TABLE I.
The Effect of Various Amino Acids in Reversing the Toxicity of Thioproline for *Escherichia coli*. Organism incubated 16 hr at 37°C.

No.	Reversing agent	Mg per 10 ml medium	Galvanometer readings* Thioproline (μg per 10 ml) 0	300	1000	3000
1.	Blank	—	52	53	3	3
2.	DL-isoleucine	1	51	50	8	3
3.	L-histidine	1	50	50	49	4
4.	DL-leucine	1	52	51	53	5
5.	DL-valine	1	51	53	52	3
6.	DL-cystine	1	50	49	42	3
7.	DL-hydroxyproline	1	52	50	50	4
8.	DL-methionine	0.1	51	49	25	3
9.	L-aspartic acid	1	53	50	52	2
10.	L-glutamic acid	1	52	51	53	3
11.	L-lysine	1	49	50	51	3
12.	L-proline	1	50	52	53	12
13.	Glycine	1	54	50	17	3
14.	DL-alanine	1	51	49	49	3
15.	L-arginine	1	52	49	49	3
16.	DL-serine	1	54	49	3	3
17.	DL-threonine	1	51	52	3	3
18.	L-tyrosine	1	50	51	7	3
19.	L-tryptophan	1	49	53	4	3
20.	DL-phenylalanine	1	51	50	46	3
21.	1-5 above	.05 of each	53	52	52	25
22.	6-12 "	.05 " "	52	49	50	42
23.	13-17 "	.05 " "	50	52	51	34
24.	18-20 "	.05 " "	53	51	52	3
25.	1-12 "	.05 " "	53	54	51	42
26.	1-5, 13-17 above	.05 " "	51	52	52	43
27.	6-17 above	.05 " "	50	50	51	40
28.	Proline and cystine	.05 " "	50	51	51	42

* A water blank gives a zero reading; an opaque object reads 100.

Prolongation of Penicillin Blood Level by Implantation of Procaine Penicillin Tablets.* (17626)

F. HUIDOBRO, R. CROXATTO, AND A. LUCHINI. (Introduced by J. T. Lewis.)
From the Department of Pharmacology and Biochemistry and Clinical Hospital of the Catholic University of Chile, Santiago, Chile.

Many attempts have been made to prolong the penicillin blood level. Numerous procedures have been used to prolong the levels of penicillin in the blood. The three methods most commonly employed have been: *a*) a mixture of calcium penicillin with peanut oil and beeswax(1), *b*) the blockade of the renal elimination by carinamide(2,3), and *c*) the parenteral administration of relatively insoluble penicillin, such as procaine penicillin(4,5, 6). It has recently been demonstrated that implantation of tablets of procaine penicillin

* Aided by the Gildemeister Foundation.

1. Romansky, M. J., and Ritman, G. E., *New England J. Med.*, 1945, v233, 577.
2. Beyer, K. H., *Science*, 1947, v105, 94.
3. Seeler, A. O., Collins, H. S., and Finland, M. F., *Am. J. Med. Sci.*, 1948, v216, 241.
4. Herrell, W. E., Nichols, D. R., and Heilman, F. R., *Proc. Staff Meet. Mayo Clinic*, 1947, v22, 567.
5. Thomas, E. W., Lyons, R. H., Romansky, M. J., Rein, C. R., and Kitchen, D. K., *J. A. M. A.*, 1948, v137, 1517.
6. Boger, W. P., and Flippin, H. F., *J. A. M. A.*, 1949, v139, 1131.

TABLE I.
Penicillin Blood Serum Level After the Implantation of Procaine-Penicillin Tablets, in Days.

	Intramuscular				Subcutaneous				
	B.S.	M.P.	R.V.	M.E.*	M.E.*	F.S.	R.C.	L.A.	J.F.
	1.9	1.83	1.45	1.9	1.79	1.93	1.92	1.025	3.645
Doses per kg body wt	31.9	42.8	24.3	28.1	30.0	38.2	22.3	20.4	81
No. of tablets implanted	2	2	1	2	2	2	2	1	3
Oxford U. of Penicillin in 1 cc of Blood Serum.									
Time after implantation									
4-6 hrs	1.7	—	.36	.72	.62	—	.30	.20	4.34
1 day	.43	—	.28	.82	.36	.48	.62	.20	.55
2	.68	—	.18	.20	.40	.41	.56	.25	1.10
3	.68	.40	.18	.31	.50	.36	—	.22	.90
4	.43	.32	.20	.28	.38	.33	.37	.20	.84
5	.38	.39	—	—	.36	—	.40	—	—
6	.35	.35	.26	.32	.48	.36	.36	.20	.62
7	.30	.27	.22	.37	.40	.31	.24	.28	.48
8	.28	—	.25	.25	.25	.33	.32	—‡	.40
9	.29	.33	.21	.19	.21	.40	—	.24	.40
10	.31	—‡	.10	.14	—	.32	.30	—	.45
11	.34	—	.04	.05	.27	.27	.40	—	—
12	.40	—	.00	.00	—	—	—	—	—
13	.35	.36§			.28	.06	—	.01	.55
14	.38				—‡	.00	—		—‡
15	.22				.18		—		—
16	.15				—		.21		—
17	—‡				—		—		.21
18	.19				.00		.15		—
20	.00								.25
21-23									.40
24-28									.00

* Not the same patient.
† Doses implanted in thousands of units.
‡ Patient discharged from the hospital.
§ Patient lived more than 60 km from the hospital.

into the subcutaneous tissue of rabbits prolongs the penicillin blood level for 7 days, and that there is no local reaction in the site of the implantation. When procaine penicillin is mixed with fat, the subcutaneous implantation prolongs the penicillin blood level for 11 days(7). Implantation of pure procaine-penicillin tablets in human beings was attempted according to these results.

