had available animals with a natural fever due, usually, to infection and abscess formation at the point where peptone had been injected. This group of animals included 9 rabbits, 6 guinea pigs, 8 albino rats and 6 cats. We made no systematic study of these but injected them with various doses of camphor in oil. In the entire group of 29 animals, 24 or 83% showed no change or increased fever after injecting camphor, in 4 animals the temperature fell toward normal and 1 animal died.

Finally, we considered the possibility that camphor given by stomach tube in the form of Spirit of Camphor, B.P., might be antipyretic. Six groups of 13 rabbits each were injected with peptone and 3 hours later given respectively 0, 0.01, 0.1, 0.5, 1.0, and 5.0 ml of Spirit of Camphor by stomach tube, washed down with water. Again camphor failed to exhibit any antipyretic activity.

These 5 experiments convinced us that camphor has little or no antipyretic activity and that statements to the effect that the internal use of camphor is "supposed" or "considered" to have some antipyretic value should be deleted from textbooks, thus in some measure, even though small, lightening the burden of information which the medical student, physician and pharmacologist have to learn.

Summary. Camphor was administered parenterally and by stomach tube, in a wide range of doses, to some 500 animals, including albino rats, guinea pigs, rabbits and cats with a fever induced by previous injection of peptone and, in a few instances, fever from infection. Under these conditions, phenazone was found to be antipyretic in rabbits, but no evidence was obtained that camphor possessed antipyretic properties, at least to any marked degree.

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Blood Chemical Changes Following Intravenous Administration of a Casein Hydrolysate to Human Subjects.*

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To determine the criteria for the proper administration of Parenamine,‡ one of the commercially available casein hydrolysates which are used parenterally, and as a part of an investigation of its clinical effectiveness, a study was made of some of the blood chemical changes that occurred when this preparation was injected intravenously. The clinical studies have been reported elsewhere.[1]

Forty-five g of Parenamine (equivalent to 6 g of nitrogen) dissolved in 1000 cc of distilled water were injected intravenously into 30 hospital control subjects at a commonly used clinical speed of 300 to 350 cc per hour. The injections were made in the morning, breakfast having been withheld. Blood samples were drawn at the beginning, middle and end of injections and at 1 and 2 hours after the injection was completed. Plasma amino acid nitrogen concentrations were de-

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‡ Kindly furnished by Frederick Stearns and Company, Detroit, Mich. Parenamine is an acid hydrolysate of casein, fortified with 1% d, l-tryptophane. It is put up in 15% solutions in bottles containing 100 cc. The method of preparation of Parenamine is essentially that described by Sahyun.[7] An analysis of the distribution of the amino acids in the preparation has been reported by Block and Bolling.[8]

[1] Kozoll, Donald D., Hoffman, William S., and Meyer, Karl A., *Arch. Surg.*, 1945, **51**, 59.

TABLE I.
Blood Chemical Changes Following Intravenous Injection of 45 G of Casein Hydrolysate.

Blood Constituent Analyzed	No. of Cases	Mean Levels During and After Injection					Avg. Max. Change	Modal Time of Max. Change
		At Start of Inj.	Middle of Inj.	End of Inj.	1 Hr. After	2 Hr. After		
Amino Acid N, mg N per 100 cc Plasma	30	5.1 ±1.5* 2.5-8.4†	9.4 ±1.4 6.1-11.2†	9.2 ±1.2 7.2-11.2†	7.0 ±1.2 4.5-9.0†	6.0 ±1.1 4.0-8.0†	+4.9 ±1.7	Middle of Inj.
Urea N, mg. N per 100 cc blood	19	11.5	13.6	15.7	17.4	17.3	+6.6	1 Hr. after Inj.
Inorganic Phosphate, mg P per 100 cc Plasma	18	3.6	3.1	3.5	3.9	4.0	—0.5	Middle of Inj.
CO_2 Combining Power, cc per 100 cc Plasma	13	63	62	61	62	64	—4	End of Inj.

* Numbers after ± represent standard deviation.
† Range.

termined by the naphthoquinone method adapted to the photoelectric colorimeter by one of us (W.S.H.),[2] inorganic phosphate photoelectrically by Fiske and Subbarow's method,[3] urea by the method of Hoffman and Osgood[4] and CO_2 combining power by the method of Van Slyke,[5] and glucose by the method of Hoffman.[6]

The results are summarized in Table I. The initial plasma amino acid N levels ranged between 2.5 and 8.4 mg per 100 cc averaging 5.1 with a standard deviation of ±1.5. These values are slightly higher than those obtained with the ninhydrin method.[9] The amino acid N levels rose during the injection reaching a maximum in the majority of cases in the middle of the injection, in the remainder at the end of the injection. Thus the rate of removal of amino acids from the blood stream eventually became faster than the 15 g per hour of injection. The average maximal rise was 4.9 mg per 100 cc. At the end of 2 hours the amino acid N concentration had returned almost to the base level. The amino acid curves on the whole agreed with those found by Landesman and Weinstein[10] for intravenous injection of Amigen.

