Amino acid tolerance curves obtained after oral ingestion of 45 g of Parenamine (in another study from this laboratory[12]) were similar to those after intravenous injection except that the average maximal rise was only 3.4 mg per 100 cc, the amino acid N level seldom rising above 10 mg per 100 cc.

Since glucose is frequently administered intravenously along with amino acids, it was found desirable to study the blood chemical changes when a liter of 4.5% solution was injected following the intravenous administration of a liter of 5% glucose. There was no appreciable effect upon the various curves. One such experiment is shown in Fig. 1. The glucose curve fell promptly to normal following the injection. The serum phosphate level, depressed by the glucose injection was further lowered by the amino acid injection, reaching in one case the low level of 1.5 mg per 100 cc. The rise to normal levels was rapid.

Summary. Injection of 45 g of Parenamine intravenously at slow speeds produced an average plasma amino acid N rise of +4.9 mg per 100 cc during the injection with a return to normal in 2 hours. Rises to levels above 10 mg per 100 cc produced by rapid injection may be associated with nausea and vomiting. A progressive though slight rise in blood urea takes place during and after the injection, accompanied by increased urea excretion. Serum inorganic phosphate is lowered during the injection and returns to normal by the end of the injection. Only a negligible drop in CO_2 combining power occurred during the injection. Intravenously injected glucose did not alter the curves produced by the amino acid injection.

[12] Hoffman, William S., and Dyniewicz, H., *Gastroenterology*, in press.

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Is Normal Human Urine Toxic?*

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Much investigation has been devoted to the question of whether normal urine is toxic. It has been suggested that the increase of a toxic urine constituent is associated with disturbance of renal function (e.g. uremia, eclampsia). Aschheim and Zondek, however, in developing the hormonal pregnancy test concluded that human urine is non-toxic for the mouse, since injections of very large doses of human urine are tolerated by this animal.

Rachmilewitz[1] on the basis of experiments with fibroblast cultures *in vitro* concluded that human urine, native as well as dialyzed, contains, even in a dilution of 1:50, a powerful toxic substance which inhibits the growth and brings about the degeneration of cells. Uremic and normal urine were found to contain this toxic substance in about equal amounts.[1] It is, however, uncertain whether results of experiments carried out *in vitro* can be applied also *in vivo,* especially where toxicity is in question, since a cell (fibroblast) *in vitro* may lack detoxication potentialities which characterize the intact organism. Many substances whose toxic effect *in vitro* is notorious (e.g. para-chloro-xylenol[2] and many others) are completely non-toxic *in vivo.* Although dialyzed human urine inhibits the growth of fibroblasts *in vitro*[1] we found that it has no toxic action on a surviving frog

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[1] Rachmilewitz, M., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 497; *Arch. Int. Med.*, 1941, **67**, 1132.

[2] Zondek, B., *Nature*, 1942, **149**, 334; *J. Urol.*, 1942, **78**, 747.

TABLE I.
Amounts of Normal Human Urine Tolerated Without Toxic Reaction by Different Animal Species.

Animal	Wt.	cc of urine and distribution of dose	Route of injection	Urine / body wt.
mice	7.5 g	6 X 0.4 = 2.4	s. c.	$\frac{2.4}{7.5} = \frac{1}{3}$
"	10 "	30 (as 3 cc of dialyzed and conc. urine)	"	$\frac{30}{10} = 3$
rats	30 "	90 X 1 = 90	"	$\frac{90}{30} = 3$
"	100 "	30 X 10 = 300	"	$\frac{300}{100} = 3$
rabbit	1500 "	9 X 10 = 90	i. v.	
"	1000 "	250 (as 20 cc of dialyzed and conc. urine)	"	$\frac{250}{1000} = \frac{1}{4}$
dog	15 kg	160	"	

heart (Straub preparation). Native human urine added to the surviving frog heart caused immediate cessation of the heart beat (hypertonic salt content). Urine was dialyzed and after 5-fold concentration, rendered isotonic with NaCl. This preparation was entirely without toxic effect on the surviving heart. The experiment shows that though dialyzed urine may contain a constituent which is *in vitro* toxic to fibroblasts, such urine even in 5-fold concentration *in vivo* is non-toxic not only in respect to the intact organism but even in respect to a surviving organ.

