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Iodide Transfer at Four Cerebrospinal Fluid Sites in the Dog: Evidence for Spinal Iodide Carrier Transport

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In the adult dog under pentobarbital, cerebrospinal fluid (CSF) was sampled from the lateral ventricle and from the cisternal, lumbar, and parasagittal subarachnoid spaces. The choroid plexuses of the lateral ventricle were also excised. Values of the net iodide uptake in these samples were compared at 2 hr after an intraperitoneal injection consisting of 2.0 mc $Na^{131}I$ combined with doses of $Na^{127}I$ varying from 1.0 to 800 mg/kg. Similar samples were analyzed from dogs whose lumbar subarachnoid space had been isolated from intracranial carriers by thoracic transection or epidural ligation. In another series of dogs, the effect of saturating levels of $Na^{127}I$ in the spinal subarachnoid space isolated from intracranial carriers was tested by continuous thoracolumbar perfusion with artificial CSF containing $Na^{131}I$ and $Na^{127}I$. The existence of a spinal iodide carrier system was suggested by the small net uptake of iodide in normal lumbar CSF, and by the progressive rise in this uptake as saturating doses of $Na^{127}I$ were added to the blood. The similar behavior of lumbar CSF iodide uptake after isolation of the spinal subarachnoid space implicated an extracranial mechanism. That this mechanism was a carrier transport system was strongly supported by the finding, during perfusion of the isolated thoracolumbar subarachnoid space, of decreased clearance of iodide from perfused artificial CSF when saturating levels of $Na^{127}I$ were added to the perfusion fluid. The site of action of the spinal iodide carrier system is unknown, but certain restrictions upon the anatomical possibilities are noted.

Introduction

Intracranial iodide active transport mechanisms involving the choroid plexuses are now well known (2, 4, 10, 11, 13, 15, 25–27, 33). The present study describes a spinal iodide carrier-mediated transport system, unrelated to the choroid plexuses, and of unknown histological localization.

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Methods

Intraperitoneal Iodide Injection. Adult male or female mongrel dogs weighing 6–17 kg were anesthetized with pentobarbital 40 mg/kg, and immobilized in a head holder in sphinx position. Pentobarbital was repeated in smaller doses as needed.

The cranial convexity and the laminae of the fifth and sixth lumbar vertebrae were exposed. A mixture of 2.0 mc of carrier-free $Na^{131}I$ with $Na^{127}I$ was given intraperitoneally, half on each side. Stock $Na^{127}I$ solutions of 4 or 900 mg/ml were used to provide intraperitoneal doses of 1, 100, 200, 300, 400, or 800 mg/kg in a volume of 2–10 ml.

Cranium and lumbar laminae were removed to allow exposure of the dura. Samples of CSF were taken always in the order convexity subarachnoid space, lateral ventricle, cistern, and lumbar. The CSF sampling began 122 min after intraperitoneal iodide injection, and ended at up to 171 min after the injection. The ventricular CSF was withdrawn through a stainless steel, 26-gauge cannula, inserted dorsoventrally by a stereotaxic manipulator. All other samples were taken into 50-μl syringes of 28-gauge tip size (Hamilton 705), held by one of us while another withdrew the plunger. The dura was not punctured more than once at a given site of sampling.

Convexity sampling at a dose of 1.0 mg/kg $Na^{127}I$ was completed within 6 min of dural exposure in 16 of 20 samples, the remaining times being 7, 13, 16, and 24 min. Within this range longer exposure times were not associated with greater iodide uptake. Exposure times were similar at other doses of $Na^{127}I$.

Lumbar samples were taken after passing the needle of the microsyringe through a thin but intact layer of laminar bone; or after the dura was exposed by removing the last layer of bone either with rongeurs or by scraping with a blunt dural hook. This last proved to be the method of choice.

Lateral ventricle and cistern samples were taken approximately instantaneously after puncture, with no prior exposure.

Heart blood samples were withdrawn into heparinized syringes and 1.0-ml alliquots saved at 5, 10, 15, 60, and 120–180 min after the intraperitoneal iodide injection.

