TABLE I. Survival of Eviscerate Rats with and without the Administration of Vitamins.

Vit dose/24 hr/rat	Min survival — Vitamins N	Avg	Range	No vitamins N	Avg	Range
ml						
B-complex .05	10	6102	4491-7310	11	6202	5169-7511
.125	12	6367	5441-7447	12	6424	5914-7528
.25	12	5540	4792-6566	12	5753	4670-7226
.50	12	5804	4538-6761	12	6167	5010-7178
Rutin 1 mg; ascorbic acid 1 mg	15	5938	4717-7631	14	5955	4514-7493
" 2 "; " " 2 "	10	6279	5078-6940	11	6193	5221-7759
A— 80 u; D—12 u; E—4 mg	12	5749	5256-6805	11	5892	4680-6875
A—160 u; D—24 u; E—8 mg	10	5537	4214-6925	10	5687	4894-6493

otherwise treated in an identical manner. The data on treatment, number of rats per group and times of survival are summarized in Table I. The results were negative.

Discussion. These data do not exclude the possibility that other vitamins or combination of vitamins not tested here would affect the survival of the eviscerate rat. It has been suggested to us that exogenous vitamins may be unable to act in the eviscerate rat without the addition of their coenzymes. The mitochondria fraction of rat liver extracts has been added to exogenous vitamins in a few animals on the assumption that this would provide the coenzymes of vitamins but the results of these preliminary tests were negative. Several extracts of beef liver have been tested in the eviscerate rat without a favorable effect upon survival. One of the control eviscerate rats of this series survived for 138 hours, the longest survival of any eviscerate mammal of which we are aware.

Summary. Male eviscerate rats were fed intravenously with solutions of 0.9% NaCl, glucose, insulin, streptomycin, and penicillin with and without the following mixtures of vitamins: B_{12}, folic acid, thiamine, riboflavin, pyridoxine, pantothenate and nicotinamide; rutin and ascorbic acid; and vit. A, D, and E. The results were negative.

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Effect of Phenylbutazone on Uric Acid Excretion in Patients with Gout and Rheumatoid Arthritis. (20432)

CHARLES BISHOP AND LAWRENCE BEECHER. (Introduced by Fred R. Griffith, Jr.)

From the Chronic Disease Research Institute, Buffalo, N. Y.

Phenylbutazone* (3,5 dioxo-1,2-diphenyl-4-n butylpyrizolidine sodium) is one of the newer drugs used in the treatment of gout and rheumatoid arthritis. Although phenylbutazone is not a steroid it seems to promote a sense of well-being in certain gouty and arthritic patients, over and above its simple analgesic action(1).

The experience in both this and other clinics is that the institution of phenylbutazone therapy is usually followed by a noticeable decrease in the serum urate level. Studies have been undertaken in this laboratory to see if this effect can be explained on the basis of simple uricosuric action. A preliminary study is reported in this paper.

Methods. Two patients with gout and 3 with rheumatoid arthritis were hospitalized. They consumed a diet uniformly low in purines and constant in nitrogen and caloric content.

* Butazolidin kindly supplied by Geigy Pharmaceuticals Division of the Geigy Co., New York City.

TABLE I. Urinary Uric Acid Output after Phenylbutazone Therapy.

Patient, Sex	Age, diagnosis†	Therapy*	No. of days	Mean daily uric acid excretion (mg)	Stand. dev. (mg)	T test	P value	Serum urate
W, ♀	64, RA	C	7	311	53			4.7, 4.9
		C + P	7	355	69	$T_{12} = 1.34$	P>10%	4.4, 3.2
		P	7	354	35	$T_{13} = 1.77$	"	2.6, 2.1, 2.5
B, ♀	54, RA	C	7	359	49			4.0, 4.5, 3.9
		C + P	7	415	66	$T_{12} = 1.64$	"	3.8, 0.9, 1.3
		P	7	390	85	$T_{13} = 1.09$	"	1.3, 1.8
H, ♀	50, RA	0	7	446	45			6.4, 6.1, 5.6
		P	11	513	92	$T_{12} = 1.65$	"	4.8, 4.4, 3.2
		0	10	404	93	$T_{13} = 1.13$	"	4.0, 7.5, 7.9
Q, ♂	82, NG	0	7	296	65			9.2, 8.5, 9.4
		C + P	7	374	61	$T_{12} = 2.50$	5%>P>2.5%	9.4, 7.7, 7.9
		P	14	374	52	$T_{13} = 3.03$	1%>P>0.5%	7.0, 11.0, 7.3, 4.9
		0	7	368	104	$T_{14} = 1.60$	P>10%	4.5, 5.8, 5.6
E, ♂	72, TG	0	7	398	52			11.3, 12.9
		B	7	627	136	$T_{12} = 4.12$	P<0.5%	10.5, 11.0
		P	8	514	121	$T_{13} = 2.27$	5%>P>2.5%	11.4, 11.1, 10.0
		B + P	7	618	83	$T_{14} = 5.58$	P<0.5%	7.6, 7.7

* C = Codeine (P.R.N., not more than 1 grain daily). P = Phenylbutazone (200 mg 2 times daily). B = Benemid (500 mg 4 times daily).

