CLINICAL AND EXPERIMENTAL STUDIES ON PARALDEHYDE * †

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THE use of paraldehyde as a hypnotic was introduced, nearly sixty years ago, by Cervello (1) of Palermo and Strahan (2) of Northampton. The drug gradually acquired a measure of popularity and, nowadays, is used quite extensively for sedation in alcoholics, psychoneurotics and others, and especially as an analgesic and amnesic in obstetrics, where it is given rectally, or orally, frequently in combination with some other drug, such as benzyl alcohol, morphine, sodium amytal, pentobarbital, or ether.

On the basis of toxicologic and pharmacologic studies, as well as clinical experience, paraldehyde is regarded as a relatively safe and nontoxic drug. However, that it is not altogether without danger has been brought out in several reports. A case described by Kotz, Roth and Ryon (3), in 1938, presented the following features: The patient, while in labor, was given 31 cc. of paraldehyde by rectum. Ten minutes later she was in deep sleep; the respiration and heart rates increased and within a half hour she became cyanotic and went into coma. Soon, cardiac failure developed. Death occurred 8 hours and 20 minutes after the paraldehyde was given.

A somewhat similar case was reported by Jinkins and Herrod (4). The patient was a 27-year old white primigravida, who had been followed since the sixth week of pregnancy. The only abnormalities noted, antenatally, were a rapid pulse ranging from 90 to 130, electrocardiographic evidence of a sinus tachycardia, and a slight albuminuria during the last month of pregnancy, which cleared on a low-protein, salt-poor diet. On admission to the hospital on Nov. 7, following rupture of the membranes, the physical findings were normal except for a blood pressure of 140/100. Labor began the following day at 6:15 a.m. and progressed normally; at 3 p.m. the pains were regular and of good quality, lasting 45 seconds. At 3:15 the patient was given, rectally, 24 cc. of paraldehyde in 60 cc. of olive oil. During the instillation of the enema the patient complained of tingling of the hands and feet and of numbness over the entire body. She fell into a deep sleep ten minutes later and remained in this condition until 7:30 p.m. when the pulse became weak and thready. The rate increased from

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90 to 112 and the respirations from 20 to 28. A catheterized specimen of urine contained 1+ albumin, coarse and finely granular casts and an abnormal number of pus cells. At 9:25 p.m. the pulse was estimated at 160. Coramine and caffein sodio-benzoate were given hypodermically and 50 cc. of 50 per cent. glucose intravenously. Respirations became more labored. The patient, now deeply comatose, was placed in an oxygen tent. Further therapeutic measures included: caffein and sodio-benzoate, repeated at 10:55 p.m.; ephedrine gr. ¾, and atropine gr. 1/100 at frequent intervals during the night; glucose and saline intravenously. At 2:15 p.m. the following day, the patient had a slight convulsion; the pulse was 150 and respirations 54 per minute. At 3:15 p.m., or 24 hours following the administration of the paraldehyde, the patient was essentially moribund, although the twitchings of the hands and movements of the arms and legs were noted. A cesarean section was performed without further anesthesia. A living female infant was delivered without difficulty and responded quickly to slight stimulation. The patient seemed to withstand the operation rather well, though the respiration continued to be rapid (62 per minute). Caffein, coramine and ephedrine were given at 4:30 p.m. A blood transfusion was given at 5:30 p.m. The oxygen tent was removed. Other postoperative measures included administration of morphine and of glucose and saline intravenously and by hypodermoclysis. At 8:30 the following morning (41 hours after becoming comatose) the patient responded to questions. At 9 a.m. the CO_2-combining capacity of the blood was found to be 34 volumes per cent Hartman's solution (1500 cc.) was given in the morning and repeated at 7:15 p.m.

The subsequent course was stormy, owing to development of aspiration pneumonia, followed by empyema. However, after a short period of convalescence in the hospital and a longer period at home, the patient recovered and now seems perfectly well. The infant developed severe diarrhea on the seventh and succumbed on the eighteenth day.

The two instances just cited illustrate that severe and even fatal intoxication may follow the administration of moderate doses of paraldehyde. Other cases include the two cited by Leschke (5); in one, death resulted from the ingestion of 25 Gm. of the drug, and in the other from the ingestion of 52 Gm. Two fatalities in children due to overdosage have been reported from Australia (6). It may be assumed that there have been other instances of fatal paraldehyde poisoning which were not recorded in the literature. On the other hand, recovery is known to have occurred following the administration of 100 Gm. (Underhill 7), and even of 150 Gm. (Leschke 5) of paraldehyde.