When fluid sampling was completed the dog was killed by an overdose of cardiac pentobarbital. The whole brain was then removed, the lateral ventricle from which CSF had been sampled was incised, and the entire choroid plexus of that ventricle was removed. Serial weights were extrapolated to the time of ventricular incision. Time from exposure to air until completion of the first weighing was 1.7–3.3 min.

All fluid and tissue samples were then counted in a well scintillation counter to a probable error of 1%. All fluid samples were immediately examined against a white background, under 2× magnification. All colored samples were excluded from the data herein presented.

Net uptake of iodide, expressed either as an iodide apparent space (14), or as iodide concentration, endogenous iodide ignored, was calculated for CSF, and for choroid plexus.

The iodide apparent space was expressed as:

$$\frac{100 \times \text{net count/min/ml tissue water}}{\text{net count/min/ml plasma water.}}$$

Tissue water, estimated by drying to constant weight at 100 C, averaged 0.84 g per gram wet weight. Plasma water was estimated after measuring plasma proteins by a modification of the method of Meulemans (22).

Corrections were made for protein binding, measured by ultrafiltration (1); for the Donnan equilibrium; and for residual plasma and red blood cells, both of which contain iodide, using standard labelling techniques with ^{125}I-albumin and ^{51}Cr on a separate series of dogs.

Iodide concentration was expressed as milligrams iodide per milliliter tissue water. The full calculation of iodide concentration was as follows: Iodide apparent space × 0.01 × milligram iodide per milliliter plasma ÷ c, where c = milliliters plasma water/milliliter plasma.

In one group of dogs the thoracic cord (T 2–3) was doubly ligated extradurally, while in another group it was transected between pairs of extradural ligatures before the iodide mixture was injected intraperitoneally.

Spinal Iodide Perfusion. In another group of dogs anesthetized with pentobarbital, the spinal subarachnoid space was perfused via polyethylene cannulae (PE 60) providing inflow at T 7–8 and outflow at L 6–7 vertebral levels after appropriate laminectomies and, in 13 of 16 dogs, extradural ligation at T 7. A modification of the method of Pappenheimer *et al.* (19, 23, 24) was used. A constant speed infusion pump (Braun, Bronwill Sci. Div., Rochester, N.Y.) provided continuous perfusion of artificial CSF which contained: (Meq/liter) NaCl 126.1, $NaHCO_3$ 25.0, $NaH_2PO_4 \cdot H_2O$ 0.5, KCl 3.22, $CaCl_2$ 2.03, $MgSO_4 \cdot 7H_2O$ 1.3, $MgCl_2 \cdot 6H20$ 0.3. Just before use, the following were added to the perfusion fluid: Dextrose, 800 milligram/liter, finely ground blue dextran (Pharmacia, Piscataway, N.J.), .80 mg/ml (4), $Na^{131}I$ to give 1–4 million CPM/100 ml (Mallinckrodt Nuclear Corp., St. Louis, Mo.), and either NaCl, 46.4 mg/100 ml or $Na^{127}I$ 120 mg/100 ml. In some experiments, the amount of $Na^{127}I$ used was either 60 or 30 mg/100 ml. Osmolality averaged 312 mosmole/ml as estimated with an Advanced osmometer.

Perfusion could be changed from the NaCl (low iodide) to the $Na^{127}I$

(high iodide) solution without interruption by turning a four-port, double throw, gas-tight valve (Hamilton Co., Whittier, Calif.).

A water manometer placed in the system just before the inflow catheter entered the subarachnoid space allowed monitoring of inflow pressure, which ranged from 14 to 26 cm of fluid. Outflow was set at 12 cm below the auditory meatus. Inflow rate was 0.1 or 0.15 ml/min, allowing samples of 1.1–2.4 ml to be collected from the outflow cannula in tared test tubes over 10- to 15-min periods. The outflow rate was found by weighing, the radioactivity counted to a 1% probable error in a well scintillation counter, and the blue dextran concentration measured at 620 mμ in a colorimeter (Spectronic 20, Bausch & Lomb), modified to measure samples of 1.0 ml or more. The outflow rate, outflow radioactivity, and outflow dextran concentration were expressed as percentage of similarly measured aliquots of the inflow solutions. Adequate perfusion was judged by stability of the parameters measured in the outflow fluid, and by absence of leakage of the solution from the cannulated sites. The placement of the cannulae was verified by carefully incising the dura post mortem.

