THE METABOLISM OF IODINE IN CEREBROSPINAL FLUID*†

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LITTLE attention has been paid to the penetration of thyroid hormone into cerebrospinal fluid (CSF), although the marked effect of thyroid hormone on the growth, development and function of the central nervous system is well documented. Congenital absence of thyroid hormone may result in the permanently impaired intellect of cretinism. Even adult myxedema results in marked dulling of mental activity, personality changes and occasionally frank psychosis (1). Conversely, overabundance of thyroid hormone, as in Graves' disease, results in mental agitation and occasionally manic or toxic psychosis (2, 3).

In myxedema, cerebral blood flow is decreased and cerebral vascular resistance is increased (4, 5). Whether there is a decrease in cerebral oxygen and glucose consumption is in dispute (4, 5). Myxedema causes characteristic changes in the electroencephalogram, consisting of a low voltage, slow frequency, absence of alpha waves, and absence of reaction to light stimulus (5).

In hyperthyroidism, cerebral oxygen and glucose consumption are unaltered (4, 6, 7). Increased cerebral blood flow and decreased cerebral vascular resistance have been reported (4, 6), but not by all workers (7). Abnormalities in the electroencephalogram in hyperthyroidism have been demonstrated (8).

The iodine content of CSF has received relatively slight attention.

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Gildea and Man (9) found an average CSF total iodine concentration of 0.2 γ per 100 ml. in 6 normal human patients. In 8 other patients, after the ingestion of Lugol's solution, when the total iodine of serum was increased to more than 100 γ per 100 ml., only a 1 to 6 per cent rise occurred in CSF.

Greenberg and associates (10) studied in dogs the passage of radioiodide and other ions from the serum into CSF. The order of permeability into CSF of the various halides was found to correspond inversely to the order of their ionic diameters, ($Cl^- > Br^- > I^-$). Iodide concentration in cisternal CSF achieved a constant level in one to two hours. When at apparent equilibrium with serum iodide, CSF iodide showed a concentration of only 12 per cent of the serum value.

The concentration of thyroxine and triiodothyronine in brain tissue has been found by several workers to be extremely low compared to the concentrations in most of the other body tissues (11, 12, 13). The problem of thyroid hormone in brain tissue is, however, quite distinct from that in CSF, and will not be considered here in detail.

No reports are available concerning the identification of thyroid hormone or other organic iodine compounds in CSF. The purpose of the present study is to measure the concentration in CSF of inorganic iodide and of any organic iodine-containing compounds that may be present.

METHODS

Samples of radioactive CSF and blood were obtained from patients at the Memorial Center who had received radioiodine (I^{131}) for the treatment of thyroid carcinoma, hyperthyroidism, or heart disease. The patients with thyroid cancer received doses in the range of 50 to 300 millicuries. Those with hyperthyroidism or heart disease received 20 to 30 millicuries. Clinical data on these patients are given in Table 1. Spinal fluid (10–25 ml.) was withdrawn by lumbar puncture. Serum protein-bound iodine (PBI) determinations were made by a modification of the method of Barker (14, 15).

In 5 patients the metabolism of inorganic iodide was studied. Samples of serum and CSF in this group were withdrawn within the first eight hours after administration of the isotope.

In 6 other patients, blood and CSF samples were withdrawn forty-eight hours after administration of the isotope, for the study of organic iodine compounds. In general, the patients who received the larger doses of radioiodine were included in the latter group, since the techniques for organic analysis demanded somewhat higher levels of radioactivity.

Two patients with mammary carcinoma who were clinically euthyroid received tracer doses of radioactive *l*-thyroxine intravenously. Samples of blood and CSF were withdrawn at forty-eight hours.

To determine at any time the ratio of total radioactivity in CSF compared to that in serum, an aliquot (1–3 ml.) of CSF was counted in a well-type scintillation counter against an equal volume of a 1:50 or 1:100 dilution of the serum.

To determine the fraction of radioactivity in CSF which was dialyzable, a measured sample (3–5 ml.) of a 1:10 dilution of the fluid was dialyzed by the method described

