previous injections. In 2 of these animals, no symptoms were visible until 40 cc. had been injected, while after 45 cc. the reaction was marked but consisted only of vomiting and passage of feces. In the third dog, these symptoms were not present until the injection of 60 cc. Electrocution was performed one-half hour later, and this time post-mortem examinations revealed perfectly normal gall bladders. A comparison of the results in the 2 series of animals leads us to the conclusion that the reaction obtained after the last injection in the first series was an anaphylactic response, since it required much less albumen to produce a response in the previously sensitized dogs than in the control animals. Furthermore, the constriction of the arterioles in the liver in the first series of animals is suggestive of anaphylactic change.

8208 C

Effects of Phenacetin and Aspirin Respectively upon Action of Phenobarbital.

ALFRED GILMAN AND HENRY G. BARBOUR.

From the Department of Pharmacology and Toxicology, Yale University.

Some practical advantages of combining an analgesic with a hypnotic drug have been suggested by the work of Loewe and others. In particular, Käer and Loewe[1] investigated the hypnotic and toxic effects of members of 2 different analgesic groups in combination with barbital, namely, aspirin and phenacetin.

Aspirin was found to antagonize to a similar extent both the hypnotic and toxic effects of barbital. Phenacetin, on the other hand, while also antagonizing the toxic effects of barbital, appeared to enhance the milder hypnotic effects of the latter drug. This would suggest a better "therapeutic ratio" for a mixture of barbital and phenacetin than for barbital alone. In addition, such a mixture would have the additional therapeutic advantage of supplementing the hypnosis with analgesia.

We have completed an investigation along this line in which aspirin and phenacetin have respectively been used in combination with another member of the barbiturates, namely phenobarbital.

Rats were used as experimental subjects. The animals were

[1] Käer, E., and Loewe, S., *Arch. f. exp. Path. und Pharm.*, 1926, **116**, 140; 1926, **118**, 108.

fasted 24 hours before the administration of the drugs which were given by stomach tube. Phenobarbital was administered in solution in the form of the magnesium salt. In those experiments in which an analgesic was added, it was suspended in 2% acacia in the phenobarbital solution. To make all experiments comparable, 2% acacia was also added to the magnesium phenobarbital. In all cases the volume administered was kept constant (1.0 cc./100 G. rat), increased dosage being accomplished by increasing the concentration of drug in solution or suspension. All narcotized animals were kept in a warm room (constant at 31°C.) to minimize heat loss while anesthetized.

Phenobarbital was administered at 2 levels of dosage, minimal and toxic, the lower level to determine the effect of the addition of an analgesic upon the minimal hypnotic dose, the higher level to ascertain the toxicity of the combination of drugs. The proportion of phenacetin to phenobarbital was 5:1 by weight, the analgesic being given in the higher dosage. This proportion represents the ratio of the average therapeutic dosage of the drugs.

Results. Minimal hypnotic dose. It was found that magnesium phenobarbital when fed orally to rats in amounts of 25 mg./kilo produced symptoms of excitement followed by slight hypnosis. The administration of 50 mg./kilo produced more pronounced effects, the animals remaining depressed for several hours.

The addition of acetyl salicylic acid in amounts equal to the phenobarbital proved definitely antagonistic. Thus animals receiving 50 mg./kilo of magnesium phenobarbital plus 50 mg./kilo of aspirin failed to show signs of any excitement or depression.

On the other hand, the combination of phenobarbital plus 5 times the amount of phenacetin behaved in exactly the same manner as the phenobarbital controls. Rats receiving 25 mg./kilo of magnesium phenobarbital plus 125 mg./kilo of phenacetin showed excitement and slight hypnosis, whereas double this amount produced a depression lasting for several hours.

Toxic doses. In view of the fact that phenacetin was in no way antagonistic to the hypnotic action of phenobarbital, a large series of animals was fed toxic amounts of these 2 drugs in the same 5:1 ratio to determine the effect of the addition of the analgesic upon the toxicity of phenobarbital. The results are summarized in Table I. As can be seen from the table, the combination of phenacetin and phenobarbital proved to be less toxic than phenobarbital alone.

No difference could be observed between the 2 groups of animals

TABLE I.
Comparative Toxicity of Magnesium Phenobarbital and Magnesium Phenobarbital Plus Phenacetin.

Dose Mg. Phenobarbital mg./K	Phenacetin mg./K	No. Rats	Deaths 12 hr.	24 hr.	48 hr.	72 hr.	Total	%
200		30	1	—	1	—	2	7
225		30	—	5	—	—	5	17
250		10	3	—	1	—	4	40
275		10	3	2	—	—	5	50
300		10	3	1	—	1	5	50
Total		90	10	8	2	1	21	23.5
200	1000	30	—	—	1	—	1	3
225	1125	30	3	—	1	1	5	17
250	1250	10	1	—	1	—	2	20
275	1375	10	2	—	—	—	2	20
300	1500	10	1	1	—	—	2	20
Total		90	7	1	3	1	12	13.5

with respect to the time of onset of hypnosis, the duration of anesthesia, and the recovery period.

Conclusion. The above results confirm for phenobarbital those reported by Loewe for barbital. It is apparent that when an analgesic is given simultaneously with a hypnotic drug, care must be exercised in the choice of the former. Thus, whereas acetyl salicylic acid antagonizes the hypnotic action of phenobarbital, phenacetin in no way diminishes its activity. Furthermore, the evidence shows that phenacetin may exert a protective influence by antagonizing the toxic effects of phenobarbital.

8209 C

Effect of Diet upon Blood Phosphorus Partition of Rats with and without Insulin.

NATALIE VAN CLEVE AND AGNES FAY MORGAN.

From the Laboratory of Household Science, University of California, Berkeley.

Beginning with the work of Harden and Young and followed by that of Embden and his associates, it has been evident that phosphorus may play some rôle in the oxidation of carbohydrate. This idea became more fixed after the isolation of insulin when it was shown that not only blood sugar but also urine phosphate and blood