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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(Introduced by A. R. Kemmerer.)

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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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† Butazolidin was supplied by Geigy Pharmaceuticals, Geigy Co., New York.

a blood specimen on one day preceding institution of therapy. A routine urinalysis, a routine blood count, platelet count and erythrocyte sedimentation rate were performed at the beginning of the experiment. After a 2-day control period on the diet, 400 mg of Butazolidin were administered orally in 2 divided daily doses. The students were instructed that medication must always be taken following meals and that any unusual symptoms be reported at once to the physician in charge. During the treatment period of 10 days, blood specimens and 24-hour urine samples for Butazolidin levels were obtained on the 1st, 3d, 5th, 7th, and 10th days. Approximately 12 hours elapsed between time the last medication was ingested and the blood sample obtained. Five male and 1 female patients with indisputable rheumatoid spondylitis were similarly treated. The patients ranged in age from 19 to 40 years. The patient with osteo arthritis had been on a daily dose of 400 mg of Butazolidin for 2 weeks. At the time the medication was discontinued the plasma level was 10.3 mg % and the rate of disappearance of the drug from both plasma and the urine was carefully followed for 12 days. On the 15th day the drug was started again and its reappearance and rise in the urine and plasma was studied for an additional 18 days. On the day the specimens were obtained, determinations for each individual were estimated in duplicate. In the plasma procedure the original method was modified in order to eliminate the formation of permanent emulsions. Ground glass stoppered test tubes of 50.0 ml capacity were substituted for glass bottles and antifoam‡ was added to the mixture before shaking. The final estimations were made by reading the optical density at 265/u in a Model DU Beckman Spectrophotometer. Recoveries of Butazolidin added to plasma and to urine were satisfactory (100% ± 4%).

Results. Butazolidin was demonstrated in both plasma and urine in all 17 subjects. Its definite absorption from the intestinal tract was thus established. With the exception of female students W. O. and S. A. no other individuals gave evidence of any toxic reactions to the drug. No member of the group of normal students reported loss of appetite, symptoms of gastric disturbance, insomnia or euphoria. There was no development of edema and no significant weight gain. No symptoms were detected which could be referred to ingestion of Butazolidin. The results for normal stu-

TABLE I. Butazolidin Plasma Concentrations.*
6 patients with rheumatoid spondylitis.
Control = 0 mg %.

Subjects	Days on treatment 1	3	5	7	10
	mg %				
K. K.	3.8	9.3	9.6	14.0	13.4
S. G.	.8	4.1	11.3	13.2	12.6
R. N.	1.0	4.6	7.4	9.1	10.2
B. P.	1.6	7.4	9.8	8.2	11.9
N. D.	1.2	7.7	12.8	13.7	13.1
Mc. A.	.0	10.7	11.4	11.8	12.4
Avg	1.4	7.3	10.5	11.7	12.3
11 normal students					
B. B.	3.8	6.2	11.0	12.6	14.0
D. D.	3.3	3.8	8.8	16.1	15.3
P. N.	3.9	7.2	8.9	11.9	14.5
S. L.	2.6	5.6	9.5	11.2	14.9
W. R.	3.5	7.6	12.4	14.4	12.8
W. L.	.0	5.8	11.5	12.7	13.8
B. W.	4.7	11.7	14.4	14.5	15.8
Mc. D.	2.6	8.2	9.5	11.7	14.5
S. D.	.0	6.8	7.7	14.7	13.1
Avg	2.7	7.0	10.4	13.3	14.3

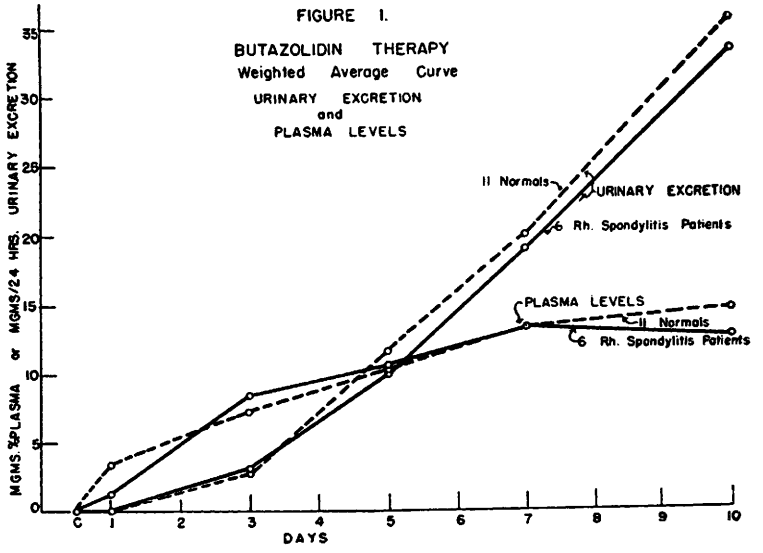
* Daily dose 400 mg Butazolidin.

