluble proteins.* In order to study the incorporation of iodine into both soluble and particulate protein, the specific activity of radioactive iodine (^{125}I) was measured as a percentage of administered dose per g of stable iodine (^{127}I) in the nodular and paranodular tissue. A ratio could thus be obtained (SA of particulate protein/SA of soluble protein) that would be useful to define whether the insoluble protein was incorporating more labeled material per μg of ^{127}I than the soluble fraction. This seems to be the case for nodular tissue where ratios of 1.47, 6.47 and 1.05 were obtained for patients ERC, ES and IF. In the paranodular tissue the ratios were lower as compared with nodular homogenate, with values of, respectively, 0.45, 1.26 and 0.79 for ERC, ES and IF.

In two patients (ES, IF) it was possible to measure specific activity of both isotopes (^{125}I, ^{131}I) as related to protein. By the double-labeling technique it was intended to measure the rate of turnover of labeled iodine in both particulate and soluble protein. For the particulate iodoprotein it was observed, in both patients, that the SA two to three weeks after the tracer dose (^{125}I) was higher than at 24 hours (^{131}I). Particulate iodine was six to ten times higher after two to three weeks than after 24 hours of the tracer dose. This suggested a slow turnover of iodine in this insoluble iodoprotein (Table 2; Fig. 1).

For the $10^5 \times g$ supernatant the specific activity at 24 hours was higher than two to three weeks after the tracer dose. This suggested a more active incorporation and release of iodine in the soluble iodoproteins. Furthermore, for both ^{125}I and ^{131}I higher values were found for the SA in the soluble fractions than for the insoluble material (Table 2; Fig. 1).

3. *Solubilization of particulate iodoprotein.* Trypsin proved to be an active agent in solubilizing the particulate iodoprotein (7). Following exposure to 0.4% trypsin for ten minutes, followed by an equal amount of soybean trypsin inhibitor, 78–85% of the radioactivity came into the $10^5 \times g$ supernatant.

Gel filtration on Sephadex G-200 was carried out on the solubilized iodoproteins from four specimens (2 nodules and 2 paranodular tissues). In every case the solubilized iodoprotein came out between fractions 50 and 70, at a rate of 3 ml/10 min. Purified human thyroglobulin from a



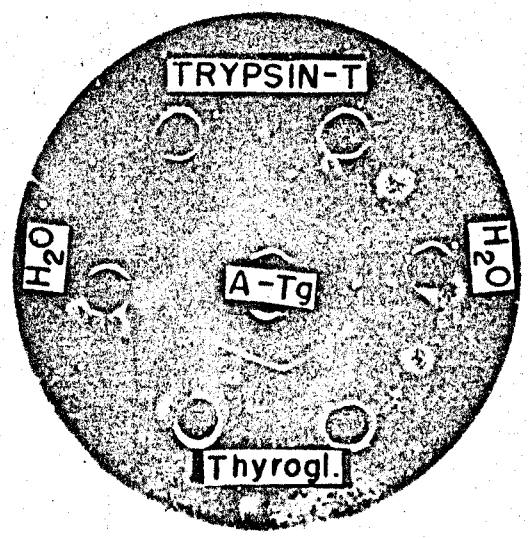


FIG. 2. (*Top*). Note that the solubilized iodoprotein (SolProt) did not react with antihuman thyroglobulin as did purified thyroglobulin (THY). (*Bottom*). Trypsin-treated thyroglobulin did react with antihuman thyroglobulin. Purified thyroglobulin (Thyrogl.) as control.

normal thyroid gland was also treated by trypsin and soybean trypsin inhibitor and then submitted to gel filtration under the same conditions. It came out of the column in the first 15 tubes as normal human thyroglobulin.

Trypsin-solubilized iodoprotein and purified human thyroglobulin were taken to agar plates for testing for antigenicity against goat antihuman thyroglobulin and rabbit antihuman albumin[1] by the Ouchterlony agar gel diffusion method (7). Simul-

[1] The antisera were obtained from Nutritional Biochemical Corporation, Cleveland, Ohio.