Following the terminology of Pappenheimer *et al.* (19, 23, 24), the following qualities were calculated: $V_f = C_{BD} + (Vo\text{-}Vi)$ = rate of formation of CSF, in μliter/min; $C_{BD} = Vici\text{-}Voco \div [(ci + co)/2]$ = rate of bulk absorption of fluid, in μliter/min = clearance of blue dextran; $C_{I^-} = Vici\text{-}Voco \div [(ci + co)/2]$ = clearance of iodide in μliter/min.

Vo and Vi = respectively the rates of outflow and inflow, in milliter/min; co and ci = respectively the concentrations in outflow and inflow. For blue dextran the units are optical density units while for iodide the units are cpm/milliliter.

Mean concentrations were taken as $(ci + co)/2$ rather than as $\bar{c} = co + .37\ (ci - co)$ (19, 23, 24) because extraction ratios were not usually high, and where they were high, the chosen mean concentration value led to an underestimation of the change in iodide clearance.

Results

Intraperitoneal Iodide Injection

Heart Plasma $Na^{131}I$. Radioactivity during the second hour after injection of intraperitoneal iodide averaged 370,000 cpm/ml of plasma at a dose of 1.0 mg $Na^{127}I$/kg, increased by 20% to a mean of 445,000 at 100 mg/kg and showed random fluctuation with higher doses. Changes of similar magnitude were found for plasma $Na^{131}I$ in the rat at increasing doses of $Na^{127}I$ from trace to 10.0 mEq/kg (1500 mg/kg) (27). The reason for such changes is not known.

The mean plasma $Na^{131}I$ concentration at 2 hr was 25% less than that at 1 hr with a range of 14–31%.

Heart Plasma $Na^{127}I$. Unlabelled iodide attained a plasma concentration at 1–2 hr after injection which was directly proportional to the injected dose. Plasma $Na^{127}I$ averaged .24 mg/ml for each 100 mg/kg of intraperitoneally injected $Na^{127}I$ except for a slight decrease to .20 at the highest dose of 800 mg/kg.

Iodide Apparent Space. Net uptake of iodide in CSF and choroid plexus at 2–3 hr is expressed as an iodide apparent space for various $Na^{127}I$ doses in Table 1 and Fig. 1.

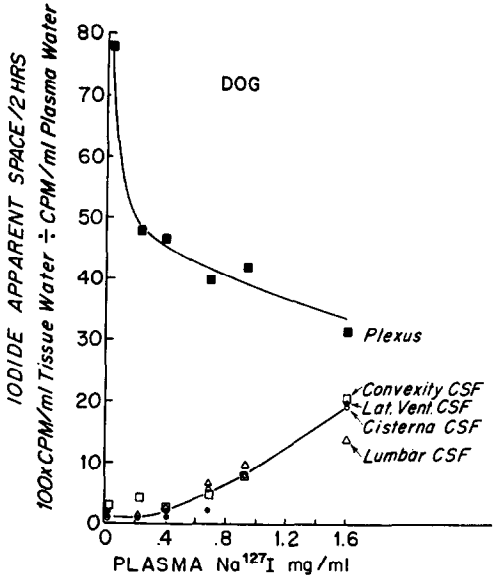

FIG. 1. Net uptake (apparent space) of $Na^{131}I$ in the choroid plexus of the lateral ventricle, CSF of the same ventricle, and in cisternal, lumbar, and convexity CSF at various plasma levels of $Na^{127}I$. To avoid confusion among the four CSF sites, only the points for cisterna CSF have been connected by a curve.

Cisternal iodide apparent space was lowest (0.75%) of all spinal fluids studied at a dose of 1.0 mg $Na^{127}I$/kg (Table 2). In comparison with the cistern, values were significantly higher at lateral ventricle (1.82%) and lumbar (1.30%) sites ($p < 0.01$) and highest (2.70%) over the convexity ($p < 0.02$).

