Uptake of Ammonia by the Brain in Hepatic Coma.* (20786)

S. P. Bessman,† J. F. Fazekas,‡ and A. N. Bessman.§
(Introduced by R. W. Berliner.)
From the Research Foundation, Children's Hospital, and the Medical Service, District of Columbia General Hospital.

The probable causal relation between the development of hepatic coma in terminal liver disease or in Eck fistula patients and the rise in blood ammonia(1) raises the question of whether the ammonia acts as a toxic agent by the inhibition of some enzyme system in brain, or whether it exerts its effect by combination with an integral cerebral metabolite.

A study of the cerebral arteriovenous difference of ammonia in a number of patients both comatose and non-comatose, with and without apparent liver disease, reveals a striking difference between patients with high blood ammonia levels and those with normal levels.

Methods. Blood ammonia is determined by a microdiffusion-Nesslerization method modified from Seligson(2) on freshly drawn blood from the femoral artery and the jugular bulb. The normal range for venous blood by this technic is from 0.30 to 1.00 γ ml. In severe hepatic disease this level is elevated, although methods which yield higher normal values through the inclusion of ammonia formed during the determination itself tend to obscure this finding(3).

Results. Table I shows the ammonia levels in the arterial and jugular bulb blood of 3 non-comatose patients, 3 cases of liver failure, and 3 cases of coma or semi-coma without apparent liver disease. In the non-hepatic cases there is no significant uptake of ammonia, and in the cases with liver disease there is a marked uptake. This phenomenon is consistent throughout all cases studied, and all cases with elevated blood ammonia show an uptake. The arteriovenous difference is roughly proportional to the arterial value.

In view of this "utilization" of ammonia, the following hypothesis is suggested. The

TABLE I.
Arterial and Cerebral Venous Blood Levels of Ammonia (Gamma per ml of Whole Blood).

Patient	Age	Diagnosis		NH_3 N., μg/ml Femoral artery	NH_3 N., μg/ml Jugular bulb	Diff.
			Awake			
M.W.	35	Old CVA	Alert	.92	.97	— .05
F.R.	53	Chronic asthmatic	"	.75	.73	.02
W.J.	77	Parkinsonism	Senile	.84	.82	.02
						.00
			Non-hepatic			
R.G.	23	Post anoxic	Coma	.60	.63	— .03
I.C.	88	Hypertensive enceph.	Semicomatose	.33	.31	.02
W.J.	73	Arteriolar nephrosclerosis	Comatose	.80	.88	— .08
						— .03
			Liver disease			
T.B.	51	Cirrhosis, Eck fistula	Semicomatose	8.44	7.12	+1.32
V.W.	65	Cirrhosis	Deep coma	2.81	2.50	+ .31
L.P.	59	"	Semicomatose	3.00	2.32	+ .68
						+ .77

* Aided by grant from the Playtex Park Research Foundation.

† Director, Biochemical Research, Children's Hospital, Washington, D.C.

‡ Chief of Staff, District of Columbia General Hospital.

§ Research Fellow in Medicine, George Washington University, Medical School.

ammonia enters the brain and combines with alphaketoglutaric acid by the reversal of glutamic dehydrogenase. This abstracts large amounts of the keto acid from the Krebs cycle, preventing regeneration of oxalacetate and further oxidative metabolism. The marked diminution of cerebral oxygen uptake which we have seen in hepatic coma(4) can thus be explained on the basis of the failure of the major oxidative pathway in the brain.

Summary. The arteriovenous difference of ammonia has been investigated in a variety of conditions and has been found to be elevated in hepatic coma, as has been the arterial level of blood ammonia. The evidence for a significant uptake of ammonia in comatose patients with liver disease suggests a mechanism for hepatic coma. This mechanism could be the reductive amination of ketoglutaric acid to form glutamate with the concomitant removal of significant amounts of ketoglutarate, preventing Krebs cycle regeneration.

1. Salaskin, Z. F., *Physiol. Chem.*, 1898, v25, 128, 449; McDermott, W. V., Jr., Adams, R. D., *J. Clin. Invest.*, 1954, v33, 1.

2. Seligson, D., and Seligson, H., *J. Lab. and Clin. Med.*, 1951, v38, 324.

3. Schwartz, R., Phillips, G. B., Gabuzda, G. J., Jr., and Davidson, C. S., *J. Lab. and Clin. Med.*, 1953, v42, 499.

4. Fazekas, J. F., and Bessman, A. N., Unpublished data.

Received December 10, 1953. P.S.EB.M., 1954, v85.

A Simple Method of Gradually Producing Permanent Occlusion of Portal Vein in the Dog.* (20787)

H. L. POPPER AND N. C. JEFFERSON.

From the Department of Gastro-Intestinal Research, Medical Research Institute of Michael Reese Hospital, Chicago, Ill.

In our studies on the effect of interference with the arterial and venous blood circulation to the liver we have found a simple method of gradually producing a permanent occlusion of the portal vein which could likewise be used to advantage in other similar problems.

Acute complete occlusion of the portal vein by any method is not tolerated by the dog and is regularly fatal. To produce portal occlusion, a procedure has to be used which leads to gradual closing of the vein. Wrapping of irritative cellophane around the vein is unsatisfactory, because it causes marked adhesions and usually only incomplete closure of the vein. Partial constriction of the portal vein with a ligature of some non-absorbable material leads occasionally to complete obstruction of the vein but is frequently without effect.

We have found that placing two constricting ties of umbilical cord (cotton No. 070 Bauer and Black, Chicago), around the portal vein at a distance of 0.3 to 0.5 cm, invariably leads to complete and permanent occlusion of the portal vein within 1-2 weeks. The ligatures should be tied as tightly as possible over the tip of a small curved hemostat. After withdrawal of the hemostat, the bowels are not cyanotic, and the afferent portion of the portal vein is not appreciably distended.

As a rule, this procedure is well tolerated. In all experiments, reoperation showed complete occlusion of the portal vein by a clot localized at the ligatures.

Summary. Gradual complete occlusion of the portal vein in the dog is obtained by placing two constricting ties around the portal vein. The procedure is recommended when gradual and complete permanent occlusion of the vein is desired.

* This investigation was supported by a research grant, from the Federal Security Agency, of the National Institutes of Health, Public Health Service. The Department is in part supported by the Michael Reese Research Foundation.

Received December 10, 1953. P.S.E.B.M., 1954, v85.