TABLE 1. CLINICAL AND I^{131} DATA

Patient	BMR (%)	Serum PBI (γ/100 ml.)	CSF protein (mg./100 ml.)	CSF pressure: (init; final) (mm. CSF)	I^{131} dose (mc.)	48-hr. I^{131} ur. excretion (% of dose)	Time of samples (hrs. after dose)	Ratio of tot. I^{131} (ser./CSF)	Ratio of iodide I^{131} (ser./CSF)
M.H. Recurr. Graves' dis.; 2 partial thyroidectomies.	+6 +39	9.8	37.8	125; 85	26*	42.5	2.0	103.5	103.5
H.K. Arterioscler. heart dis.; euthyroid.	−20 −3	4.7	52.4	125; 85	30	48.3	2.5	88.7	88.7
B.R. Graves' dis.; propylthiouracil 3 yrs.; no surgery.	+10, −7, +39	10.7	16.3	125; 50	12	19.8	4.0	62.9	62.9
G.T. Thyroid cancer; partial thyroidectomy; cerebral & skel. metast.	+22, +5, +9	1.9	50.6	370; 360	50	75.1	7.5	44.0	44.0
M.D. Recurr. Graves' dis.; partial thyroidectomy.	+17	7.0	37.4	—	30	39.1	8.0	113.0	113.0
E.G. Thyroid cancer; athyreotic; cerv. metast.; Tapazole 6 wks.	−2, +20, +16	2.5	37.9	95; 35	125	65.3	48.0	133.0	—
R.N. Thyroid cancer; 2 partial thyroidectomies; cerv. and mediast. metast.	—	1.4	30.2	200; 60	125	91.4	48.0	400.0	57.1
L.L. Thyroid cancer; athyreotic; pulm. metast.; Tapazole 8 wks.	—	1.1	38.2	360; 140	200	51.0	48.0	153.0	99.5
R.S. Thyroid cancer; athyreotic; pulm. metast.; Tapazole 6 wks.	−26	0.1	39.5	350; 190	125	57.8	96.0	—	—
A.L. Graves' dis.	—	10.4	37.5	55; 30	20	34.4	48.0	92.7	23.2
R.R. Rheum. heart dis.; intractable failure with anasarca.	—	7.5	—	—	25	30.6	48.0	97.5	—
B.C. Metastatic breast cancer; clinically euthyroid.	—	2.9	16.9	100; 60	—†	—	48.0	54.3	—
M.W. Metastatic breast cancer; euthyroid.	—	6.0	28.3	165; 35	—‡	—	48.0	78.6	—

* I^{133}.
† I.V. radiothyroxine tracer, with 41 gamma of carrier thyroxine.
‡ I.V. radiothyroxine tracer, with 48 gamma of carrier thyroxine.

subsequently for the concentration of CSF. The loss of radioactivity from the samples was evaluated by measuring them in a scintillation counter, using as standards, identical but undialyzed volumes of the same solution.

For the analysis of organic compounds, CSF was concentrated 50- to 100-fold. From 8 to 20 cc. of CSF was dialyzed in Visking tubing for twenty-four hours at 4° C. against two 3-liter volumes of a potassium phosphate buffer, 0.001 M, pH 6.6. The dialyzed fluid was lyophilized and the resulting white powder dissolved in 0.1 or 0.2 ml. of distilled water.

The concentrated CSF was analyzed by paper chromatography and electrophoresis. Ascending one-dimensional chromatography was conducted on Whatman No. 1 filter paper in two butanol solvent systems, one acid, and one ammoniacal, as previously described (16). A third system consisted of collidine:water, 100:35.5, in an atmosphere of concentrated ammonium hydroxide. Stable amino-acid carriers were streaked at the origin of the chromatograms and 0.01–0.02 ml. of concentrated CSF was then applied. In a few instances unconcentrated CSF was chromatographed by delivering 0.25-1.00 ml. of the fluid to the paper by multiple successive applications of untreated CSF. The chromatograms were run overnight, dried, and sprayed with Ninhydrin for localization of the stable carriers. Radioactivity on the strips was measured with a thin mica-window Geiger-Mueller tube and a continuously recording counting rate meter. It has previously been shown that a direct proportionality exists between the area under each peak of radioactivity and the amount of radioactivity in that area of the strip.

Zone electrophoretic analysis of concentrated CSF was conducted on Whatman No. 3 paper strips in barbital buffer at pH 8.6 for twenty-four hours at 100 volts, as previously described (17). The volume of concentrated CSF delivered was about 0.02 ml., which contained approximately 1 milligram of protein, the equivalent of 2 ml. of untreated CSF. The electrophoretic strips were counted for radioactivity in the same manner as the chromatograms described, and the proteins were then stained with bromphenol blue (16).

Identification and quantitation of iodine components

1. *Iodide.* The percentage of radioiodine as iodide in serum was estimated by planimetry of iodide areas in the radioanalysis of serum chromatograms. The percentage of radioiodine as iodide in CSF was considered equivalent to the dialyzable radioactivity, assuming negligible losses of any organic iodine compounds during analysis. This estimation was confirmed by chemical iodide analysis. It was also in agreement with values for iodide in whole CSF, derived by applying large volumes of untreated CSF directly to the chromatographic strip.

2. *Thyroid hormone.* The percentage of radioiodine as thyroxine and triiodothyronine in serum and in CSF was estimated by planimetry of areas in the radioanalysis of chromatograms.

3. *Thyroglobulin and other compounds.* The detection and quantitation of thyroglobulin discharged into serum from I^{131}-irradiated thyroid tissue, and of other organic radioiodine compounds in serum and CSF, will be discussed.