Seventeen dogs received $Na^{127}I$ doses of 1.0 mg/kg. It is of interest to inquire how often the values in individual dogs differed from the pattern shown by the means for all seventeen dogs. There were 16 dogs from

TABLE 1

EFFECT OF SATURATION ON NET UPTAKE OF IODIDE

	Dose of $Na^{127}I$ (mg/kg)	Plasma $Na^{127}I$ (mg/ml)	n	Iodide apparent space [a]		Iodide concentration [b]	
				Mean	SD	Mean	SD
Lat. vent.	1.0	.00154	16	1.82	.430	.00280	.00066
	100	.221	12	1.22	1.22	.270	.270
	200	.406	4	1.12	.100	.455	.041
	300	.680	4	2.45	.250	1.67	.170
	400	.923	2	7.83	—	7.23	—
	800	1.604	2	19.7	—	31.7	—
Cist.	1.0	.00154	15	.750	.270	.00115	.00042
	100	.221	11	1.03	.480	.228	.106
	200	.406	4	2.12	1.63	.861	.662
	300	.680	4	5.67	1.45	3.86	.986
	400	.923	2	7.77	—	7.17	—
	800	1.604	1	19.0	—	30.5	—
Lumbar	1.0	.00154	11	1.30	.450	.00200	.00069
	100	.221	7	1.52	.630	.336	.139
	200	.406	4	2.95	1.70	1.20	.690
	300	.680	3	6.28	—	4.27	—
	400	.923	1	9.65	—	8.91	—
	800	1.604	2	13.7	—	21.9	—
Convex	1.0	.00154	9	2.70	1.88	.00416	.00289
	100	.221	3	4.17	1.03	.922	.228
	200	.406	—	—	—	—	—
	300	.680	2	4.75	—	3.23	—
	400	.923	—	—	—	—	—
	800	1.604	2	20.4	—	32.7	—
Plexus	1.0	.00154	17	77.9	22.0	.120	.034
	100	.221	13	47.6	7.18	10.5	1.59
	200	.406	4	46.4	13.1	18.8	5.32
	300	.680	4	39.7	9.18	27.0	6.26
	400	.923	2	42.0	—	38.8	—
	800	1.604	3	31.3	2.08	50.3	3.37

[a] (Count/min/ml CSF or tissue water) $\times$ (10^2) $\div$ count/min/ml plasma water.

[b] (mg $Na^{127}I$/ml tissue water) $\times$ (10^2). The following are the significant p values for Cochran-Cox tests of means for spinal fluids. The numbers 1.0, 100, 200, 300, 400, refer to dose of intraperitoneal $Na^{127}I$: $p < .01$. Cistern 1.0 vs. lumbar 1.0, lateral ventricle 1.0, lateral ventrical 100, cistern 300, and cistern 400. Lateral ventricle 1.0 vs. lateral ventricle 100, lateral ventricle 200, and lateral ventricle 400. Lumbar 1.0 vs. lumbar 300, lumbar 400; $p < .02$: Cistern 1.0 vs. convexity 1.0; $p < .05$: Cistern 100 vs. convexity 100.

TABLE 2
EFFECT OF CORD TRANSECTION OR LIGATION ON NET UPTAKE OF IODIDE IN CSF

Dose $Na^{127}I$	Iodide Conventration [a]			
	1.0 mg/kg		480 mg/kg	800 mg/kg
Operation	(Cut [b])	(Tie [c])	(Tie [c])	(Tie [c])
CSF sample				
Cistern	.00103	.00077	7.62	18.0
Lumbar	.00154	.00103	6.04	16.0
Convexity	.00185	—	7.94	12.8
Lat. vent.	.00231	.00200	4.24	15.2

[a] (mg $Na^{127}I$/ml CSF) × 10^2.

[b] Transection of cord and meninges between pairs of epidural ligatures: Mean value for three dogs.

[c] Double epidural ligation: Value for one dog.

which two or more CSF sites could be sampled, including six dogs from which all four sites were represented, another six in which three loci were sampled, and four dogs with two sites represented. Cisternal iodide apparent space was lower than that for the lateral ventricle in all 14 dogs from which both sites could be sampled. The stability of pattern may relate to the protected nature of these two compartments, or to an inherent consistency of process from one dog to another.