The fact that paraldehyde is a comparatively safe drug may explain why it has not been more thoroughly investigated. Kotz, Roth

and Ryon (3) described their case as one of idiosyncrasy to paraldehyde, although they clearly pointed out that the heart failure could be explained on an anatomical basis. Necropsy in their case also revealed a toxic hepatitis of long standing. In considering the second case it seemed to us (J. L. J. and M. B.) that even if the hypersusceptibility to the paraldehyde were due to causes, as yet unknown, the possibility that liver impairment may have been a factor in limiting the destruction of the drug, and, therefore, in intensifying and prolonging its action, could not be ignored.

The empiricism which has characterized the use of paraldehyde is also evident from the fact that practically nothing is known concerning the concentrations attained in the blood following administration of the drug, or the concentrations which correspond to varying levels of consciousness. In view of these circumstances, investigation of the problem of paraldehyde narcosis from an experimental and clinical standpoint seemed justified.

Analysis.—Since the analytical procedure of Nitzescu, Georgescu and Timus (8) did not meet our requirements, a method was devised for the determination of paraldehyde in blood, urine and other biological fluids (Levine and Bodansky (9)). In this method the paraldehyde is removed from the fluid under specified conditions by vacuum distillation and bubbled through a standard potassium dichromate-sulfuric acid oxidizing mixture. The excess dichromate is titrated iodometrically with sodium thiosulfate.

In collecting blood for analysis alcohol sponges should not be used, nor should alcohol be used in sterilizing the needles. Alcohol, like paraldehyde, is oxidized by dichromate, and therefore, its presence as a contaminant in the blood specimens would give erroneously high values.

Fate of Paraldehyde in the Body. As reviewed elsewhere, the fate of paraldehyde in the body is a subject obscured by contradictory opinions. Thus, Solis-Cohen and Githens (10) have remarked: "Little destruction occurs in the body, the drug being eliminated very slowly, chiefly by the lungs." Kane and Roth (11) have stated: ". . . it almost wholly escapes combustion, the greater part being excreted as paraldehyde, mainly in the lungs and kidneys." Cushny (12) thought that paraldehyde was excreted mainly in the urine and in part by the lungs. According to a report by Nitzescu, Georgescu and Timus (13), rats given intraperitoneal injections of paraldehyde, excreted 100 per cent. of the drug via the lungs in ten hours. They found that in rabbits the pulmonary excretion was considerably less, 22.8 per cent. on a dose of 1 Gm. per Kg. of body weight. Defandorf (14) found that during a 7-hour period following the administration of paraldehyde (1.8 Gm. per Kg. in dogs), the pulmonary excretion amounted to only 2.8 per cent. and the urinary excretion to 1.3 per cent.

The last values for pulmonary excretion are considerably lower

than those obtained in our laboratory under experimental conditions which assured the recovery of practically all the paraldehyde excreted in the expired air and in the urine (15). Normal dogs given 1.0 Gm. per Kg. excreted an average of 13.2 per cent. by the lungs and 1.0 per cent. by the kidneys. On a dose of 1.5 Gm. per Kg. the pulmonary excretion was 22.9 per cent. and the urinary excretion 2.1 per cent. On a dose of 2.0 Gm., the pulmonary excretion averaged 28.8 per cent. and the urinary excretion 1.1 per cent.

Comparable doses given to liver-damaged dogs invariably resulted in a greater percentage of pulmonary excretion: averages of 25.9 per cent. on a 1 Gm./Kg. dose, 28.8 per cent. on a 1.5 Gm./Kg. dose; 37.0 per cent. on a 2 Gm./Kg. dose. The urinary excretion for all liver-damaged animals was 2.1 per cent., compared to 1.1 per cent excreted by the normal controls.

The data just presented show that the greater part of paraldehyde is destroyed in the body, and since such destruction is quantitatively less in the presence of hepatic disease, it may be assumed that the liver is involved in the metabolism of the drug. This does not necessarily exclude the participation of other organs either in removing the paraldehyde from the circulation or in its destruction. However, experiments now in progress (Levine, Seybold and Kahler (16)) indicate that the kidneys are of limited importance with regard to destruction of paraldehyde. The blood paraldehyde curve following its administration is essentially the same the day following bilateral nephrectomy as before operation.

The blood paraldehyde curve is significantly modified in the presence of liver damage (17). Though the maximum level may be no higher than that attained normally, the time required for the elimination of the drug is greatly prolonged, and is accompanied by a prolongation of the narcotic effect. These results are in keeping with the conception that hepatic insufficiency is possibly a major factor contributing to the hypersusceptibility displayed by some individuals to paraldehyde.