TABLE 3. Chromatographic distribution of labeled iodocompounds after pancreatic digestion of the particulate (P_1) and soluble (S) iodoproteins (results in per cent of the total applied to the paper)

Patients		Origin	Iodide	MIT	DIT	T_3/T_4	Ratio iodotyrosines / iodothyronines
ERC	P_1	6.3	43.8	16.9	24.7	4.4	9.445
	S	7.2	13.8	25.1	38.3	15.6	4.069
ES	P_1	5.7	55.8	13.7	21.0	3.8	11.761
	S	6.4	24.5	20.0	35.8	13.2	4.227
	P_1	6.5	37.4	19.6	20.0	6.4	6.187
	S	6.2	34.1	14.3	20.0	15.3	2.241

taneously, standards of human albumin, normal human thyroglobulin and trypsin-treated normal human thyroglobulin were tested for reference. As can be seen in Fig. 2, there was no reaction between the solubilized iodoprotein and the antithyroglobulin or the anti-albumin sera in either the 1.0 or the 0.5% concentration. Both normal human thyroglobulin and trypsin-treated human thyroglobulin reacted with antithyroglobulin.

The particulate iodoprotein from nodular and paranodular tissue was digested with pancreatin and then chromatographed by using both the Dowex resins and the paper methods. Little radioactivity was recovered in the iodothyronine zones; 4.4, 3.8 and 6.4% of the total radioactivity was in the form of T_3+T_4 for patients ERC, ES and IF (Table 3). There were no significant differences in chromatograph distribution of iodocompounds between particulate proteins from nodular or paranodular tissues. The mean ratio of iodotyrosines/iodothyronines was 9.13 for three specimens studied. The proportion of inorganic iodide was abnormally high, with a mean of 30.1% of the total radioactivity. It may be possible that some iodide was split from the protein during the hydrolysis procedure.

4. *Ultracentrifugal studies on the $10^5 \times g$ supernatant.* The $10^5 \times g$ supernatants of nodular and paranodular tissue of two patients (ERC, ES) were studied by analytic ultracentrifugation. In the nodular tissue of ERC 85.1% of the sedimenting material was in a peak of $S_{20,w}=4.2$. Only 12.7% could be identified as 19S protein and 2.2% was present as 25S protein. In the paranodular tissue of the same patient 92.1% of the sedimenting material was in a peak of $S_{20,w}=4.2$ and only 7.9% as 19S protein.

A similar pattern of protein distribution was found for patient ES. In the nodular tissue 90.1% of the sedimenting protein was 4.2S and 9.9% was 25S. There was no detectable 19S protein. In the paranodular tissue 95.6% of the protein sedimented in a peak of $S_{20,w}=4.2$ and 4.4% in a peak of $S_{20,w}=19.0$ (Fig. 3).

5. *Pancreatic hydrolysis of the $10^5 \times g$ supernatant.* After pancreatic digestion the protein in the $10^5 \times g$ supernatant of both nodular and paranodular tissue yielded more iodothyronines than the particulate protein of the same specimen; 15.6, 13.2 and 15.3% of the total radioactivity was present at the T_3/T_4 site for patients ERC, ES and IF. The mean iodotyrosine/iodothyronine ratio was 3.51 as compared to 9.13 obtained from the particulate iodoprotein (Table 3).

Discussion

Several investigators (2–7) have described a number of abnormalities of thyroidal iodoproteins in congenital hyperplastic goiter. This suggests that, besides an enzymatic defect in certain specific steps of hormonogenesis, a defective system for thyroglobulin biosynthesis may be present