In contrast are the values for lumbar and convexity CSF. In six (38%) of 16 dogs from which samples were obtained from two or more loci, the over-all pattern was different from the pattern of the means for all dogs. The difference was always in a single locus for a given dog. In three of the six the departure was due to a "high" lumbar value, in one to a "low" lumbar value, while in the other two dogs it was due to a "low" convexity value. Thus the variability of lumbar and convexity values could be due either to some artifact related to the exposure of the compartment prior to sampling, or to a genuine variability in the normal mechanism of net iodide uptake.

At doses above 1.0 mg $Na^{127}I$/kg, iodide apparent space increased progressively at all CSF sites except the lateral ventricle (Table 1). The differences between sites became obscured as iodide apparent space increased.

Using the values at 1.0 mg $Na^{127}I$/kg as a baseline, significant increases in iodide apparent space occurred at 300 mg/kg for cisternal and lumbar fluids while lateral ventricular fluids showed a definite increase at a dose of 400 mg $Na^{127}I$/kg. At 200 mg/kg, lateral ventricular fluid showed no tendency towards increased iodide apparent space; cisternal and lumbar fluids both showed upward trends (doubled means) but these trends were

not statistically significant. Iodide apparent space in lateral ventricle fluid also differed from that at other sites in showing a significant decrease at 100 mg/kg. Data for convexity fluid were less complete but they showed a significant increase by the time a dose of 800 mg/kg was reached.

After ligation of the meninges, with or without thoracic cord transection, the iodide apparent space showed similar patterns with respect to sample site and dosage of $Na^{127}I$. The iodide apparent space was generally smaller than that obtained in dogs who had no thoracic surgery. This was associated with lower plasma iodide concentrations in the dogs which had this surgery; the mechanism for the smaller iodide apparent space, however, is not known.

At a 1.0 mg/kg dose of $Na^{127}I$, the mean iodide apparent space in choroid plexus was 77.9%. (Table 1, Fig. 1). This decreased to 47.6% at 100 mg/kg and then dropped more slowly to reach 31.3% at 800 mg/kg. The curve for plexus thus contrasts sharply with that for CSF.

Iodide Concentration. At a dose of 1.0 mg $Na^{127}I$/kg, the iodide concentration of course had the same topographical distribution as did iodide apparent space (Table 1), with cisternal CSF showing the lowest value of .0000115 mg/ml. The curves of tissue concentration of iodide with increasing levels of plasma $Na^{127}I$ showed a suggestively hyperbolic form for plexus and, again in contrast, a gradually increasing slope for CSF (Fig. 2).

Lumbar iodide concentration caudal to the cord ligation or transection again showed a sharp rise as plasma $Na^{127}I$ was increased (Table 2).

Spinal Iodide Perfusion. In one dog, serial perfusions were done to find the iodide concentration which gave maximal saturation effect. The solutions contained respectively 0, 2, and 4mM $Na^{127}I$, the osmolality being kept the same by the addition of NaCl to the first two solutions. Decrease in iodide clearance was maximal at 2 mM $Na^{127}I$ (Fig. 3), thus suggesting that the 8 or 4 mM solutions, which were used routinely in all other experiments, were adequate to show a saturation effect if such an effect was possible.

Perfusions with both low (zero) and high (8.0 or 4.0 mM) iodide solutions were done in 16 dogs. In four dogs iodide clearance was not decreased by the high iodide solution. The absence of any decrease in iodide clearance in these four dogs could not be traced to placement of inflow or outflow catheters, or to any other variable in the experimental procedure. In the remaining twelve dogs, the decrease in clearance ranged from 15 to 84% of the control (low iodide) clearance. The mean decrease for all 16 dogs was 36.1%.

