Summary. Growth of rats was obtained when the sole source of nitrogen in the diet was provided by parenterally injected casein digest.

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Development of Tolerance to Gold Salts in Rats.

RUTH CORTELL AND R. KOHN RICHARDS.

From the Abbott Laboratories, North Chicago, Ill.

The minimum lethal dose of gold sodium thiosulphate intramuscularly in rats was found to be approximately 35 mg/kg. The rats which survived this dose were given repeated doses of 35 mg/kg every other day and then tested for the maximum tolerated dose of gold sodium thiosulphate, as compared to normal rats (Table I).

TABLE I.
Tolerated Doses of Gold Sodium Thiosulphate in Normal and Tolerant Rats.

Dose, mg/kg	Normal rats		Tolerant rats*	
	Survived, No.	Fatal, No.	Survived, No.	Fatal, No.
25	7	0		
40	1	3		
50	1	21		
100	1	31	7	0
150			3	0
200			0	3
250			0	3
300			0	2

*This group received 4 doses of 35 mg/kg every other day and was tested on the second day after the last chronic dose.

Whereas normal rats tolerated less than 40 mg/kg, animals that had received 35 mg/kg of gold sodium thiosulphate intramuscularly every other day for 4 doses tolerated 150 mg/kg, an increase of over 200%.

The relation of the size and number of doses to the development of tolerance is shown in Table II. The criterion of tolerance formation was survival following the injection of 100 mg/kg of gold sodium thiosulphate, a dose that is practically invariably fatal in normal rats. 35 mg/kg were given every other day to 36 rats, and the test dose of 100 mg/kg was given after a varying number of doses. As few as 2 chronic doses were found to be sufficient to cause the formation of tolerance to gold sodium thiosulphate, although not

TABLE II.
Development of Tolerance to Gold Sodium Thiosulphate in Rats.

Dose, mg/kg	No. of doses*	Days between last chronic dose and test dose (100 mg per kg) †	Rats survived, No.	Rats fatal, No.
35	13	2	3	0
	10	2	7	0
	5	2	3	0
	5	16	1	2
	4	2	4	0
	4	4	3	0
	4	8	3	0
	4	16	1	1
	2	2	5	1
	2	16	2	0
20	5	2	3	0
	8	2	2	0
10	5	2	0	2
	8		0	3

*Doses given every other day.
†30 out of 31 normal rats died on 100 mg/kg of gold sodium thiosulphate intramuscularly.

in all of the rats. Four doses produced tolerance in all the rats. Rats were tested not only on the second day after the last chronic injection, but also at varying intervals after this, up to the sixteenth day. On the eighth day the tolerance was still present, but on the sixteenth day, the tolerance had begun to disappear, even in rats that had received a larger number of doses.

Smaller doses than the maximum tolerated dose of gold sodium thiosulphate were found capable of producing tolerance, as for example, 20 mg/kg, but reduction of the dose to lower levels resulted in no tolerance formation.

Normal rats were found to tolerate 74 mg/kg of gold sodium thiomalate. Six rats given 55 mg/kg of gold sodium thiomalate intramuscularly every other day for 8 doses were tested with 185 mg/kg of gold sodium thiomalate, a dose invariably fatal in normal rats. All of the rats survived. Thus, it was demonstrated that tolerance could be formed to gold sodium thiomalate as well as to gold sodium thiosulphate. Three rats given chronic doses of gold sodium thiomalate survived 100 mg/kg of gold sodium thiosulphate, and similarly, 3 rats given chronic doses of gold sodium thiosulphate, survived 185 mg/kg of gold sodium thiomalate, revealing a cross tolerance between the two drugs.

Summary. Tolerance to both gold sodium thiosulphate and to gold sodium thiomalate can be developed in rats, as well as a cross tolerance between the 2 compounds. A minimum dose is necessary for tolerance formation, but with a sufficient dose, tolerance can be developed with only 2 doses. The tolerance lasts for considerable time.

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Distribution of Body Water Following Hemorrhage.

A. M. LANDS AND WALTER JOHNSON.

From the Department of Physiology, Schools of Medicine and Dentistry, Georgetown University, Washington, D.C.

Circulating blood increases its water content following hemorrhage.[1] This dilution is generally believed to result from the passage of non-vascular extracellular water into the vascular space due to a reduced capillary pressure following a reduction in blood volume. On the other hand, a few investigations as those of Milroy,[2] Gamble, Ross and Tisdall,[3] Kerr,[4] and Stewart and Rourke[5] have suggested the possibility that cellular fluids may be drawn upon to replace a deficit in blood volume.

The development of practical methods whereby the volume of extracellular water may be determined (Crandall and Anderson,[6] Gregerson and Stewart,[7] Brodie and Friedman,[8] Wallace and Brodie[9]) has suggested the desirability of applying these technics in an attempt to determine the changes in the volume of cellular and extracellular water that take place following hemorrhage. This was attempted by measuring the volume of sulfocyanide available water

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