RESULTS

The ratio of total radioiodine concentration in serum compared to CSF in different patients at various times after oral administration of the isotope is indicated in Table 1. It appeared to be unrelated to the size of the dose administered. In the 5 patients included in the inorganic iodide

TABLE 2. DISTRIBUTION OF RADIOACTIVITY 48 HOURS AFTER I^{131} THERAPY

A. Iodide I^{131} in Serum and CSF

Patient	Ratio of tot. I^{131} (ser./CSF)	Per cent of total I^{131} in serum or CSF in form of*												PBI (γ/100 ml.)	
		I^-		T_4		T_3		T_G		X		Z			
		Ser.	CSF	Ser.	CSF	Ser.	CSF	Ser.	CSF	Ser.	CSF	Ser.	CSF	Ser.	CSF†
R.N. Thyroid Ca.; myxedema.	400.0	10.0	71.0	17.0	17.7	0	0	52.6	0	20.4	3.8	0	7.5	1.4	0.0036
L.L. Thyroid Ca.; myxedema.	153.0	61.5	94.5	4.5	3.5	0	0.3	27.5	0	6.5	0.7	0	1.0	1.1	0.0057
R.R. Rheum. heart dis.; euthyroid.	97.5	78.6	66	21.4	34	0	0	0	0	0	0	0	0	7.5	0.122
A.L. Graves' dis.	92.7	10.0	40	81.0	60	2	0	7	0	0	0	0	0	10.4	0.083
B.C.‡ Breast Ca.; euthyroid.	54.3	5.4	13.6	94.6	86.4	0	0	0	0	0	0	0	0	2.9	0.0674

B. Organic I^{131} in CSF

	Ratio of tot. I^{131} (ser./CSF)	Per cent of I^{131} in *dialyzed* CSF in form of						PBI (γ/100.ml.)	
		I^-	T_4	T_3	T_G	X	Z	Ser.	CSF
R.S., Thyroid Ca.; myxedema.	—	0	54.0	7.0	0	33.0	6.0	0.1	—
E.G., Thyroid Ca.; myxedema	133.0	0	60.0	5.0	0	10.0	25.0	2.5	—

* I^- = Iodide. T_4 = thyroxine. T_3 = triiodothyronine. T_G = thyroglobulin. X = compoundX(Robbins). Z = unidentified material (*see* text).

† Calculated.

‡ Received a tracer dose of *l*-thyroxine.

study (samples withdrawn within eight hours after isotope administration), the serum/CSF ratios lay in the range of 44/1 to 113/1. The value of 44/1 occurred in a patient with increased intracranial pressure due to cerebral metastases and should be considered in that light. Serum/CSF iodide ratios calculated for 3 other patients at forty-eight hours after radioiodide administration ranged from 23.2/1 to 99.5/1.

When organic radioiodine was present, the serum/CSF ratios fell in the range of 50/1 to 150/1 with few exceptions. A single much higher value of 400/1 was observed in Patient R.N. This case did not differ clinically from other cases of thyroid carcinoma.

Organic compounds in CSF

Thyroxine was detected in the serum and CSF of all patients in whom organic analyses were performed.

Table 2A shows the percentage distribution of serum and CSF radioiodine in inorganic iodide and various organic iodine compounds in 5 patients.

Thyroxine accounted for 4.5 and 17.0 per cent, respectively, of the total serum radioiodine at forty-eight hours in the 2 patients with thyroid cancer who were at that time myxedematous. A euthyroid patient (R.R.) had 21.4 per cent of serum radioiodine residing in thyroxine at forty-eight hours. The value was 81 per cent in Patient A.L. with Graves' disease. The percentage of CSF radioiodine as thyroxine was in a similar range to that of serum. It constituted less than 20 per cent of total CSF radioiodine in the myxedematous thyroid cancer patients, and a higher percentage in the euthyroid and hyperthyroid patients studied.

Utilizing these percentages and the serum/CSF ratios for total radioiodine, the relative concentration of thyroxine in CSF as compared to serum was calculated:

Assuming that the specific activity of all iodine in CSF approximately equals that of serum, then

$$\frac{C'}{C} = \frac{S'}{S}, \quad \text{or} \quad \frac{C}{S} = \frac{C'}{S'}$$

where

C, S = concentration of stable iodine in CSF and serum, respectively, and

C', S' = concentration of radioactive iodine in CSF and serum, respectively.

Since there were several radioactive compounds and the ratio of only one of them is desired, correction for this must be made. Where

$T_{C'}$ = the fraction of radioactivity in CSF present as thyroxine, and

$T_{S'}$ = the fraction of radioactivity in serum present as thyroxine, then

$$\frac{C'}{S'} \cdot \frac{T_{C'}}{T_{S'}} = \frac{\text{PBI CSF}}{\text{PBI ser}}$$

or

$$\text{PBI} \cdot \text{CSF} = \frac{C'}{S'} \cdot \frac{T_{C'}}{T_{S'}} \cdot \text{PBI ser.}$$

With knowledge of the serum PBI level, a value for PBI in CSF can then be obtained. The results are indicated in Table 2A, final column.The values ranged from 0.0036 γ per 100 ml. in a patient with myxedema to 0.122 γ per 100 ml. in a euthyroid patient.