This saturation effect could be reversed by changing the perfusion solution to the original low iodide artificial CSF, but then the rise in clearance

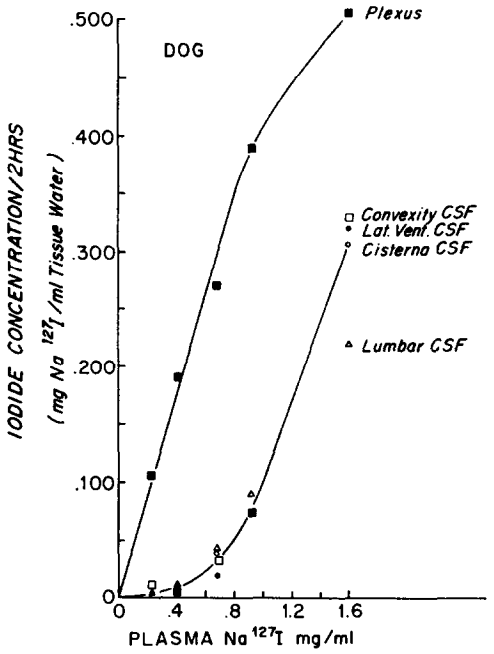

FIG. 2. Net uptake (concentration) of total iodide, $Na^{127}I$, in the choroid plexus of the lateral ventricle, CSF of the same ventricle, and in cisternal, lumbar, and convexity CSF at various plasma levels of $Na^{127}I$. To avoid confusion among the four CSF sites, only the points for cisterna CSF have been connected by a curve.

of iodide from the fluid occurred only gradually and progressively over a period of 60–130 min. Finally the clearance could again be lowered, sometimes to almost the original amount, and only slightly less promptly than at first by perfusing a second time with the high iodide solution.

Clearance of iodide from the artificial CSF during the control (low iodide) periods was 81–236 μl/min in 16 dogs, with a mean of 130 μl/min. The means for the dogs with and without thoracic cord ligation were 135 and 115 μl/min, respectively.

No definite increment of CSF formation could be attributed to the isolated spinal subarachnoid space, the mean V_f values for low and high iodide solutions being respectively -5 and -2 μl/min. Mean bulk absorption of fluid (C_{BD}) was 12 μl/min with the low iodide solution, and 2 μl/min with the high iodide solution. However, changes in iodide clearance did not correlate significantly with change in either C_{BD} or V_f.

Discussion

Evidence for a Spinal Iodide Carrier System. The evidence for spinal iodide carrier transport is three-fold.

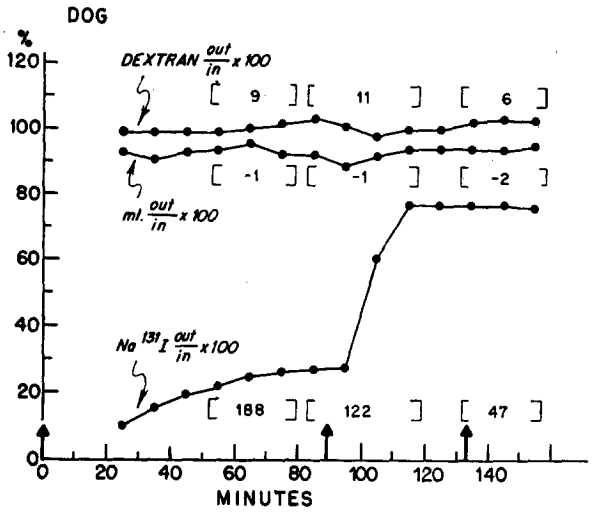

FIG. 3. Spinal perfusion at an inflow rate of 0.15 ml/min. Each of the three arrows marks the start of a different perfusion solution. The first is the control low-iodide (0 mM $Na^{127}I$) solution, the second and third being high-iodide solutions containing 2 and 4 mM $Na^{127}I$, respectively. Mean values in brackets are, top row, bulk fluid absorption (blue dextran clearance) = C_{BD}; middle row, CSF formation = V_f; and bottom row, iodide clearance = C_{I^-}; all values being in μliter/minute. A rise in the percentage of radioactivity remaining in the outflow fluid (lower curve) indicates a fall in iodide clearance from the perfusion fluid (bottom row brackets). The values in brackets are means for the three or four samples embraced by the brackets.