† RA = Rheumatoid arthritis. NG = Non-tophaceous gout. TG = Tophaceous gout.

During the entire study all urine was collected daily and the uric acid output was determined using the method of Folin(2). After a control period, phenylbutazone therapy was instituted (2 x 200 mg daily). During the control period two of the arthritic patients had been receiving codeine (P.R.N., not more than 1 grain daily) to control their pain and this was continued for the first period of phenylbutazone therapy. In these cases a second period of phenylbutazone therapy was instituted during which the codeine was eliminated and only the phenylbutazone was given. A final control period was used wherever practical. In one of the gouty patients, Benemid† (p-(di n-propyl sulfamyl) benzoic acid) and phenylbutazone were administered both separately and together in order to compare the action of phenylbutazone with that of a known uricosuric agent(3). The details of the regimens and the results are summarized in Table I.

Discussion. It is apparent from Table I that phenylbutazone caused a lowering of the serum urate level in every subject except S.E. Phenylbutazone appeared to cause a small increase in uric acid excretion in the three arthritic patients but the increase was not statistically significant when the data were tested by the t test. With the gouty patients, however, the increase was unequivocal. Thus it would appear that at least in certain situations, phenylbutazone acts as a uricosuric agent. Whether this is its only mechanism of action for lowering the serum uric acid concentration cannot be deduced from this type of study.

Since phenylbutazone does have a uricosuric action, it may be difficult by means of balance studies to show that the uric acid that disappears from the serum does or does not equal the "extra" uric acid excreted in the urine. The difficulties of attempting to equate such factors have already been discussed for the drug Benemid(3).

Summary. Phenylbutazone was shown to cause a statistically significant increase in urinary uric acid output in two gouty subjects. Such an increase could not be demonstrated in three patients with rheumatoid arthritis.

† Benemid, kindly supplied through the courtesy of Sharpe and Dohme, Philadelphia, Pa.

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Antibiotic Combinations and Resistance to Antibiotics: Penicillin with Other Antibiotics Against Penicillin-Resistant Staphylococci.* (20433)

MAXWELL FINLAND AND CLARE WILCOX.

From the Thorndike Memorial Laboratory, 2nd and 4th Medical Services, Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

In a previous study(1) it was shown that the development of resistance to penicillin, streptomycin or erythromycin *in vitro* may be delayed and depressed by the use of a combination of erythromycin with either penicillin or streptomycin. The organisms used in that study were originally susceptible to small or moderate concentrations of each of these antibiotics, and when they were repeatedly subcultured in the combination of 2 antibiotics, these were present in increasing concentrations, but always in a constant ratio. In the present study an attempt was made to determine whether the presence of a moderately high concentration of an antibiotic to which bacteria are originally resistant would also serve to delay or depress the development of resistance to another antibiotic following repeated exposures to increasing concentrations of the latter.

Materials and methods. The 8 strains of *Staphylococcus aureus* used in the present study had been isolated from infected materials during a recent survey(2); they were each inhibited by 25 μg/ml of streptomycin and 0.2 μg/ml of erythromycin but grew well in the presence of 1000 μg/ml of penicillin. They were all hemolytic, coagulase-positive and produced penicillinase. Each of the strains was subcultured on 3 parallel series of blood agar plates: one contained no antibiotic, the second contained penicillin 200 μg/ml plus graded (2-fold) concentrations of streptomycin [as in the plate-dilution test for sensitivity(3)], while the third contained the same amounts of penicillin and similarly graded concentrations of erythromycin. The inoculum for the antibiotic-containing plates was obtained in each instance by scraping a 3 mm loopful of the surface growth from the plate containing the maximum concentration of antibiotic on which nearly full growth occurred after 48 hours incubation, suspending this in 0.2 ml of broth and streaking a 1 mm loopful of the suspension on a similar series of plates. This method is similar to the one employed in previous studies(1,4-8). At the completion of 25 such subcultures (except strain 31, which was subcultured 29 times) all of the resulting strains were tested simultaneously for sensitivity to penicillin, streptomycin, erythromycin, carbomycin and neomycin by the usual plate-dilution method(3). Sensitivity of any strain to a given antibiotic is defined as the minimum concentration of that antibiotic in which there is no visible growth after 48 hours.

Results. Resistance to streptomycin and erythromycin. The changes in the sensitivity of the strains during successive transfers in the presence of a constant concentration of penicillin and increasing concentrations of either streptomycin or erythromycin are depicted in Fig. 1. The development of resistance to streptomycin in the presence of penicillin was uniformly rapid and was virtually complete after from 5 to 8 transfers. Resistance to erythromycin under similar circumstances developed somewhat more irregularly,

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