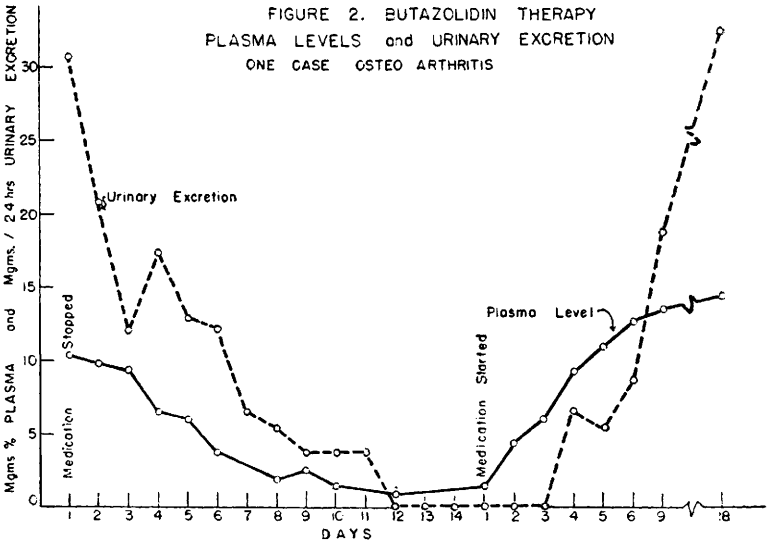
TABLE II. Butazolidin Urinary Excretion Values.*
6 patients with rheumatoid spondylitis.
Control mg/24 hr = 0.

Subjects	Days on treatment 1	3	5	7	10
	mg/24 hr				
K. K.	2.5	2.8	27.1	21.2	37.2
S. G.	.0	2.8	9.6	35.6	34.0
R. N.	.0	4.3	10.0	13.7	15.3
B. P.	.0	2.2	9.8	16.1	17.6
N. D.	.0	1.4	15.2	32.4	25.9
Mc. A.	.0	5.1	5.1	19.7	36.9
Avg	.4	3.1	12.8	23.1	27.8
11 normal students					
B. B.	.0	3.2	20.3	32.3	41.4
D. D.	.0	3.8	16.9	20.4	27.8
P. N.	.0	.0	2.2	7.4	23.6
S. L.	.0	2.2	11.1	17.2	14.3
W. R.	.0	.6	10.5	12.4	43.8
W. L.	.0	2.2	13.0	19.2	30.3
B. W.	2.0	7.0	18.8	46.8	69.0
Mc. D.	.0	2.9	7.7	17.7	48.1
S. D.	.0	2.2	9.0	21.0	17.3
Avg	.2	2.7	12.2	21.6	35.1

* Daily dose 400 mg Butazolidin.

‡ Dow Corning Antifoam A. Silicone Defoamer.





dents, W. O. and S. A. were eliminated from all but the weighted mean calculations. Butazolidin concentrations in the plasma for the remaining 9 normal students and for the group of patients with rheumatoid spondylitis are presented in Table I.

Butazolidin urinary excretion values for the two groups studied appear in Table II.

Fig. 1 represents the weighted average graph§ of both plasma concentration and urinary excretion values for the 2 groups. On the 10th day the difference in plasma levels in the 2 groups was significant at the 1% level. At no other time were the differences significant in either plasma concentration or urinary excretion values. The average weight of the group of normal individuals was 22 pounds higher than the average weight of the patients with rheumatoid spondylitis. When individual values for all subjects were arbitrarily con-

§ The weighted mean derived by averaging remaining values after discarding those which fell outside the mean plus or minus the standard deviation. (Values between $X \pm S_x$).

verted to gamma per pound of body weight instead of mg % the significant value mentioned above was no longer evident. We believe it can be explained on a weight difference basis and should be disregarded. The conversion to gamma per pound of body weight did not alter the fact that none of the differences in urinary excretion values was significant.

On the 10th day of treatment the weighted mean average Butazolidin plasma level for both groups was 14.0 mg % or roughly 350 mg in the total circulating plasma. This represents approximately 88% of a daily dose. On the same day the weighted average urinary excretion value for the two groups was 35.0 mg/24-hours or approximately 8.8% of a daily dose. Fig. 2 shows a curve representing the daily rates of disappearance of Butazolidin in the plasma and urinary excretion for 1 patient with osteo arthritis. Butazolidin did not disappear from the urine until the 12th day after the drug was discontinued. A total of 129 mg had then been excreted. On the 3d day after Butazolidin had completely disappeared from the urine, medication was started again in a daily dose of 400 mg. It did not reappear in the urine until the 4th day following reinstitution of therapy.

