resistance to penicillin required 48 hours to complete the fermentation of lactose, whereas the control strain effected the same result in 24 hours. A similar delay was noticed in the fermentation of glucose by the penicillin-resistant strains of the gonococcus.

Far more difficulty was encountered in developing penicillin-resistant strains than sulfathiazole-fast strains of the gonococcus *in vitro*. These observations suggest that penicillin-resistant strains of the gonococcus are less likely to become established in the population at large than sulfathiazole-resistant strains, although this possibility should be given consideration.

Summary. Five strains of ***Neisseria gonorrhoeae*** were made resistant *in vitro* to concentrations of penicillin 8, 64, 128, 200, and 400 times greater than the initial concentration permitting growth. Morphological changes of the gonococcus and a delayed fermentation of glucose were observed in the strains during the development of resistance to the drug.

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Action of Certain Sulfonamides on Anaerobic Activity of Respiratory Center of Young Animals.

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Earlier reports have shown that the anaerobic activity of the respiratory center of young animals, as indicated by the gasping pattern of the ischemic or completely isolated head, is altered by various anesthetic agents and tissue poisons[1] and by the carbohydrate stores of the nervous tissue.[2,3] Glucose greatly prolongs survival and the number of gasps of the second series. Insulin and iodoacetic acid diminish or completely abolish the second series: cyanide diminishes the first.[4] These results suggest that the prolonged survival of the respiratory center of young animals is due to an anaerobic source of energy resulting from the breakdown of carbohydrates by enzymes.

Because the sulfa drugs are known to interfere with certain enzymatic processes, it was thought desirable to study the action of these on the gasping pattern and survival of the unperfused isolated head of the young animal. The respiratory center of such a preparation, unlike that of the whole animal with circulation intact, cannot be influenced secondarily by changes in other parts of the body.

Methods. Employing a technic previously described,[1,4] rats 12-15 days of age and weighing 18-26 g were used as test animals. The gasping pattern of the isolated head of rats of this age consists of 28-35 mandibular movements lasting approximately 5 minutes and is composed of an initial or aerobic series having a relatively constant number of gasps, averaging about 9, and a second or anaerobic series having a somewhat variable number (19-26) averaging about 23. A pause or period of complete inactivity between the end of the first series and the beginning of the second (the interseries interval) lasts 35 to 50 seconds. In previous experiments on 65 litters comprising 445 animals, the standard deviation of the mean number of gasps for untreated littermates was found to be slightly less than 2; the average variation for survival was 8.4% and that for number of gasps of the second series was 6.1%.

The drugs employed were sulfanilamide and the sodium salts of sulfathiazole, sulfadiazine, and sulfamerazine. These were injected intraperitoneally in doses of 3, 4.5, and 6 mg. Toxic

1 Selle, W. A., PROC. SOC. EXP. BIOL. AND MED., 1942, **51**, 50.

2 Selle, W. A., *Am. J. Physiol.*, 1944, **141**, 297.

3 Hiestand, W. A., Tschirgi, R. D., and Miller, H. R., *Am. J. Physiol.*, 1944, **142**, 153.

4 Selle, W. A., PROC. SOC. EXP. BIOL. AND MED., 1943, **54**, 291.

TABLE I.
Influence of Certain Sulfa Drugs on Survival of Isolated Head of 12-15-day-old Rats.

Drug	Dose, mg	No. animals	Increased respiratory activity based on avg control values: After 1 hr — No. anaerobic gasps, %	After 1 hr — Total survival %	After 2 hrs — No. anaerobic gasps, %	After 2 hrs — Total survival %	After 3 hrs — No. anaerobic gasps, %	After 3 hrs — Total survival %
Sulfanilamide	3.0	10	19	29	48	59	39	47
	4.5	12	31	42	61	69	48	62
	6.0	12	39	45	72	78	62	54
Sodium Sulfathiazole	3.0	12	16	22	42	48	32	43
	4.5	10	26	33	55	49	40	51
	6.0	10	34	38	60	66	53	50
Sodium Sulfadiazine	3.0	8	2	0	3	2	4	0
	4.5	10	2	—4	6	3	6	4
	6.0	10	4	8	8	6	4	5
Sodium Sulfamerazine	3.0	8	0	0	—3	—4	0	0
	4.5	10	2	6	4	3	4	8
	6.0	8	4	7	2	7	3	7

manifestations were not observed with the doses employed. Control animals were given an amount of vehicle (.9% NaCl) equal to that used in the treated animals. Following intervals ranging from ¼ to 18 hours, the head was quickly isolated and the ensuing gasps were mechanically recorded by a technique previously described. Deviations from control values were expressed in percent.