The blood urea N concentration began to rise slowly during the injection reaching a maximal value in 11 cases at 1 hour after the injection, and in 8 cases at 2 hours after the injection. The average maximal urea N concentration was 17.4 mg per 100 cc. The highest maximal concentration was 27.1 mg

[2] Hoffman, William S., *Am. J. Clin. Path.*, 1945. **15**, 57.

[3] Fiske, C. H., and Subbarow, Y., *J. Biol. Chem.*, 1925, **66**, 375.

[4] Hoffman, William S., and Osgood, Bess, *J. Lab. and Clin. Med.*, 1940, **25**, 862.

[5] Van Slyke, D. D., *J. Biol. Chem.*, 1917, **30**, 347.

[6] Hoffman, William S., *J. Biol. Chem.*, 1937. **120**, 51.

[7] Sahyun, M., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 14.

[8] Block, R. J., and Bolling, D., *Am. J. Pharm.* 1944, **116**, 368.

[9] Woodruff, C. W., and Man, E. B., *J. Biol. Chem.*, 1945, **157**, 93.

[10] Landesman, R., and Weinstein, V. A., *S. G. and O.*, 1945, **75**, 300.

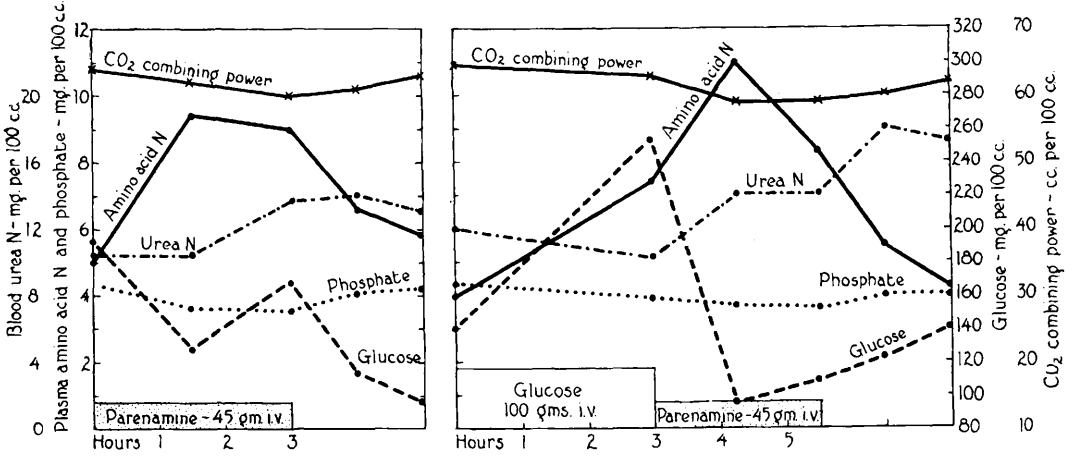

Fig. 1.

per 100 cc; this was in a patient whose initial level was 18.3 mg per 100 cc and who therefore may have had an early renal insufficiency. With one other exception, the remaining subjects showed maximal urea concentrations within the limits of normal such as might be found in patients on a high protein diet. Urea clearance determinations made in the successive intervals in 8 cases were too variable to indicate any direction of change, but at least they gave no clear evidence that the rise in blood urea concentration was due to a diminished rate of renal excretion.

A rather surprising finding was the drop in serum inorganic phosphate. This decline was small, about 0.5 mg per 100 cc, but was statistically significant. It occurred in all experiments, and the t value[11] for statistical significance of the difference between the average initial level and that at the middle of the injection was 2.9, a value above the 2.5 required to make it improbable that the decline was fortuitous. The maximal decline occurred at the midpoint at the same time that the amino acids were most rapidly leaving the blood stream.

Since Parenamine is furnished as an unneutralized mixture of amino acids having a pH of about 4.2, it is important to determine whether injections of this product produce any appreciable changes in CO_2 combining power. The results summarized in Table I indicate that the fall in CO_2 combining power is negligible. The range of maximal change was from +3 to —11 cc per 100 cc with an average fall of 4 cc per 100 cc. In 8 out of 13 cases, the fall occurred at the end of the injection. A return to the initial levels had occurred at 2 hours after the completion of the injection.

In 30 experiments listed in Table I, vomiting occurred in 2 cases at or near the end of the injection. In both cases the amino acid N levels were over 11 mg per 100 cc. Two other patients complained of nausea at a time when the amino acid levels were over 10 mg per 100 cc. In all 4 cases the rate of injection was somewhat faster than the average of 3 hours for the 1000 cc. In 5 additional cases not listed, injections were purposely made at fast rates ranging from 90 to 120 minutes for the 1000 cc. In 2 of these experiments, the maximal amino acid N concentration was over 12 mg per 100 cc and were associated with a sense of fullness, nausea, and vomiting. Thus it appears that if the plasma amino acid N concentration rises considerably above 10 mg per 100 cc, there may be symptoms produced comparable to those in acute overeating. It may be that the increase in concentration of a certain amino acid, such as glutamic or aspartic acid, is actually responsible for the symptoms.

[11] Snedecor, G. W., *Statistical Methods Applied to Experiments in Agriculture and Biology, Collegiate Press, Inc.*, Ames, Iowa, 1937.

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

* Partially aided by a grant from the Ella Sachs-Plotz Foundation.

[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.