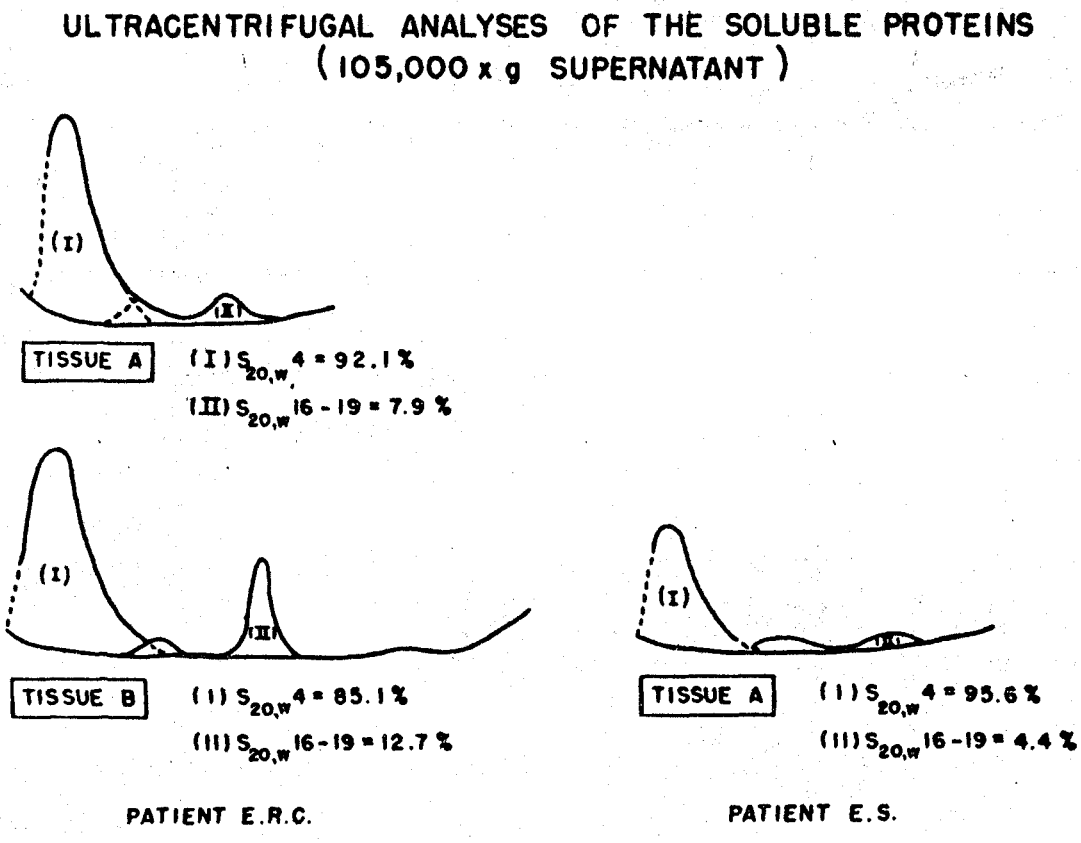


FIG. 3. Ultracentrifuge pattern of soluble iodoproteins for patients ERC and ES; a very low proportion of 19S protein was observed for both tissues of patient ERC; practically no 19S was present in the $10^5 \times g$ supernatant of patient ES.

in these cases. This abnormality would aggravate the dishormonogenesis and would help to explain the hypothyroidism of these patients. Our patients had large and hyperplastic glands and borderline hypothyroidism. A constant daily loss of iodide could be expected from these glands because of impaired organification. When the gland was examined it was noted that, microscopically, it was microfollicular and with scant colloid. A number of cellular abnormalities were also observed such as unusual variations in shape and size of the cells, a rather larger nucleus in relation to cell volume, often with two nucleoli. Nuclei with an irregular, indented margin commonly occurred.

When subcellular fractions were analyzed for radioactive and stable iodine, it was found that a large proportion sedimented with the insoluble protein fractions. This abnormal component had relatively more stable than radioactive material when compared to the soluble fraction. A significant amount of iodine was thus sequestrated from the normal iodine pathway into a dense particulate protein. The nodules were more active in incorporating iodine into particulate proteins than into soluble proteins. The inverse was observed in the paranodular tissue. A tentative explanation for these phenomena would be that in the nodular tissue much more iodine is sequestrated into particulate protein because of a very low production of normal soluble proteins.

The double isotope labeling technique suggested that the amount of sequestrated

iodine was rising over a period of two to three weeks. The iodine turnover was considerably faster in the soluble proteins (Fig. 1).

The latter observation suggests that only a small fraction of the iodide trapped by the gland is actually used for hormone synthesis. In patient ES, for example, a marked decrease in the specific activity of soluble iodine was observed 14 days after the dose as compared with the SA obtained at 24 hours (Fig. 1).

Incorporation of iodine into the insoluble protein with very small return to the intraglandular pool of iodine could constitute a significant net loss of metabolic iodine. Westra *et al.* (13) found that particulate iodoprotein in rats seems to contain a fraction that is relatively slowly but tenaciously labeled by ^{131}I. They also noted that particulate iodine is gradually labeled to a considerably higher specific activity than the soluble fraction, with a slower loss of label in the former as compared with the latter protein. Medeiros-Neto and Stanbury (7) also suggested that particulate iodoprotein would have a considerably slower turnover as compared with thyroglobulin. These findings suggest that the insoluble iodine is not a participant in hormonogenesis.

