The recovery times shown in Table I, which furnish a rough index of the relative persistence of action of the compounds, indicate that they are all rather short acting. The longest acting of the new compounds has a duration of action of the same order as that of pentobarbital; the shortest acting, of the same order as that of evipal.

The first 3 of the new compounds show a brief delay in the full development of anesthesia after an intravenous injection. In the mice receiving the dose 1.25 times the AD 50, the mean lag for these three compounds was, respectively, 3 min, ½ min, and 5 sec. The other 4 new compounds had no appreciable lag.

Early work with the barbituric acids led to certain inferences regarding the relation between structure and activity. It is these generalizations, doubtless, that have discouraged further investigation of derivatives of the type presented here. For example, the generalizations arrived at by one worker in this field[2] included these: (1) That the sum of the carbon atoms in the 2 substituent groups in the 5-position is 7 in the most effective compounds; (2) that the greatest dissimilarity in the 2 groups gives the greatest activity; (3) that if both groups are larger than ethyl, less effective compounds result. The activity of the compounds studied here shows that none of these rules is generally applicable.

Summary. The anesthetic activity in mice of seven new 5,5-dialkyl-barbituric acids has been studied. Intravenous anesthetic doses, intraperitoneal anesthetic doses, intraperitoneal lethal doses, and duration of action were measured.

13756

Nature of the X-ray Effect in CO Recovery.*

JOHN A. CAMERON. (Introduced by C. W. Turner.)

From the Department of Anatomy, University of Missouri, School of Medicine, Columbia, Mo.

Rapid recovery from severe carbon monoxide poisoning under X-ray treatment[1, 2] and spectrographic evidence of the reduction of

2 Shonle, H. A., *Ind. Eng. Chem.*, 1931, **23**, 1104.

* This study was aided by a grant from the Research Council of the University of Missouri.

1 Cameron, John A., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 29.

2 Cameron, John A., *Radiology*, 1941, **36**, 486.

blood CO after X-ray treatment[3] have previously been reported. A recent publication has described progressive discontinuous stages of decreased resistance to CO among young rats and rabbits during the first few days after birth.[4]

Some attempts have lately been made to determine the factors responsible for these phenomena. Each of several kinds of effects has been considered and there may be others not yet investigated.

The release of reserve red cells from the spleen in response to X-ray injury to circulating cells has often been described,[5] but a latent period, or lag, of 6 hours or more is associated with this process. In CO recovery the effect must be maximal within so short a time after the onset of asphyxia that the release of this reserve seems to be ruled out.

Possible recombination of CO and O_2 in the blood and tissues to form CO_2 and reduce the amount of CO present was checked in 12 experiments carried on in CO and O_2 saturated water at body temperature. In none of these tests was the amount of CO_2 (determined as carbonate) significantly increased by X-ray exposures of 500-2,000 *r*. Actual differences in cc of standardized HCl used were: 0.4-0.55; 0.45-0.5; 0.07-0.27; 0.35-0.3; 0.45-0.42; 0.4-0.25; 0.18-0.1; 0.1-0.15; 0.2-0.25; 0.1-0.05; 0.2-0.15; 0.3-0.41, an average of 0.09 when a difference of 0.2 might be significant. Dr. Daniel Mazia and Dr. Lloyd B. Thomas kindly advised me in this work. Dr. L. J. Stadler, of the U. S. D. A. and the Department of Field Crops, University of Missouri, generously provided the X-ray services for the work discussed here.

A series of experiments with whole blood of Rhesus monkeys, saturated with CO by shaking in a flask while connected to a tank of CO were next undertaken. Half of each CO saturated sample was placed in each of 2 petri dishes and 1 was exposed to 650-1000 *r*. Spectrographic analysis by Dr. Victor Ells showed no significant difference in the CO content of X-rayed and control samples. Actual readings were 1.17-1.21; 0.90-0.96; 1.11-1.117; 1.47-1.48; 1.17-1.21; and 1.31-1.40; an average difference of 0.05 when a difference of 0.10 is necessary for significance.

The reduction of CO in the blood of intact animals is almost always accompanied by striking changes in the depth and frequency of breathing. The inspirations of animals in deep CO coma are not only much shallower but much less frequent than in similarly

3 Cameron, John A., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 558.

4 Cameron, John A., *J. Cell. and Comp. Physiol.*, 1941, **18**, 379.

5 Downey, Hal, *Handbook of Hematology*, 4 Vol., New York, 1938.

exposed animals after X-ray. The spikes on the kymograph records of "CO plus X-ray animals" are 3 to 5 times as high as those on the records of "CO animals." In monkeys[2] the rate of inspiration per minute was 78 for "CO animals" and 132 for "CO plus X-ray animals." (Average of data from 6 pairs of experimental animals). These observations suggest that the X-ray effect is brought about by stimulation of the nervous system to produce greater and more effective ventilation at the critical time during recovery.

In newborn rats and rabbits the survival time in CO is 10 times that of the adults, or even more. During the first weeks of life the survival times decrease by 5 discontinuous steps to the adult level.[4] These shifts in susceptibility take place during the early postnatal period when the development of the nervous system is being completed. The longer survival in CO of younger subjects may be due to the greater resistance of the respiratory center in control during early life. The abrupt changes to shorter survival periods can perhaps be correlated with the shifting of respiratory control to higher and more delicate centers with increase in age.

When revival by X-ray treatment is attempted on rats and rabbits under 8 days of age no favorable results are obtained. In 20 littermate pairs of rats and 19 littermate pairs of rabbits between 1 and 8 days of age no significant prolongation of life among the X-rayed animals was noted. This seems to support the concept of respiratory center stimulation rather than that of direct effect on the respiratory chemistry of the organism. Apparently CO inhibition of the center of respiratory control in very young animals is not subject to X-ray reversal.

It is suggested that during the process of CO poisoning in older animals the respiratory centers may be successively inhibited from higher to lower, reversing the sequence by which they assume control during the first 3 weeks of life.[4] Inhibition of the usual center of respiratory control in older animals by CO may then be subject to X-ray relief because the X-ray excites to temporary functional activity centers early discarded by the developing animal. These centers need only remain active until the usual adult centers have recovered sufficiently to resume their normal rôle.