In a patient who received intravenous thyroxine and in whose serum and CSF nearly all radioactivity at forty-eight hours was still present in thyroxine, the PBI concentration in CSF was 0.0674 γ per 100 ml. (Table 2A).

Thyroxine-protein association in CSF. Contrary to reports of other workers (18), the patients with myxedema in this study showed no elevation of the CSF protein (Table 1).

The proteins of concentrated CSF, separated by zone electrophoresis in this and numerous other studies (19, 20, 21) provide a pattern similar to that of the serum proteins. A well-defined albumin and the various globulins are present in proportions more or less like those in serum. A consistent finding in this study was the presence of a small component with mobility faster than albumin, which has been reported by numerous workers (19–22).

The binding of CSF thyroxine by CSF protein is demonstrated in Figure 1. The upper portion shows a butanol-dioxane-ammonia chromatogram of CSF from a patient with Graves' disease, indicating that all the radioactivity in the dialyzed CSF is present as thyroxine. In the electrophoretic separation of this same CSF (Fig. 1, bottom) the thyroxine is separated into two peaks, one corresponding to the albumin component in the CSF protein, the other to an alpha-globulin. This pattern of thyroxine distribution, resembling qualitatively the binding of thyroxine by the proteins in serum (23), was seen also in the CSF of Patient R.R. (euthyroid), where thyroxine was similarly the sole organic iodine compound; but in the 2 patients who received intravenous radiothyroxine, the electrophoretic separation of the radioactivity differed from this example. The serum in these patients exhibited an entirely normal electrophoretic pattern for thyroxine, but in the CSF the radioactivity was bound by virtually all of the CSF proteins (Patient B.C., Fig. 2).

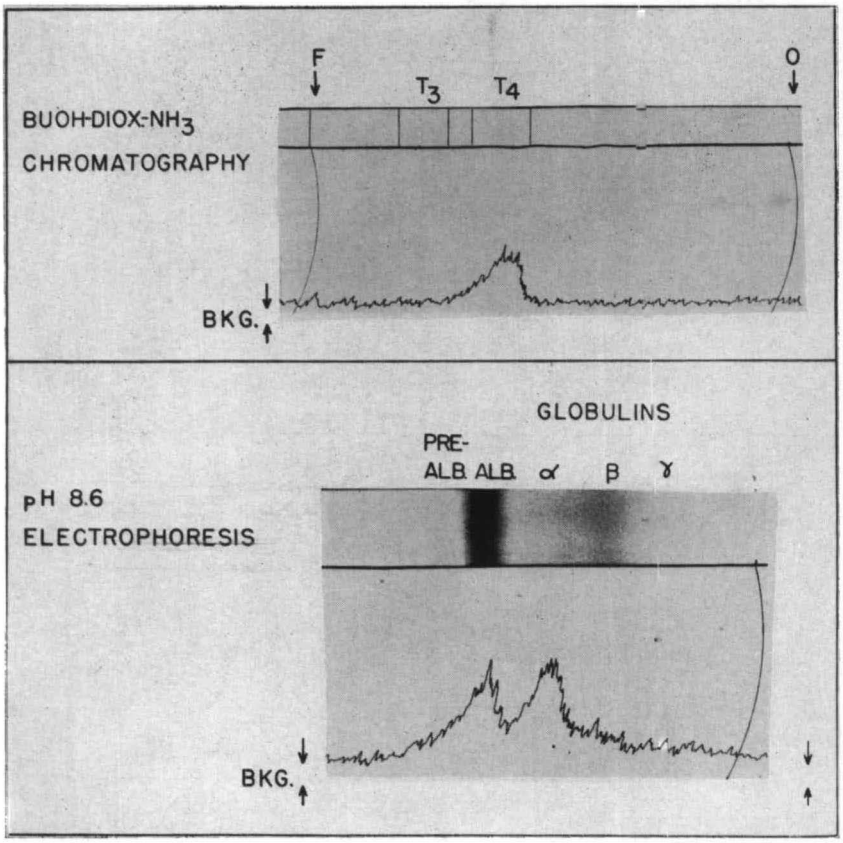

FIG. 1. Paper chromatography and electrophoresis of radioiodine in dialyzed CSF from Patient A.L. (Graves' disease), who received 20 millicuries of I^{131}. Recordings of radioactivity are mounted beneath the paper strips.

Triiodothyronine was noted in small amounts in the serum and/or CSF of 4 of the 6 patients in whom organic analyses were performed

Thyroglobulin, discharged from I^{131}-irradiated thyroid tissue, was detected as radioactivity which remained at the origin in all the chromatographic systems, and which in zone electrophoresis had a mobility between the alpha-1 and alpha-2 globulins of serum. Radioactivity fulfilling these criteria was detected in the serum of all patients who received doses of radioiodine of 50 millicuries or more. Its presence in CSF could not be demonstrated.

