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Therapeutic Effectiveness of Single Oral Doses of Penicillin.

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Very few chemotherapeutic agents are effective when administered as single oral doses in acute bacterial infections. Robinson, Smith and Graessle¹ reported 80% survival with a batch of crude streptomycin, using a single oral dose of about 1500 mg per kilo, in an acute *Salmonella* infection in mice.* These investigators also found that a single oral dose of about 500 mg per kilo of crude streptothricin (assumed potency 300 units per mg) saved 76% of mice in a similar infection.² Finally, each of several analogues of pantothenic acid, administered as a single oral dose of 500 mg per kilo, has produced 100% survival in an acute hemolytic streptococcal infection in mice.

It is the purpose of the present communication to report preliminary results of a study of the therapeutic effectiveness of single oral doses of penicillin.

Methods. The penicillin powder used in this work was labelled "Crude, Penicillin G, pH 5.0 salt." It was supplied by Lederle Laboratories, Pearl River, N. Y. Its potency was determined as 650 *Staphylococcus* units per mg. Thus, on the basis of 1667 units per mg of pure penicillin G, the purity of the powder was considered to be approximately 39%.

The untreated experimental streptococcal infection is characterized by rapidly develop-

ing septicemia uniformly terminating in death within 48 hours. Treated animals alive on the 21st day after infection are considered to be completely protected.

Results. The therapeutic effect which can be obtained with a single oral dose of penicillin is shown in Table I. It is evident that

TABLE I.
Therapeutic Effectiveness of Single Oral Doses of Penicillin.

Organism: <i>Hemolytic streptococcus</i> ; Group A; strain C203.		
Mice: Vanderwerken; 18-22 g.		
Infection: Intraperitoneal; 0.5 cc of a 10-5 broth dilution of a 6-hour TSP-blood broth culture; 4000 $\pm$ 400 organisms.		
Treatment: Penicillin powder containing 650 units per mg; single dose by stomach tube immediately after infection.		
Single dose mg/kg	Survival on 21st day after infection alive/total No.	Dose calculated as pure penicillin G mg/kg
4000	10/10	1600
2000	10/10	800
1000	10/10	400
500	10/10	200
250	30/30	100
200	30/30	80
150	30/30	60
100	30/30	40
50	30/30	20
25	29/30	10
Untreated controls	0/40	—

a single dose of only 25 mg (equivalent to 16,000 to 17,000 units) per kilo of mouse produced a marked effect (97% survival).

Discussion. The fact that 97% survival was obtained with crude penicillin powder (650 units per mg) administered orally as a single dose of 25 mg per kilo suggests clinical applications for streptococcal infections. Thus, an equivalent dose for a 60-kilo patient would be 1.5 g; expressed as pure penicillin G, this dose would be only 0.6 g.

¹ Robinson, H. J., Smith, D. G., and Graessle, O. E., PROC. SOC. EXP. BIOL. AND MED., 1944, **57**, 226.

* The dosage reported was 3000 units. The dose given above was calculated on the assumptions that the streptomycin sample contained 100 units per mg and that the average mouse weight was 20 g.

² Robinson, H. J., and Smith, D. G., *J. Pharm. and Exp. Therap.*, 1944, **81**, 390.

Such doses appear to be "massive" only when expressed as "units." The advantages of therapeutic administration of penicillin in a single oral dose, or in oral doses given once or twice a day, are obvious.

Further work is in progress to determine the effectiveness of single oral doses of dif-

ferent lots of penicillin in the streptococcal and other infections in mice.

Summary. Survival of 97% was obtained in a streptococcal infection in mice with crude penicillin powder containing 650 units per mg, administered in a single oral dose of 25 mg per kilo.

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Adenosine Triphosphatase Activity and Weight of Corpora Lutea During Reproductive Cycle of the Rat.*

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Adenosine triphosphate (ATP) and the ATP-splitting enzyme, adenosine triphosphatase (ATP-ase), have been found in tissues other than muscle,¹ and evidence has been presented that the ATP system links the energy-requiring reactions of tissues with the energy-yielding reactions.² These results suggested an investigation of the ATP-ase activity of ovarian structures since these tissues undergo rapid changes in growth and function during which large amounts of energy must necessarily be involved.

Materials and Methods. The method of DuBois and Potter¹ was used in determining the ATP-ase activity of corpora lutea and remaining ovarian tissue of female rats during estrus, diestrus, pseudopregnancy and lactation at the intervals indicated in Table I. This method measures the amount of inorganic phosphorus released by the enzyme of homogenized tissue when ATP is used as substrate in a buffered solution (pH 7.4) containing calcium. The corpora lutea were dissected from the ovaries using sharp-pointed scalpel blades and spectacle loupes. The identification of the corpora of pregnancy and corpora of the post-partum ovulation through-

out lactation was based on the differences in size, shape and color. That these criteria were adequate was confirmed by marking the corpora of pregnancy with fine silk thread. The corpora and ovarian residue were weighed and homogenized prior to adding to the incubation mixture. Each ATP-ase value in the table is the average of 9 determinations (3 for each of 3 rats), and each weight is the average of the corpora lutea obtained from 3 rats.

Results and Discussion. In diestrus there was a slight increase in the ATP-ase of the corpora lutea and ovarian residue above the estrus level. The average weight of the diestrous corpora was essentially the same as that found in estrus. During pseudopregnancy the weight of the corpora increased somewhat from the estrus level, but the ATP-ase activity did not change significantly. As pseudopregnancy progressed a definite decrease in the value of the ovarian residue was noted. At 11 days estrus was imminent, and the results suggest an inverse relationship between estrogen level and ATP-ase of the extra-luteal tissues.

The ATP-ase activity of the corpora lutea during pregnancy, when calculated on a per mg of tissue basis, did not show marked variation despite the fact that the average weight of the corpora lutea progressively increased. Late in pregnancy an increase in activity was found which continued until the

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¹ DuBois, K. P., and Potter, V. R., *J. Biol. Chem.*, 1943, **150**, 185.

² Potter, V. R., *J. Cell. and Comp. Physiol.*, 1945, **26**, 87.