Rate of Excretion of Glutamyl Polypeptide and Its Polymers in Humans. (20323)

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Further work on the polyglutamic acid previously investigated by us with reference to its mode of formation(1) has revealed characteristics relating to the use of this peptide and its derivatives as a plasma volume extender. The one major defect is its rapid disappearance from the blood stream and high rate of excretion by the kidney. Thus, the glutamyl peptide, prepared as previously described(1) with a molecular weight of 12,000 to 15,000, is completely cleared from the blood stream of humans within 2 hours after injection. As much as 85% of the injected material is found in the urine within 3 or 4 hours after injection.

Since rate of excretion from the blood stream is a function of such molecular properties as size, shape, surface configuration and charge, various derivatives of the peptide have been prepared and studied to provide a correlation of physiological properties with such physico-chemical properties. One result obtained of considerable interest in the problem of plasma volume extenders is concerned with molecular diameter and rate of renal excretion of these macromolecules. This result, as demonstrated in humans, is reported herewith.

Materials. The substances tested were glutamyl polypeptide and glutamyl polypeptide polymerized with some of its partial degradation products. The molecular dimensions of the glutamyl polypeptide were estimated to be 11 A by 150-200 A(1). The average number molecular weight of the glutamyl peptide was 12000-15000, that of the partial degradation products was 2000-3000. These molecular weights were obtained by both formol titration of the terminal amino group and the dinitrophonyl fluoride end group determination of Sanger(3), the methods agreeing within 10%. The molecular weights of the polymers have not yet been accurately determined, but are estimated to be 80000 on the basis of data obtained during their preparation. The method of preparation of these polymers, as well as a method for the quantitative determination of both the peptide and these polymers, will be published elsewhere(2). There was no notable change in molecular length, the increase in molecular weight being associated with increase in molecular diameter. Both *glutamyl peptide and its polymers* were injected intravenously as 3% solutions of sodium salt in isotonic saline. Sterilization was achieved by filtration. All solutions were tested for pyrogenicity and sterility prior to use. Each subject was administered 3 g of the material being tested during the course of one hour. Control analyses for blood and urine level were taken prior to injection. Blood levels were taken 10 minutes after the end of injection, and then at suitable intervals. Urinary excretion of the material was determined from the start of the injection and followed at least 24 hours.

Results. It is evident in Fig. 1 that the

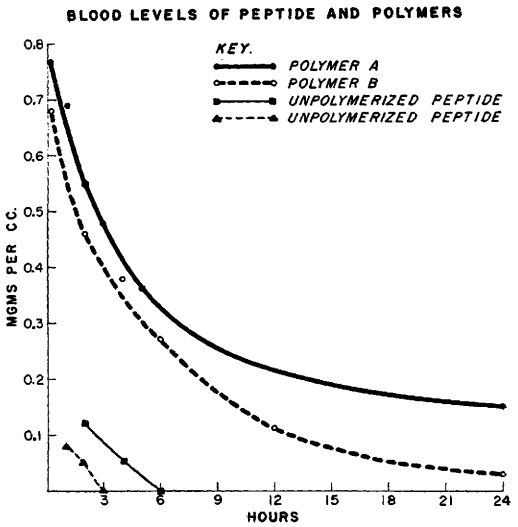

FIG. 1.

* We are indebted to Merck and Co. for a gift of the glutamyl peptide used in this work.

half-life of the glutamyl peptide in the human blood stream is increased by polymerization. As a corollary, the rate at which the polymerized material is excreted in the urine is decreased. It is pertinent to state here that there was no significant change in temperature, pulse, or respiration in either subject during the course of administration or at any time during the next two days. Subjectively the patients experienced no symptoms whatsoever.

It is evident that the rate of disappearance of the polymer of glutamic acid from the human blood stream can be decreased by increasing the diameter of the molecule, other factors such as the length and composition of the molecule being kept constant. The molecular length of both the peptide and the polymer are approximately that of serum albumen.

Summary. The half-life of glutamyl polypeptide in the blood stream of humans can be increased by polymerization leading to an increase in the molecular diameter.

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Butazolidin Plasma Concentration and Urinary Excretion in Normal Individuals and in Patients with Rheumatoid Spondylitis.* (20324)

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The current use of 3,5-dioxo-1,2-diphenyl-4-n-butyl pyrazolidine (Butazolidin)† in the treatment of rheumatic diseases has become widespread in this country as well as in Europe. Although there are many references regarding its use and the resultant clinical response(1-4) there has been no satisfactory report concerning plasma concentration and the urinary excretion of the drug. At the time of the initial report on the use of Butazolidin in 188 patients(3), information regarding the absorption of the drug was not available. It was known that the absorption was occasionally incomplete because some patients observed the intact tablets in the stool. Studies on drug concentrations were instituted in an attempt to establish definite absorption, optimum dosage, and to arrive at a possible explanation of the toxic reactions frequently encountered during therapy(2,4-6). Experience indicates that Butazolidin is more effective in the treatment of rheumatoid spondylitis than in any other type of rheumatic disease. For that reason this study was limited to the results from treated spondylitis patients.

This paper reports plasma concentrations and urinary excretion of Butazolidin for 11 normal individuals and 6 patients with rheumatoid spondylitis who were treated in the same manner. Rates of absorption and disappearance of the drug in plasma and urine are reported for one patient with osteo arthritis.

Methods. The normal control group consisted of 6 male and 5 female university students between the ages of 19 and 25. Each individual was carefully instructed and later checked to make certain that his diet was of adequate caloric and vit. C content as well as one which supplied a minimum of one gram of protein per kilogram of body weight. All meals were provided at the same dining hall on the campus. Twenty-four hour urine samples were collected on 2 consecutive days and

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