An iodinated compound (X), previously detected in the serum of some patients with thyroid carcinoma (24, 25), was noted in the serum of all the patients with that diagnosis included in this study. Like thyroglobulin, this substance remains at the origin in paper chromatography, but it has an electrophoretic mobility corresponding to that of serum albumin. This

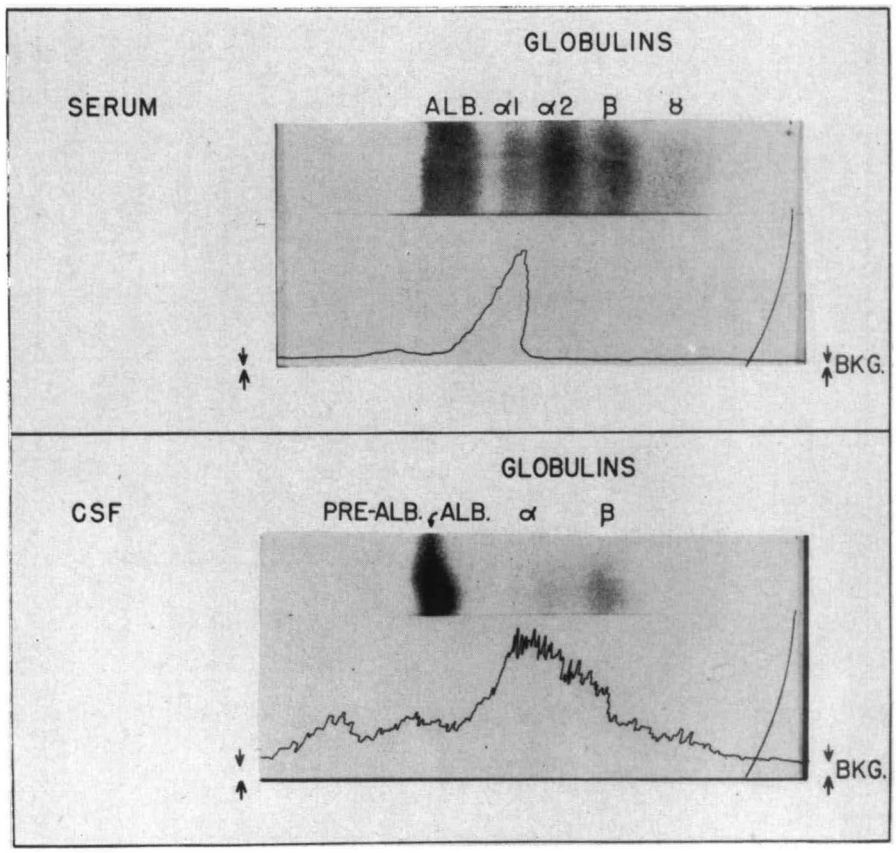

FIG. 2. Paper electrophoresis at pH 8.6 of serum and dialyzed CSF from Patient B.C. (euthyroid), who received intravenous radiothyroxine.

compound was also present in the CSF of these patients. Indeed it could be detected in concentrated CSF in most cases more easily than in the serum, where its concentration relative to thyroglobulin was often small (R.N. and L.L., Table 2A). In CSF, however, thyroglobulin was evidently not present, and virtually all of the radioactivity remaining at the origin in chromatography could be accounted for in the CSF albumin fraction by electrophoresis, and was thus attributable to this thyroid cancer compound.

An *additional unknown substance* was detected in the concentrated CSF of thyroid cancer patients who received radioiodine doses greater than 100 millicuries. It was not noted in the serum of these patients. This compound had an Rf in butanol-dioxane-ammonia chromatograms of 0.08 to 0.09, which is like that of mono- and diiodotyrosine. In collidine-water the Rf was 0.53, just in advance of mono-iodotyrosine; but in butanol-acetic acid, the substance moved well beyond the iodinated tyrosines, and was poorly

separable from the broad peak of thyroxine which was also present. The actual Rf for this compound in butanol-acetic-acid, detected by a two-dimensional technique (electrophoresis and chromatography) was 0.87. Binding of this compound to CSF proteins, as shown by electrophoresis, is not certain; in the 4 patients in whom it was detected, no consistent pattern was evident, but elution of electrophoretic strips in butanol-acetic acid chromatography suggested that its mobility is like that of the CSF "pre-albumin" (Fig. 4). To characterize this CSF compound further, the portion of a butanol-dioxane-ammonia chromatogram (from Patient L.L.) which contained the unidentified radioactivity in question was cut out and attached as the origin of an ascending chromatogram, in a system

