Klein, The Wilson Laboratories, Division of Wilson and Company, Chicago, Ill.

The methionine and glycine were obtained through the courtesy of Dr. Julius Johnson, The Dow Chemical Co., Midland, Mich.

The dried whey was supplied through the courtesy of the Western Condensing Co., Appleton, Wisc.

The liver extract (reticulogen) was supplied by Lilly Laboratories, Indianapolis, Ind.

Received December 1, 1950. P.S.E.B.M., 1951, v76.

Effects of Oxygen, Analeptics, and Artificial Respiration on the Toxicity of Procaine.* (18388)

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The introduction into the blood stream of procaine in sufficient amount to cause a sudden high concentration is thought to cause circulatory collapse or "cardiac death," while a gradual increase in blood procaine produces first a central stimulation which is followed by depression with eventual respiratory failure(1-4). If this be true the most frequent cause of death from slow intravenous infusions of procaine should be respiratory failure. Such has been reported to be the case (5-8), although cardiac and respiratory failure may occur almost simultaneously(2,9). Experiments designed to study the effect of anesthesia and the rate of injection on blood levels and toxic reactions during intravenous infusions of procaine permitted preliminary observations on the cause of death from such administrations. In 81 out of 83 experiments on dogs, the heart continued to beat for from 30 seconds to 8 minutes after respiratory movements ceased. In the other 2, heart apparently stopped at the same time as respiration. It is of interest that these 2 dogs were anesthetized with ether, which has been shown to sensitize animals to procaine(10,11). These observations stimulated us to study in more detail the cause of death from slow intravenous infusions of procaine and to evaluate experimentally the therapeutic effectiveness of analeptics, oxygen, and artificial respiration.

Experimental. Controls. Eleven experiments were run in which the dogs breathed air. Blood pressure and respiratory movements were recorded on a kymograph by means of a mercury manometer and a Manning pneumograph. The condition of the heart was also checked with a stethoscope and respiratory movements by close observation of the animal. Ether was administered to produce light anesthesia for from 30 to 45 minutes before the procaine infusion was started. The procaine hydrochloride was injected as a 1 to 5% solution in normal saline by way of the right femoral vein at a constant rate of 2 mg/kg/min. The infusion of procaine was continued until respiratory movements ceased, at which time it was stopped. The ether was discontinued when the procaine infusion was started and thereafter was administered in the minimal amount

* This research was supported in part by a contract with the Office of Naval Research.

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TABLE I. Oxygen and Analeptics on the Toxicity of Procaine.

Exp. procedure	No. of dogs	Mean			
		Time of resp. failure, min.	Survival time after resp. failure, min.	Blood levels mg %	
				Procaine	P.A.B.A.
Ether-air	11	21.6 ± 4.3	1.7 ± .3	3.22 ± .3	0.66 ± .14
Ether-oxygen	10	44.3 ± 5.1	5.1 ± .5	5.78 ± .4	1.13 ± .10
Ether-oxygen nikethamide	11	37.8 ± 4.9	3.9 ± .35	4.65 ± .46	1.18 ± .10
Ether-oxygen metrazol	10	42.8 ± 5.8	3.6 ± .7	4.80 ± .4	1.29 ± .34
Ether-oxygen picrotoxin	6	38.0 ± 6.3	4.2 ± .5	4.93*	1.19*
Ether-oxygen lobeline	2	35.0‡	3.5	†	†
Ether-oxygen continued	4	47.0‡	18.2	5.2	0.94

* Only 3 blood obtained. † Bloods not obtained. ‡ Number too small.

necessary to prevent voluntary movements. The times for both respiratory and cardiac failure were noted. At the moment of respiratory failure, blood was obtained from the left femoral vein and its content of procaine and p-aminobenzoic acid determined by a modified Bratton-Marshall method for sulfonamides (12).

Oxygen. Ten dogs were treated in the same manner as the controls with the exception that they were allowed to breathe 95% oxygen at atmospheric pressure. A constant flow of oxygen was employed and rebreathing was not permitted. The oxygen was administered from the start of the procaine injection until respiratory failure, at which time the oxygen was discontinued.

Analeptics. Other groups of dogs received in addition to oxygen, intravenous injection of analeptics as soon as possible after complete cessation of all respiratory movements. The dose of these drugs varied and was given either as a single injection or in divided amounts at 30 second intervals. The total amounts of the drugs given, expressed as mg/kg were as follows: Nikethamide, 70 to 500; Metrazol, 25 to 150; Picrotoxin, 1 to 10; and Lobeline 0.4 to 0.9.