First, lumbar iodide is kept at a very low level (1.3% of plasma) when plasma iodide is low, whereas one might expect the lumbar concentration to be higher were diffusion from plasma the sole mechanism.

Second, saturating levels of iodide in plasma are accompanied by lumbar CSF levels which rise progressively, finally reaching about 13% of the plasma level at the highest dose used. This rise is similar whether or not the lumbar CSF is isolated by cord transection or ligation. Therefore the surgical procedure of ligation or transection does not cause an artifactitious increase in the lumbar uptake of iodide, nor does lumbar uptake depend upon flow from rostral areas. Transection of the cord combined with ligation also rules out the participation of any flow in the central canal such as has been described by Bradbury and Lathem (5) in the rabbit. Further, the curves of lumbar CSF iodide concentration, with and without thoracic cord ligation, are compatible with a saturable process moving iodide from CSF to blood. Were diffusion or another nonsaturable process responsible, the lumbar CSF concentration would be a linear function of plasma concentration. It is clear from Fig. 2 and Table 2 that such is not the case.

Third, iodide leaves the spinal subarachnoid space when the space is perfused with low iodide artificial CSF, iodide clearance being 130 μl/min at perfusion rates of 0.1–0.15 ml/min. When saturating levels of iodide are added to the perfusion fluid, however, loss of iodide slows, the mean decrease in iodide clearance being about 36%. Bulk absorption of 12 μl/min is present, perhaps via spinal arachnoid villi, but does not correlate with iodide clearance. Also, no formation of CSF occurs in the spinal perfusions, so that the iodide carrier system is not related to CSF formation.

Any of these three findings alone is suggestive of a carrier-mediated process, but each has possible alternative explanations. Taken together, however, they furnish strong evidence for a carrier process. That this process is also capable of uphill transport is then suggested by the very low concentration of lumbar CSF iodide when plasma iodide is low, but it would be desirable to demonstrate by direct experiment whether uphill transport does occur.

The function of the spinal iodide carrier system is unknown. It could serve to exert a sink action on the spinal cord, as the intracranial CSF has been suggested to do for the brain (14). It would seem not to be linked with CSF production, since little or no production was found in the isolated spinal subarachnoid space.

An effective transport arrangement would be the combination of a restricted degree of passive transfer with a significant active transport, so as to remove toxic solutes from the CSF to the blood and also to prevent them from entering the CSF from the blood. The data suggest, however that iodide transfer from lumbar CSF to blood is not achieved in the same way in all dogs. First, there are deviations from the typical pattern of accumulation in CSF after intraperitoneal iodide injection, and the majority of these deviations relate to variation in the amount of lumbar accumulation. Second, saturation during spinal perfusion has a much greater effect upon iodide clearance in some dogs than in others, even when comparison is made between dogs which have about the same iodide clearance during perfusion with low iodide (control) solution.

The location of the spinal iodide carrier system is also unknown. Possibilities include spinal arachnoid villi or diverticuli, or both (16, 34, 36, 37), subarachnoid blood vessels, or central or peripheral nervous tissue. However, the possibilities can be narrowed to: (*a*) the lumenal membrane of the endothelial cell of the capillary within neural tissue; (*b*) arachnoid structures; or (*c*) subarachnoid blood vessels. This limitation is inferred because "proximal-type" graphs (9) were plotted from the iodide content of pieces of rabbit spinal cord (4) and of lumbar CSF in the dog during saturation. To decide between *a, b,* and *c,* additional data will be needed.

Spinal Carriers for other Solutes. Many substances attain measurable

concentrations even below an epidural ligature which isolates the thoracolumbar space from the rest of the CSF pathway. This has been noted for strychnine (20), urea (6), salicylate (6), sodium (12), glucose (28, 29), and bromide (32). Similar findings have been reported in patients with spinal subarachnoid block for RISA (30, p. 128), and ^{24}Na (30; 31, p. 130). Thus the solute content of the CSF in the spinal subarachnoid space does not entirely depend upon the composition of the CSF which leaves the cranium and enters the spinal region. However, it is clear that the passage of a solute into the CSF below a spinal block cannot be taken as proof for carrier-mediated transport. The suggestion has been made (17, 18) that lumbar glucose transfer in the dog is carrier-mediated because glucose entry is faster for lumbar than for cisternal CSF (35). Two other observations are compatible with glucose carrier transport. A carrier system moving glucose from CSF to blood could explain the identical lumbar and cisternal CSF glucose concentrations in the dog (4). It could also explain the low lumbar CSF sugar concentration in man compared to cisternal concentration (7, 8, 21) (see below). Further studies will be required to determine whether carrier transport is necessary and sufficient to account for these findings.