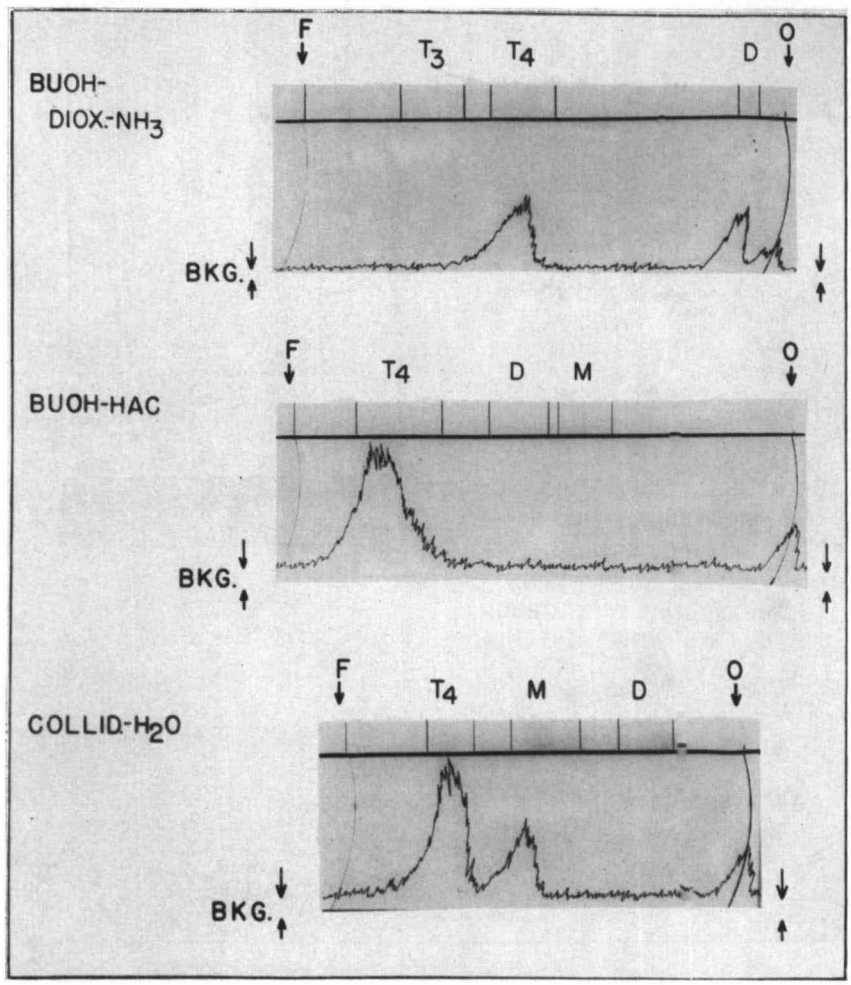

FIG. 3. Paper chromatography in three solvent systems of dialyzed CSF from Patient E.G. (thyroid carcinoma), who received 125 millicuries of I^{131}.

consisting of ether, glacial acetic acid, and water; 150:30:5. All of the radioactivity in this chromatogram advanced to a single peak at the solvent front.

With Patient L.L., further analyses were performed in order to define more conclusively certain features of the CSF organic iodine content. The