Artificial respiration. Series A. Three experiments were performed in which oxygen was administered under slight pressure. This procedure was the same as those with the oxygen experiments except that the oxygen was continued after respiratory movements had stopped. Series B. Three experiments were performed as under oxygen with the institution of artificial respiration at respiratory failure. In these experiments the procaine infusion was not stopped until the blood pressure had fallen almost to zero. Series C. Eight dogs were infused with procaine in the same manner as the controls. After the respiratory movements had stopped, and a blood sample had been taken, the blood pressure was carefully watched until it began to fall rapidly and the heart sounds became weak. At this point artificial respiration was started in an attempt to save the animal.

Results. A summary of the results obtained from the experiments with air, oxygen, and analeptics is given in Table I. In all experiments the heart continued to beat after respiratory movements ceased. The length of time that the heart continued to beat varied from 1 to 8 minutes, and all animals failed to recover. The individual values obtained for survival times and blood concentrations also showed considerable variation. In general the blood concentrations of both procaine and p-aminobenzoic acid were higher the longer the infusion was continued. These findings

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confirm our earlier reports(11,13,14). It is evident, however, from the standard errors of the means that there was a true difference between the groups breathing oxygen and the control group breathing air. The animals receiving oxygen required twice the amount of procaine to produce respiratory failure as did the controls. The length of time that the heart continued to beat after respiratory failure was also prolonged by oxygen. This beneficial effect of oxygen on the heart was much greater when the oxygen was continued under slight pressure until cardiac failure. It can also be seen from Table I that the addition of stimulant drugs was without effect, even though the dose of the drugs was large enough to produce twitching in at least half the cases.

In the experiments where artificial respiration was instituted at the time blood pressure began to fall rapidly, 6 of the 8 animals recovered after from 3 to 18 minutes of artificial respiration. Two animals failed to recover but here the artificial respiration was withheld for 3 and 4 minutes respectively, and the blood pressure had fallen almost to zero.

Further evidence that heart failure is, to a large extent, due to asphyxia was obtained from the three experiments (Table II) where artificial respiration was instituted as natural respiration failed and the procaine infusion was continued until heart failure. In 2 of the experiments the dogs received a continuous injection of 2 mg kg/min procaine HCl. In the first dog respiratory movements ceased after 18 minutes with a blood procaine level of 1.5 mg %. The artificial respiration machine was then connected and the injection of procaine continued at the same rate for 6 hours, at which time the experiment was terminated. The terminal blood levels are shown in Table II. No reflexes could be evoked during this time and the only symptoms were intermittent muscular tremors. In the second dog,

TABLE II. Artificial Respiration on the Toxicity of Procaine.

Dose of Procaine HCl mg/kg/min.		Time in min.		Terminal blood levels mg %	
Until resp. failure	With art. resp.	Resp. failure	With art. resp.	Procaine	P.A.B.A.
2	2	18	360*	3.3	16.7
2	4	12	153	26.7	20.8
4	8	12	43	27.0	5.4

* Experiment terminated dog in good condition.

respirations ceased at 12 minutes. As the artificial respiration was started the dose of procaine was doubled. The heart did not stop until 2 hours and 33 minutes later. The blood concentrations were 4.2 mg % procaine and 1.7 mg % p-aminobenzoic acid at the time of respiratory arrest. A third dog was studied by the same experimental procedure with the difference that 4 mg/kg/min procaine was given until respiratory failure and then 8 mg/kg/min until the heart stopped. Respiratory movements ceased at 12 minutes and the heart continued to beat for another 43 minutes. The blood levels for procaine in the second and third dogs were more than twice as high as any fatal levels(11) seen in dogs not receiving artificial respiration (Table II).

Conclusions. 1. The primary cause of death from intravenous procaine when used as an adjunct to general anesthesia is hypoxia due to respiratory failure. 2. If hypoxia is great at the time of respiratory failure, heart failure may occur almost simultaneously. 3. Nikethamide, Metrazol, Picrotoxin, and Lobeline are of no value in respiratory failure resulting from prolonged intravenous infusions of procaine. 4. Oxygen administration and artificial respiration are life saving if instituted promptly.

The technical assistance of Dale Mattmiller, Daniel Kahle, and John Preston is gratefully acknowledged.

Received December 5, 1950. P.S.E.B.M., 1951, v76.

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