Although the presence of Butazolidin was not detected in the urine after 12 days it was present in the plasma in small amounts (0.84-1.24 mg %) even 15 days after the drug was discontinued.

Discussion. This study was not designed to show differences in response to Butazolidin therapy between normal individuals and patients with rheumatoid spondylitis. Rather, both groups were incorporated for the purpose of establishing information on the absorption and urinary excretion of the drug. The results show that Butazolidin was absorbed from the intestinal tract in all individuals treated. Not until the 7th and 10th days of treatment was the plasma level in any way commensurate with the daily drug intake. When the urinary excretion value was highest only about 10% of the daily dose of butazolidin was being excreted as such.

It is interesting to note the slow disappearance of the drug from both the plasma and the urine in the patient with osteo arthritis. On the day the medication was discontinued there were roughly 300 mg in the total circulating plasma. In the 12 days required for the Butazolidin to disappear completely from the urine, only 129 mg were excreted. The drug was still present in small amounts in the plasma on the 15th day when medication was again started.

A number of possibilities have been considered to explain the disposition of Butazolidin by the body but as yet we have little actual proof to substantiate them.

Summary. 1. Four hundred mg of Butazolidin were administered orally for 10 days to 11 normal students and to 6 patients with rheumatoid spondylitis. Plasma concentrations and total 24-hour urinary excretion values for the drug were estimated. 2. Butazolidin was demonstrated in the plasma of all individuals between the 1st and 3d days on treatment and appeared in the urine between the 1st and 5th days thus proving its definite absorption in all 17 subjects. With the exception of 2 mild cases of edema in 2 females in the normal group, no toxic effects of the drug were encountered during therapy. There were no significant differences in the reactions in the 2 groups. No sex differences were noted in the rate of absorption or excretion of the drug although the number of subjects admittedly was small. 3. Butazolidin did not completely disappear from the urine in one patient with osteo arthritis until 12 days following cessation of therapy and it was still detected in small amounts in the plasma at the end of 15 days. 4. We have at this time no adequate explanation regarding the disposition of the drug by the body although there is some evidence to suggest that a part of it is stored as Butazolidin in the tissues or carried in the circulating blood.

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Effect of Initial Length on the Work of the Cardiac Atrium.* (20325)

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Atrial contraction may insure adequate cardiac filling in patients with mitral or tricuspid stenosis. Factors that affect the work done by atrial systole became of great importance in such cases. The relationship between ventricular initial length and systolic work has been studied(1-2); apparently similar relationships for mammalian atrial muscle have not been investigated. Such information may be valuable in interpreting atrial pressures, particularly in cases of valvular dysfunction.

Method. Strips of atrial muscle 2 by 0.5 cm were removed carefully from the beating left atrium of dogs anesthetized with sodium barbital. The strips were placed in warm Tyrode's solution modified to contain 0.008% NaH_2PO_4 and 0.013% $CaCl_2$. The solution was oxygenated with 95% O_2 and 5% CO_2, and maintained at 39°C. One end of the muscle strip was fixed by a support and the other end suspended by a simple lever. Weights ranging from 0.5 to 10 g were placed on the free arm of the lever, and the resulting muscular stretch was recorded by projecting the movement of the lever onto a photokymograph. Muscular contractions were elicited by maximal induction shocks, and the height of the contractions was recorded. All records were corrected for magnification and were expressed as the actual movement in mm of the free end of the muscle strip. The work performed by each contraction was calculated in gram-centimeters. Muscular stretch was calculated as percent of the original 2 cm length.

Results. A total of 131 observations on strips from 9 atria were satisfactory for analysis. The amount of work performed varied widely among muscular strips. However, in each case the amount of work increased with increase in initial length until a

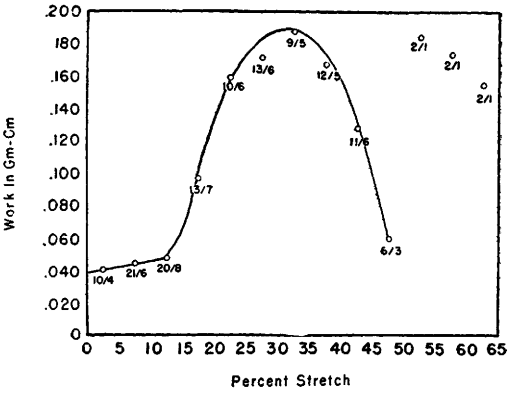

FIG. 1. Work-stretch diagram of left atrial strips. Circles are avg work performed. Upper figures are number of observations, lower figures are number of animals. The three points in upper left of plot were all from the same animal.

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