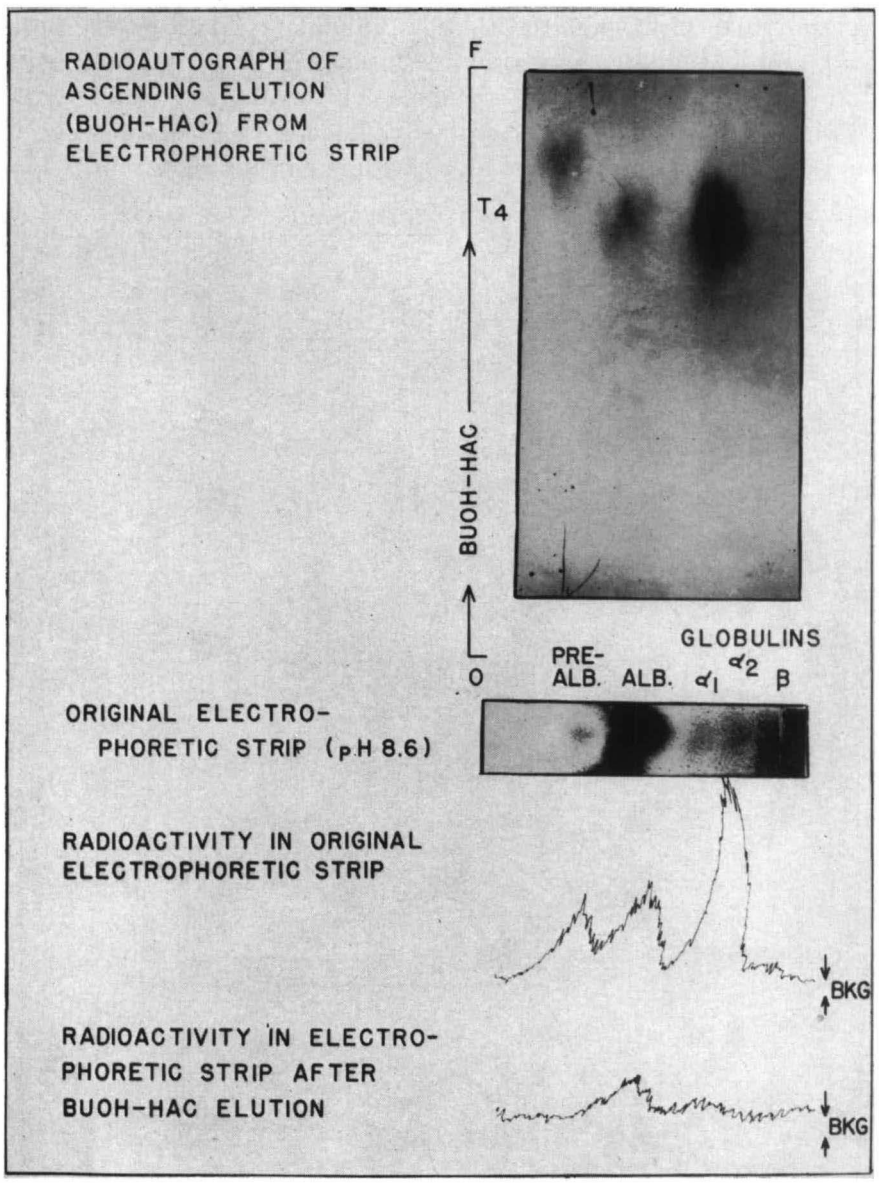

FIG. 4. Two-dimensional radioanalysis of dialyzed CSF from Patient L.L. (thyroid carcinoma), who received 200 millicuries of I^{131}. The electrophoretic strip was eluted in BuOH-HAc; the resulting chromatogram is mounted above the strip.

CSF of this patient exhibited four radioactive compounds by chromatography. The patterns resembled those of Patient E.G. (Fig. 3; Table 2B). Thyroxine and triiodothyronine constituted 68 per cent of the organic radioiodine activity; compound X accounted for 13 per cent; and the unidentified substance (Z), 19 per cent. The electrophoretic pattern of this same CSF (Fig. 4, middle) showed three peaks, corresponding to pre-albumin, albumin, and inter-alpha globulin. The upper portion of Figure 4 is the radioautograph of the activity which was eluted upward from the electrophoretic strip, when it was utilized as the origin of an ascending chromatogram in the butanol-acetic acid system. Radioactivity with the Rf of thyroxine has ascended from the alpha-globulin region; a smaller amount with similar Rf has ascended from the albumin component; and from the pre-albumin, activity has ascended to a position just beyond that of thyroxine. The lower portion of Figure 4 indicates the distribution of radioactivity which remained in the same electrophoretic strip after the elution. Considerable radioactivity was removed from all the components. (In addition, 40 per cent was lost due to radioactive decay). In the albumin portion, significant radioactivity remained, which presumably corresponded to compound X. Nearly all of the radioactivity in the alpha-globulin portion was removed with the elution of thyroxine. If radioactivity had remained in this position, it would correspond to thyroglobulin, which has an electrophoretic mobility like that of the thyroxine-binding protein. These data and similar considerations in the cases of E.G. and R.N. indicate that thyroglobulin is not present in CSF.

DISCUSSION

The presence in CSF of very low concentrations of iodine in several forms is confirmed in these investigations. The values reported here are generally lower than those reported by other workers. For example, CSF iodide concentration in this study averaged 1.35 per cent of the serum value compared to a value of 12 per cent found by Greenberg and his co-workers in dogs (10). Similarly, for total iodine, CSF concentrations in these patients were 0.26 to 2.3 per cent of those in serum; whereas Gildea and Man, in 8 euthyroid patients, found values ranging from 1.6 to 4.5 per cent of the serum values.

Because only a single CSF sample was procured from each patient it was impossible to construct a time curve for the entry of radioiodine or its various forms into CSF. In the values for the serum/CSF iodide ratio, there is considerable variation (Table 1, final column). The data might at first suggest that the CSF concentration of iodide relative to serum was still increasing at four hours after radioiodine administration, but this is controverted by the values for M.D. at eight hours (serum/CSF = 113.0),

and L.L. at forty-eight hours (serum/CSF = 99.5). It is probable that a steady state for iodide is achieved within two hours after radioiodine administration, and that the data reflect a rather wide individual variation in the relative concentration of iodide in serum and CSF. The work of Greenberg (10) and others indicates that the relative ease of entry of the various halides into CSF is in the inverse order of their ionic diameters. It is unlikely, however, that the ready passage of iodide across the blood-brain barrier is prevented primarily by its larger ionic size. If it is assumed that larger molecules such as proteins enter CSF by transudation from serum (and the major spectrum of CSF protein resembles that of serum), then it may also be assumed that the iodide ion is not excluded from CSF on the basis of its size. The very low concentration of iodide in CSF supports the argument that diffusion alone cannot account for the composition of CSF, but that energy is expended, either in the selective secretion of certain substances into CSF, or in the maintenance of a concentration gradient.

The derived values for PBI concentration in CSF (Table 2A, final column) were lowest in myxedema. The value for the patient with Graves' disease (0.083 γ per 100 ml.) was only moderately higher than that for a clinically euthyroid patient who received labeled thyroxine (0.067 γ per 100 ml.). It is surprising that the highest value (0.122 γ per 100 ml.) occurred in a euthyroid patient. In general, however, comparison between levels of serum PBI and CSF-PBI indicates a reasonably constant relationship, and suggests that CSF levels of thyroxine are a reflection of serum levels.