Previous studies have shown that particulate thyroidal iodine is heterogenous; it includes varieties which have a faster turnover than thyroglobulin (7) and others which turn over more slowly than soluble iodine. Westra *et al.* (13) have shown that severe depletion of iodine in rats seems to result in a relative and absolute rise in particulate iodoprotein, which is turned over sluggishly. In our patients endemic and chronic iodide deficiency could be assumed for every case. This may help to understand the presence of large amounts of particulate iodoprotein with slow iodine turnover.

The origin of this insoluble component is obscure (7). It behaves differently than thyroglobulin after being solubilized with brief treatment by trypsin. It has a low proportion of iodothyronines, does not react with antihuman thyroglobulin, and is eluted differently from the main thyroid protein in a Sephadex G-200 column. Nevertheless, the possibility cannot be excluded that there is a close relationship between the particulate iodoprotein and thyroglobulin.

The ultracentrifugal pattern of the soluble proteins in our patients disclosed that only a small percentage of protein could be identified with the sedimentation characteristics of thyroglobulin. Most of the protein in the supernatant had an $S_{20,w} = 4.2$. Lobo *et al.* (4) found a high relative proportion of a protein with $S_{20,w} = 4.0$ in 12 abnormal hyperplastic glands. Lizarralde *et al.* (5) demonstrated that nearly all the sedimenting material from a congenital goiter was in a peak of $S_{20,w} = 4.2$. In this patient there was no detectable 12S, 19S or 25S material. This was interpreted as an extremely depressed thyroglobulin synthesis. One of us (G.M.N.) has studied five normal thyroid gland specimens obtained from patients who underwent parathyroid surgery. In these tissues less than 10% of the total iodoprotein was particulate and 85% of soluble protein was sedimented in the 19S range (15). Thus, in our patients it is possible that, besides sequestration of iodine from the normal pool and its incorporation into an abnormal insoluble component, some abnormality in thyroglobulin synthesis impaired hormonogenesis. The presence of large amounts of 4S material in the supernatant has been found in many cases of congenital goiter (3, 5) and has been related to low output of thyroxine in those patients.

It seems reasonable to assume that the abnormalities of protein found in our patients were closely related to the partial defect found in iodide organification and probably were due to some genetic disturbances affecting not only the thyroid gland but other systems in the body. By analogy with the hemoglobin variants and their associated diseases, one might suspect

that there exists a group of abnormal iodoproteins, as thyroglobulin variants or aberrations, which have arisen through gene mutation (14). The relationship of large amounts of the insoluble component, the predominantly 4S soluble protein in the supernatant, the enzymatic defect in iodide organification and the congenital deafness is, for the moment, entirely conjectural.

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Reprinted from
THE JOURNAL OF
CLINICAL ENDOCRINOLOGY AND METABOLISM
Vol. 28, No. 8, August, 1968, pp. 1205-1213
Printed in the U.S.A.

RESUMO. No tecido tireoidiano de três pacientes portadores da síndrome de Pendred foram estudadas as distribuições do ^{127}I, ^{125}I ou ^{131}I e de proteinas. Em cada um dos pacientes uma fração apreciável do iodeto intratireoidiano era descarregada quando da administração de perclorato. Duas amostras de tecido nodular e paranodular foram estudadas em cada paciente. As proteínas iodadas insolúveis representaram de 6,4 a 33,1% da radioatividade total dos homogenados. Os tecidos nodulares eram mais ricos em iôdo ligado à fração particulada do que os tecidos paranodulares. De 1/2 a 1/3 do iôdo estável estava incorporado em proteínas particuladas. A distribuição das proteínas seguiu de maneira bastante constante a do iôdo; assim, no tecido nodular verificou-se uma maior quantidade de produtos marcados por micrograma de ^{127}I nas proteínas insolúveis do que na fração solúvel. Decorridas três semanas da administração da dose traçadora, a proteína particulada acusava maior quantidade de radioiôdo por grama do que após 24 horas. A iodoproteína particulada foi solubilizada por ataque parcial de tripsina e pôde ser separada da tireoglobulina por filtração em gel de Sephadex. A proteína assim solubilizada apresentou comportamento imunológico diferente da tireoglobulina. Em ambos os tecidos tireoidianos estudados, menos de 15% das proteínas solúveis totais estavam na faixa de 19S. Num dos nódulos não se logrou demonstrar a presença de proteína 19S no sobrenadante. Os AA. sugerem a possibilidade dos pacientes portadores da síndrome de Pendred apresentarem além de um defeito na organificação do iôdo, um defeito inato afetando a síntese da tireoglobulina.