Results and Discussion. The results for periods 1 to 3 hours after injection (Table I) show that a significant increase in the total survival time and in the number of gasps of the anaerobic series followed the injection of sulfanilamide or sodium sulfathiazole. Although the total expenditure of energy was not accurately determined, it is apparent that the overall energy liberation for both of these drugs was definitely increased. Neither sodium sulfadiazine nor sodium sulfamerazine was similarly effective in doses equal to those employed for sulfanilamide or sodium sulfathiazole. While the chief effect of the latter drugs was on anaerobic activity, aerobic series being entirely unchanged, the interseries interval was frequently prolonged (average about 35%). Periods less than 60 minutes between injection and decapitation had little or no influence on the gasping pattern; likewise periods greater than 12 hours were without demonstrable effects. Accessory gasps, which appeared in the middle and last third of the anaerobic series, were partly responsible for the marked increase in the total number of gasps. Larger doses (8-10 mg) frequently increased the number of accessory gasps without increasing further the duration of survival.

Although rhythmic, the accessory gasps were smaller and 4-5 times more frequent than the normal or dominant ones. Occurring between the regularly spaced dominant gasps, they produced a striking staircase pattern, which was of two types. In a majority of cases they showed a progressive increase in amplitude until a gasp of normal size occurred, after which this pattern was repeated 3 to 5 times. Contrasted to this "step up" type of accessory gasping was a less frequently occurring "step down" type—in which there was a gradual decrease in amplitude until a dominant spike occurred; as in the other type, the pattern was repeated several times. The accessory gasps of either type were out of phase with or independent of the dominant gasps, which usually were more widely spaced than normal.

The accessory gasps may be due to multiple ectopic pacemakers, or to recirculation of excitatory waves over one or more pathways by a process analogous to that involved in the

circus movements of the heart. Such changes in impulse formation or conduction probably represent an imbalance between the various substrates and enzymes implicated in the release of energy through glycolysis, which is known to proceed over an intricate chemical pathway involving numerous stages. High concentrations of the effective sulfa drug may alter impulse initiation or propagation within the reticular gray matter of the medulla by disturbing the enzyme-substrate relationship in one or more stages, and in this way modify the development of the unstable chemical-nervous state necessary for "toppling."[5]

It is not clear why the drugs increase the anaerobic survival. It is possible that depression of certain enzymes diminishes the rate of release of anaerobic energy and thus permits continued utilization of a limited amount of available fuel. However, the apparent increase in overall energy liberation would seem to speak for an enhancing action of certain enzyme systems and an increase in utilizable fuel.

Nor is it clear why sulfanilamide and sodium sulfathiazole were effective in producing the results described while equivalent amounts of sodium sulfadiazine and sodium sulfamerazine were not.

Summary. Sulfanilamide and sodium sulfathiazole in non-toxic doses prolonged the survival of the anaerobic activity of the respiratory center of young rats and increased the overall energy release. Neither sodium sulfadiazine nor sodium sulfamerazine acted similarly.

[5] Bard, P., *Macleod's Physiology in Modern Medicine*, C. V. Mosby Co., St. Louis, 1941, p. 555.

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Recovery of Creatinine After Ingestion and After Intravenous Injection in Man.

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It is a known fact that not all the creatinine administered by mouth is excreted in the urine.[1] The amount so excreted is at most 80% of the quantity ingested and is usually less. Although no satisfactory explanation has been offered for this incomplete recovery, creatinine is regarded by many as a waste product of metabolism.[1,2] The possibility that a small amount of creatinine may be destroyed by intestinal bacteria has been mentioned by some investigators.[3] From the fact that creatinine is not stored in the tissues, these same investigators conclude that such creatinine as is not excreted undergoes some transformation in the body.[3] This conclusion, however, is not valid unless it is proved that creatinine is completely absorbed by the intestine. The possibility that part of the ingested creatinine may not be absorbed has received practically no consideration.

We have studied the recovery of administered creatinine in several human subjects. One of these subjects (G.N.B.), as treatment for a chronic ulcerative colitis complicated by hemorrhages, had a permanent ileostomy near the cecum. This operation severed the continuity of the intestine. At the time of the experiments, the fistula was working well, hemorrhages had ceased and the man was in apparent health. Another subject (W.K.) was studied on 3 occasions. At the time of the first 2 experiments he was in good health, but at the time of the last experiment he was greatly emaciated because of a carcinoma of the esophagus. The other subjects were either volunteers in perfect health or ambulatory

[1] Hunter, A., *Physiol. Rev.*, 1922, **2**, 586.

[2] Bloch, K., and Schoenheimer, R., *J. Biol. Chem.*, 1939, **131**, 111.

[3] Beard, H. H., *Creatine and Creatinine Metabolism*, Chemical Publishing Company, Inc., Brooklyn, N.Y., 1943.