It is not understood why, in a euthyroid patient (R.R.) and in one who was hyperthyroid (A.L.), thyroxine in CSF was bound primarily by inter-alpha globulin (presumably the same as the thyroxine-binding protein of serum) and by albumin; whereas in the euthyroid patients (B.C. and M.W.) intravenously injected radiothyroxine was bound by virtually all the CSF proteins.

The serum alpha-globulin that specifically binds thyroxine seems to be present in CSF. Its actual concentration in either fluid is too small to be estimated by present techniques. Whereas thyroxine concentration in CSF is 1 to 2 per cent that of serum, protein concentration in CSF is less than 0.5 per cent the serum value. If it can be assumed that the specific thyroxine-binding protein constitutes a roughly similar fraction of the protein in both fluids, then in CSF a given quantity of thyroxine is provided only one quarter as much specific protein for binding as it is in serum. It may be that in certain patients (*e.g.*, B.C., and M.W.), for reasons not understood, the relative concentration of thyroxine-binding protein in CSF is even lower than estimated by these calculations. This

would result in a considerable degree of nonspecific binding, even for low values of CSF thyroxine.

The data in Patient B.C. (Fig. 2) suggest that thyroxine can enter CSF, at least in part, independent of serum protein, since in CSF thyroxine exists in association with protein components that do not bind it in serum, including at least one (pre-albumin) which is not even present in serum.

The results indicate that compound X can penetrate the blood-brain barrier, whereas thyroglobulin discharged from I^{131}-irradiated thyroid tissue cannot. This can be understood in terms of the relative size of these compounds. The former substance, according to sedimentation studies in the ultracentrifuge (26), has a molecular weight of about 60,000, and could be secreted by the cells of the choroid plexus in the same way that serum proteins are presumably secreted. Thyroglobulin, on the other hand, is in a size-class (M.W. 650,000) (26, 27) much larger than that of the serum proteins, and may well encounter difficulty in transfer on this basis.

The new iodinated substance (Z) detected in chromatograms of CSF in the present study remains unidentified. Its behavior in the chromatographic systems studied does not correspond to that of the amino acids ordinarily found in thyroid tissue or in biologic fluids. Glucuronic-acid and acetic-acid derivatives of the thyroid hormone may be excluded on the basis of their Rf's in certain solvent systems (28, 29), as may the alpha-keto forms of thyroxine and triiodothyronine (30). Thyroxamine has been similarly excluded. Its Rf in the butanol-acetic acid system, detected by the diazotized sulfanilamide method (31), is 0.87, which would be compatible with that of the unidentified substance. In the butanol-dioxane-ammonia system, however, the Rf of thyroxamine is 0.91, whereas that of the unidentified substance is 0.08–0.09.

The origin of substance Z is not clear. It was noted in each of 4 patients, all with thyroid cancer, all myxedematous at the time of the treatment, and all treated with radioiodine doses larger than 100 millicuries. Because it was not detected in serum it is presumably produced within the central nervous system. Moreover, its absence from the serum of these patients suggests that it is not a characteristic product of irradiated thyroid cancer tissue, particularly since central nervous system metastases were not present. If the material is a central nervous system metabolite of thyroid hormone it should be detectable in the CSF of all patients, although the possibility exists that only in those who received the larger doses of radioiodine was the activity adequate to permit detection by the present methods. On the other hand, the absence of this material in the CSF of Patients B.C. and M.W., who received intravenous radiothyroxine,

militates against this likelihood. A third possibility, still unexplored, is that the substance is produced by the central nervous system in profound myxedema.

SUMMARY

1. Iodine compounds in cerebrospinal fluid (CSF) were studied in 11 patients who received therapeutic doses of radioiodine, and in 2 patients who received tracer doses of radioactive thyroxine.

2. CSF iodide concentration in 8 patients ranged from 0.9 to 4.3 per cent of serum values, with an average of 1.3 per cent.

3. Thyroxine was detected in the CSF of all patients in whom organic analyses were performed. The average concentration in 5 patients was 1.1 per cent of serum values. Calculated values for the concentration of protein-bound iodine in CSF ranged from 0.004 microgram per 100 ml. in a patient with myxedema to 0.122 microgram per 100 ml. in a euthyroid subject. In a patient who received intravenous radiothyroxine, the value was 0.067 microgram per 100 ml. The specific alpha-globulin that binds thyroxine in serum seems to be present in CSF in low concentration. Small amounts of triiodothyronine were detected in the CSF of 3 patients.

4. Thyroglobulin discharged from I^{131}-irradiated thyroid tissue was not detected in the CSF of any patients.

5. In the CSF of 4 patients with thyroid carcinoma the presence of a compound, (X), which is associated with certain cases of thyroid cancer, was demonstrated. An unidentified substance, (Z), was also detected in the CSF of these patients. Its behavior in three chromatographic systems was unlike that of the commonly observed iodinated amino acids or the metabolites of thyroid hormone.

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