Cisternal Uptake. The low cisternal iodide concentration could be due to transport across that portion of the choroid plexus of the fourth ventricle which extends into the cisterna; bulk formation of iodide-poor CSF in the cistern; metabolism or binding of iodide by adjacent tissue; or restricted passive entry of iodide into the cistern.

Thus there are several alternative explanations for the low cisternal iodide level, and there is no direct evidence for a local cisternal iodide carrier system outside the choroid plexus, but the possibility remains.

Convexity Subarachnoid Uptake. Similar considerations apply to the higher, but still low (2.7% of plasma) level of iodide in convexity subarachnoid CSF. There is no known choroid plexus in the convexity subarachnoid space, but perfusion studies in the dog (3) suggest CSF formation there. Also, in a single experiment in a goat (23) there was no evidence of active transport of Diodrast from the subarachnoid space between frontal and occipital cannulae.

Thus there is no evidence that there need be a local carrier system in the convexity subarachnoid area, but the possibility remains.

Regional Differences in Iodide Uptake. Cisternal iodide concentration at low levels of plasma $Na^{127}I$ is lower than both lumbar and lateral ventricular concentrations. Davson has suggested that regional differences of this type are due to diffusion from the central nervous system extracellular space along a concentration gradient into the adjacent CSF. Thus the CSF concentration would progressively increase as the CSF travels away from

the fourth ventricle (14). If we apply this concept to iodide transport, the lumbar iodide concentration would be raised above the cisternal level by diffusion from the spinal cord into spinal CSF. The lumbar iodide concentration might then be expected to be considerably higher than the cisternal concentration. The existence of a spinal iodide carrier system would provide an explanation for the fact that the lumbar iodide steady state concentration is quite low, and only slightly higher than the cisternal concentration. A carrier-mediated active transport which moves iodide from CSF to blood at a spinal site would oppose any rise in the steady state lumbar CSF iodide level caused by passive movement from blood or nervous tissue into the CSF.

The data of Bito, Bradbury, and Davson (4), for steady state concentrations of K^+, Ca^{++}, and glucose in the lumbar CSF of the dog are similarly compatible with the possibility that carrier transport at a spinal level removes each of these solutes from the CSF. Specific studies are needed in each case, however, to decide the nature of solute transfer affecting the spinal CSF.

The Effect of Saturation upon Regional Uptake. Iodide apparent space and concentration at the spinal fluid sites sampled in this study show a pattern of regional variation when a low dose of $Na^{127}I$ is used. Values are lowest in the cistern, highest in the convexity, and intermediate in the lumbar and lateral ventricle samples. As the dose of $Na^{127}I$ is increased, the iodide concentration and apparent space progressively increase at all sites. At the higher doses of $Na^{127}I$ the pattern of regional variation is obscured. Saturating doses of $Na^{127}I$ apparently effect carriers, wherever situated, to allow an approach toward equalization of net uptake of iodide at all of the loci sampled. Similar effects of unlabelled iodide have been reported for cisternal spinal fluid in the rat (27), and in the rabbit (2). The location of the extraventricular carrier is discussed above.

The choroid plexus is shown to accumulate iodide *in vivo*. The type of rise in iodide concentration with saturation suggests that a more detailed study of its behavior *in vivo* along with that of CSF and brain, would help to establish the localization of iodide carriers (9).

NOTE: While this work was in progress Hammerstad, Lorenzo, and Cutler's abstract reported evidence from cisternal-lumbar perfusions in the cat indicating that there is carrier transport of iodide out of CSF in the spinal subarachnoid space. (Neurology 1968, **18**: 296–297)

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