In further experiments toleration of normal urine by different species was studied:

A dog weighing 15 kg received intravenously 160 cc of native human urine with no undesirable by-effect.

An adult rabbit received intravenous injections of 90 cc of native urine in 9 doses of 10 cc each given at intervals of 1 hour. The animal showed no toxic response. Rabbits weighing 1 kg were injected intravenously with 20 cc of dialyzed urine concentrates, the equivalents of 100-250 cc of native urine. These injections elicited no toxic after-effect.

Infantile rats (30 g) were given daily injections of 1 cc of native human urine for 3 months, *i.e.,* a total of 90 cc. The onset of sexual maturity was not affected by this protracted treatment with urine. Rats weighing 100 g received daily an injection of 10 cc of native human urine for 1 month, a total of 300 cc of urine. Nevertheless, a pregnant animal in this group produced a normal litter.

Urines were dialyzed and concentrated up to 10-fold *in vacuo*. Three cc samples of the concentrates were injected into mice weighing 10 g in 3 injections during 8 hours. The mice showed no toxic reaction to these injections, the equivalent of up to 3 times the body weight.

Our experiments show that animals tolerate normal human urine about as well as they do physiological saline (Table I).

Urine has been administered for therapeutic purposes to man in recent years both intramuscularly, rectally and orally. Ovarian dysfunction has been treated by intramuscular injections of native pregnancy urine, which is rich in gonadotropic and estrogenic hormone. In these cases, daily injections of 10-20 cc of pregnancy urine over a period of several weeks elicited no toxic effect. Rus-

sian authors have recommended treatment of severe uterine bleeding during puberty by a rectal drip infusion of several liters of native pregnancy urine. The experience of our clinic has corroborated the non-toxicity of this treatment. It may be mentioned also that Atcheson,[3] in order to save penicillin, administered urine of penicillin-treated patients to cases of chronic gonorrhea via a duodenal tube with good results.

The conclusion follows from the above findings that normal human urine is non-toxic *in vivo* for animals or man.†

Does Ether "Detoxicate" Urine? At the time of development of the pregnancy test, it was found that 7% of urine samples were unsuitable for examination by the method proposed at that time, because their injection into the mouse caused death, mostly within 24 hours. Zondek[4] reported that "toxic" urines of this type become innocuous to mice if they are first shaken with ether. This observation has since been confirmed by numerous workers. Experiments which are reported below show that the ether treatment is effective not because it extracts a specific toxic constituent but because it frees the urine from microorganisms which contaminate it during the passage over the vulva.

1. An ether extract of "toxic" urine was taken up in oil and injected into mice. It proved completely non-toxic.

Chemical restitution of the extracted urine by the re-addition of the ether extract failed to restitute toxicity.

Addition of the ether extract to non-toxic urine from another source did not render the latter toxic.

2. Ether had a bacteriostatic or a bactericidal effect on the bacterial flora of the urine. When ether-treated urine which had been allowed to stand at 37° C for 24 hours remained sterile, it proved also to be non-toxic. On the other hand, when development of bacteria occurred in the extracted urine sample during the period of the incubation, the original toxicity of the urine was found to have reverted. Proteus bacteria could be isolated from the heart blood of mice which had died following an injection of a "toxic" urine sample. Injection into the mouse of 1 cc of a broth culture of the isolated Proteus strain caused death.

3. In all cases, "toxic" urine could be rendered innocuous to the mouse by boiling.

4. Urine was taken by means of a catheter from patients whose urine had proved toxic when it had been taken in the ordinary way. It proved to be non-toxic when it was taken by catheter.

Conclusion. Tolerance tests for urine on a surviving organ (frog heart), and on different species of laboratory animals as well as clinical findings in man prove that human urine is not toxic. The delayed fatal effects which follow the injection of certain urine specimens (7%) into animals are due to infections. Ether treatment renders such urine specimens innocuous not because it removes a toxic substance from the urine but because it is bacteriostatic or bactericidal.

Our thanks are due to Dr. Daniela Weber for bacteriological tests.

[3] Atcheson, D. W., *Military Surgeon*, 1944, **95**, 58.

† Urine may, of course, contain toxic materials, either drugs or hormones, after medication, but such urines cannot be looked upon as normal urines.

[4] Zondek, B., *Klin. Wschr.*, 1930, **9**, 964.