as a central nervous system stimulant provided another avenue of approach.

The mechanism by which nembutal increases the tolerance to glutamic acid cannot be established with certainty from the present experiments. The drug may exert a depressant action directly upon the vomiting center or elsewhere along the nervous pathways, thus delaying the onset of the reflex by elevating the threshold. Another possible action would be a depression of the motility of the gastro-intestinal tract, which has been observed both *in vivo* and *in vitro* by Gruber and Gruber.[4,5] Shaw[6] has shown the site of depressant action to be both in the postganglionic fibers and in the muscle cells themselves.

The effect of epinephrine may be due to sympathetic predominance causing suppression of the vomiting reflex, with the action either central or peripheral, or both. The simultaneous administration of epinephrine, as outlined above, possesses the theoretical advantage that its action is limited to the actual duration of the infusion, because of its rapid inactivation in the body, whereas other agents given beforehand may either exert their effect still for some time after the need for them is ended, or may have such a brief effective period that a careful timing is necessary to take full advantage of the protective action. However, the physiological considerations involved in the administration of epinephrine might impose restrictive limitations upon its clinical usefulness.

From the results of 111 experiments obtained with these various agents, it would appear that the emetic effect of glutamic acid may be prevented or ameliorated in several possible ways. The administration of a suitable sedative, prior to the infusion of protein hydrolysates or amino acid mixtures prone to produce vomiting, might be attempted clinically in order to improve tolerance. This could be done either by injection or by rectal suppository.

Summary. 1. *l*+ glumatic acid, when infused at a rate of 10 mg/kg per minute in dogs induced vomiting on an average when 136 mg/kg had been administered.

2. Atropine, *d*-desoxyephedrine, tridione, or pyridoxine with thiamine had no significant effect in delaying vomiting.

3. When nembutal, 2 mg/kg was given intravenously 10 minutes before the glutamic-acid infusion, vomiting was not induced until an average of 241 mg/kg had been given, an 84% improvement in tolerance.

4. Epinephrine, infused with glutamic acid in a concentration of 2 μg/kg/min delayed vomiting until an average of 198 mg/kg had been infused, a 45% tolerance increase.

5. Tolerance to glutamic acid increased if infusions were repeated within 4 to 6 days.

6. The possible applications of these findings to the clinical use of protein hydrolysates are briefly discussed.

[4] Gruber, C. M., Jr., and Gruber, C. M., *Arch. Int. Pharmacodyn.*, 1939, **63**, Fasc. 2, 243.

[5] Gruber, C. M., and Gruber, C. M., Jr., *J. Pharm. and Exp. Therap.*, 1941, **72**, 176.

[6] Shaw, F. H., *Austral. J. Exp. Biol. and Med.*, 1942, **20**, 117.

15451 P

Experimental Acceleration of Secretion of Urine in Fetal Rats.*

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In the fetal rat, ligation of the ureter causes the development of hydroureter and hydronephrosis, while ligation of the urogenital papilla causes the storing of urine† in the

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† In collaboration with Dr. Gerald T. Evans and Miss Harriet Lamberg, the chemical composition

TABLE I.
Effects of Urea and of Ligating Renal Pedicles of Mother Upon Rate of Secretion.

Fetuses (male) Group	No.	Treatment at 2 hr preceding autopsy: Papilla	Injection of fluid under fetal skin	Body wt at autopsy g	Urine in bladder mg	mg/g
			Renal pedicles of mother not ligated			
A	8	Not ligated	0	4.1570	6.1	1.5
B	11	Ligated	0	4.1968	19.0	4.5
C	3	"	0.15 cc normal saline	4.5461	20.5	4.5
D	4	"	0.15 " distilled water	4.0568	20.7	5.1
E	6	"	0.15 " aq. sol. urea (500 mg/cc)	5.1504*	46.2	9.0
F	2	"	0.15 " " " " (150 " ")	4.7261	25.7	5.4
G	2	"	0.04 " " " " (150 " ")	4.5779	17.8	3.9
			Renal pedicles of mother ligated for period of 24 hr			
H	11	Not ligated	0	3.0679	53.4	17.4
I	3	Ligated	0	3.2652	56.1	17.2
J†	4	"	0	3.0873	33.1	10.7

* Marked edema at site of injection must have contributed to the body weight.
† Before ligating papilla, urine already in bladder was removed by means of a micro-pipette.

bladder.[1] The rate of secretion of urine, especially during the last 2 days of gestation, is much more rapid than studies in certain mammals suggest.[2]

The present account deals with attempts to speed up the rate of secretion by introducing urea into the fetal circulation and by causing metabolites to accumulate in the maternal circulation (ligation of renal pedicles of mother). Using a method recently described[3] and ether for anesthetizing the mother, each fetus except those in Groups A and H (Table I) was transferred to the abdominal cavity of the mother. The outlet of the bladder was blocked by ligating the urogenital papilla. The fetuses in Group J were subjected to laparotomy before ligating the papilla; by means of micro-pipette prepared for the purpose, the bladder was punctured and the urine already present was removed. After completing the several steps, the abdominal incision of the mother was closed (by suturing) and ether was discontinued. Subsequently, exactly 2 hours after tying off the papilla, each fetus was secured by severing the umbilical cord and killed by decapitation (decapitated at about the 16th hour before expected parturition or, in other words, at the end of the 21st day after observation of coitus). The bladder was dissected, removed from the body and weighed before and after removing the urine.