This paper demonstrates that the subcutaneous or intramuscular implantation of pure procaine-penicillin tablets is innocuous: there is no local or general reaction, and the penicillin blood level is prolonged for several days. Procaine penicillin was made according to the usual technic(8) from crystalline G sodium penicillin ("Merck"). The material was compressed very hard into tablets having a cylindrical shape 10 mm in diameter and approximately 1 g in weight. The tablets were sterilized. The blood serum penicillin titrations were made according to the technic used in the Clinic Laboratory of our hospital(9) and the results are expressed in Oxford units. As the tablets were not very small, they were laid in the subcutaneous or muscular tissue of patients a slight distance away from the surgical wound. No local or general symptom was observed, and the post operative course was very smooth. The perfect tolerance of subcutaneous or muscular tissue to procaine-penicillin tablets must be emphasized.

In Table I the results are summarized. The tablet implanted subcutaneously or intramuscularly produces a very prolonged penicillin blood serum level. The quantity of blood

7. Huidobro, F., Croxatto, R., and Vargas, L., *Bol. Soc. Biol. Chile,* to be published.

8. Salivar, C. J., Hedger, F. H., and Brown, E. J., *J. Am. Chem. Soc.,* 1948, v70, 1287.

9. Croxatto, R., Schultebraucks, Sor. C., and Kneuer, C., *Bol. Soc. Biol. Chile,* to be published.

penicillin depends on the dose used. A high penicillin blood level was obtained with 3,600,000 units of procaine penicillin. A blood serum penicillin level very superior to the minimum effective level was obtained with implantation of 1,000,000 to 2,000,000 units of procaine penicillin.

Summary. Tablets of procaine penicillin implanted in the subcutaneous or muscular tissue provide a safe procedure for prolonging the penicillin serum blood level for several days.

Received December 27, 1949. P.S.E.B.M., 1950, v73.

Biochemical Studies on the Alligator. (17627)

ROLAND A. COULSON, THOMAS HERNANDEZ, AND FRED G. BRAZDA.
From the Department of Biochemistry, Louisiana State University School of Medicine, New Orleans.

In the course of a search for a new experimental animal for certain biochemical studies it was decided to investigate the suitability of the large North American alligator, *A. mississipiensis*. Some preliminary analyses revealed a striking discrepancy between some of the results obtained in the present study and those reported earlier by Hopping(1), Dill and Edwards(2), and Austin *et al.*(3). Most of the work that had been done on the alligator was repeated by the present authors and many additional studies were conducted. This paper deals with the results obtained on the fasting alligator kept under laboratory conditions. The effect of feeding, temperature, and seasonal variation on the composition of the blood and urine is quite marked and will not be reported here.

This study includes the data obtained from 65 alligators of undetermined sex. Twelve were 3-4 years old and weighed from 1.20-7.37 kg; 5 were 2-3 years old and weighed 0.79-2.03 kg; and 48 were about one year old and weighed from 48-182 g. The animals were kept at an average temperature of about 26°C in monel metal cadaver tanks which were filled to a depth of about one inch with water. They were fed fresh skinned rats from our colony. Although the alligators were avid feeders in the early spring and summer they tapered off in October and November and ate very little in December, January, and February. Under these conditions the animals doubled their weight in a 12 month period.

Blood was withdrawn from the tip of the tail for glucose determinations. All other determinations were done on blood obtained conveniently by cardiac puncture by the method suggested by Hopping(1). Amounts up to 10 ml were drawn by this procedure without injury to the alligator. The electrolyte studies were conducted on blood kept under mineral oil using potassium or ammonium oxalate as the anticoagulant. Urine was obtained by cloacal catheterization using a number 14F catheter.

Analytical Methods. Ammonia and urea of the blood and urine were determined by the method of Van Slyke and Cullen(4), uric acid by the method of Folin(5) and Brown(6), creatinine by the method of Folin and Wu(7), and protein and N.P.N. by the micro-Kjeldahl method of Howe(8). The pH determinations were done on a Beckman Model G pH meter with the Beckman glass electrode designed for blood analyses. Chlorides were determined

1. Hopping, A., *Am. J. Physiol.*, 1923, v66, 145.
2. Dill, D. B., and Edwards, H. T., *J. Cell. Comp. Physiol.*, 1935, v6, 243.
3. Austin, J., Sunderman, F. W., and Camack, J. G., *J. Biol. Chem.*, 1927, v72, 677.
4. Van Slyke, D. D., and Cullen, G. E., *J. Biol. Chem.*, 1916, v24, 117.
5. Folin, O., *J. Biol. Chem.*, 1934, v106, 311.
6. Brown, H., *J. Biol. Chem.*, 1945, v158, 601.
7. Folin, O., and Wu, H., *J. Biol. Chem.*, 1919, v38, 81.
8. Howe, P. E., *J. Biol. Chem.*, 1921, v49, 109.