The data show that when a highly concentrated solution of urea was injected under the fetal skin the rate of secretion was accelerated (Group E). Although this is of interest in that it demonstrates the ability of the fetal kidney to secrete urine more rapidly than normally, the changes in osmosis thus produced suggest that the urea did not act solely as a specific diuretic agent. This view is supported by the data obtained from Groups F and G.

When the renal pedicles of the mother had been ligated for a period of 24 hours preceding tests,‡ it was found at autopsy that in most instances the bladder of the fetus was quite full (Group H). Ligation of the papilla for a period of 2 hours caused no significant change in the fullness (Group I).

To investigate whether the rate of secretion had been speeded up or whether some unknown factor had prevented the voiding of urine, 13 fetuses were subjected to laparotomy before tests and the urine was removed from

of such urine is being studied.

[1] Wells, L. J., *Anat. Rec.*, 1946, **94**, 504.

[2] Gersh, I., *Carnegie Inst. Wash., Contrib. to Embryol.*, 1937, **26**, 33.

[3] Wells, L. J., *Anat. Rec.*, 1946, **94**, 530.

‡ While this operation might raise the blood pressure of the mother, it does not necessarily follow that it would also raise the blood pressure of the fetus.

the bladder (Group J).§ At autopsy there were 4 cases in which the data suggest that the rate had been accelerated.‖ This sheds new light on Wolff's observation that in pregnant rabbits nephrectomy causes an increase in the amount of amniotic fluid.[4] Also, it raises again the question as to whether in human pregnancy an excess of amniotic fluid (hydramnios) may result from an abnormal accumulation of metabolites in the maternal blood stream, the metabolites acting in part by inducing an abnormally rapid formation of fetal urine.

§ In 3 additional fetuses in which the bladder was similarly visualized, squeezing it by means of blunt forceps forced its contents into the ureters and the renal pelves without causing any urine to emerge via the urethral outlet (action of sphincters?).

‖ In the other 9 cases, since the bladder was relatively empty, it is assumed that the hole made by puncturing the wall permitted urine to leak out.

[4] Wolff, B., *Arch. f. Gynäk.*, 1904, **71**, 224.

15452 P

Isolation of a Macromolecular Constituent with Properties of the Lansing Strain of Poliomyelitis Virus.*

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It has been reported from this laboratory that highly active preparations of the MV strain of poliomyelitis virus could be obtained by differential centrifugation of clarified extracts of infected medullae-cords of rhesus monkeys.[1] Application of the same procedures to brains and spinal cords of cotton rats infected with the Lansing strain resulted in appreciable quantities of high molecular materials which, however, showed only slight activity. Various modifications of the original procedure have been used in attempts to obtain highly active virus. It has been found that if the ether-clarified, aqueous extracts are frozen before they are subjected to ultracentrifugation, virus is obtained which is from 100 to 10,000 times as active on a nitrogen basis as the original clarified extract.

In the modified procedure the ether-clarified extract is prepared as previously described with the exception that filtration through celite is omitted. The slightly turbid solution is stored in 100 ml pyrex centrifuge bottles in a solid-CO_2 chest at from —35° to —60°C for at least 5 days and then allowed to thaw at room temperature. Before the ice present has completely melted, the solution is centrifuged in the cold room at 4°C in an angle centrifuge, and the supernatant liquid is removed; the sediment is extracted in the centrifuge twice with M/15 dipotassium hydrogen phosphate, and the latter extracts combined with the first supernatant liquid. The extracts obtained in this way are crystal clear, and depending on the length of time they have been frozen, contain from 75 to 51% of the nitrogen present before freezing. The appreciable amount of nitrogen precipitated is protein in nature, and as the specific activity of the extracts after prolonged freezing is the same or greater than before freezing, it appears that normal protein rather than virus is denatured during this treatment. The results of a typical experiment showing the effect of freezing for various lengths of time on the yield of soluble nitrogen and on specific activity are shown in Table I. Activity is expressed as the 50% infective dose ($I.D._{50}$) in young cotton rats and is calculated by the method of Reed and Muench.[2] The 50% infective dose is defined

* Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

[1] Loring, H. S., and Schwerdt, C. E., *J. Exp. Med.*, 1942, **75**, 395.