The possibility of utilizing paraldehyde in the determination of liver function is under investigation in our laboratory (Levine and Goldman (18)). In preliminary studies the following procedure has been used: At 8:00 p.m., after obtaining a specimen of blood for a control analysis, the patient is given, orally, a dose of paraldehyde equivalent to 0.335 cc. per Kg. of body weight (or 1.5 cc. per 10 lbs. of body weight). Specimens of blood are collected the next day, at 8 a.m., noon and at 8 p.m. (12, 16 and 24 hours after administration of the drug). The patient suffers practically no inconvenience, sleeps soundly during the night, is permitted a light breakfast consisting of 2 slices of toast, a boiled egg and a glass of milk and his regular meals at noon and in the evening. The patient's conscious state and disappearance of paraldehyde from the breath are noted, in addition to obtaining the blood paraldehyde values.

The hypnotic effect of the paraldehyde is more marked in patients with liver disease than in normal individuals. Disappearance of the drug, which is normally complete within 24 hours, is delayed. Ordinarily, little paraldehyde remains in the blood at 12 hours and none at the end of 24 hours, while in patients with liver disease the presence of paraldehyde in the blood persists. For example, in a patient with hepatic cirrhosis, the results were 13.7 mg. per 100 cc. at 12 hours, 12.9 mg. at 16 hours, 10.7 mg. at 24 hours, compared to 6.6 mg. at 12 hours and 0.0 at 16 hours in a patient without evidence of liver disease.

It is of interest to note that some patients with acute hepatitis in the regenerative phase were able to destroy paraldehyde more rapidly than normal, as shown by the rapid disappearance of the drug from the blood and the expired air.

Blood Paraldehyde Concentration in Obstetrical Analgesia.—There appear to be no published data concerning the concentrations of paraldehyde attained in the blood in obstetrical analgesia, although such use of the drug has been in vogue since 1932 (Rosenfield and Davidoff (19)). Since such data may be expected to contribute significantly to

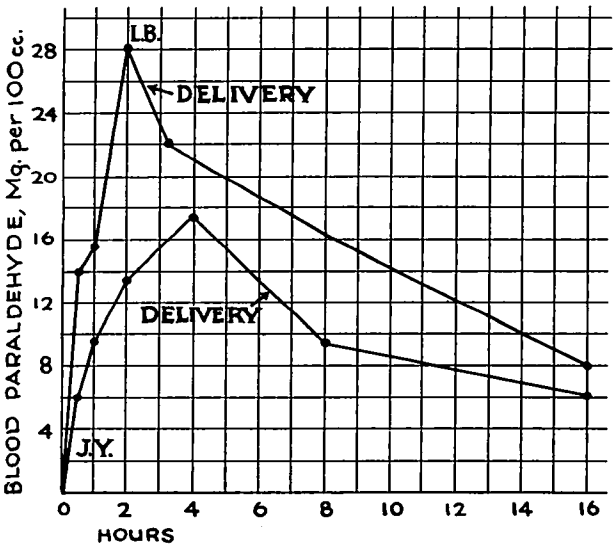

FIG. 1. Blood paraldehyde curves following a dose of 30 cc. of paraldehyde in 60 cc. of olive oil. J.Y.: rectal administration; L.B.: administration by nasal tube.

a fuller comprehension of the subject, particularly with regard to the relation, if any, of the blood paraldehyde level to the degree of analgesia and amnesia, a study has been made in this laboratory which has

been reported in more detail elsewhere (Gardner, Levine and Bodansky (20)). Here it will suffice to present for illustration the results obtained in two subjects (Fig. 1).

Subject J. Y. received a rectal administration of 30 cc. of paraldehyde in 60 cc. of olive oil. Subject L. B. received a similar dose by nasal tube. From the curves obtained we note that the blood paraldehyde rose to a higher level in subject L. B. than in subject J. Y. This difference in effect between rectal and gastric administration is usual, but not invariable. However, in both instances complete amnesia was produced until the time of delivery. No other sedatives were used. Patient L. B. (Para II) delivered without further anesthesia. From her curve, it may be assumed that the blood paraldehyde during delivery was in the neighborhood of 26 mg. per 100 cc., a value in close agreement with the concentration, 24.1 mg., in the cord blood. Patient J. B. received nitrous oxide during delivery. From her curve it may be judged that the blood paraldehyde at the time of delivery was somewhere in the neighborhood of 12 mg. per 100 cc. The cord blood in this case contained 9.8 mg. of paraldehyde per 100 cc. The maximum concentrations attained were 28.2 mg. in the case of L. B. and 17.5 mg. in the case of J. Y. The highest concentration encountered so far in any patient has been 33.2 mg. per 100 cc., obtained 2 hours after administration of the drug.

Therapeutic Measures.—In dogs, metrazol is definitely a better analeptic than picrotoxin in antagonizing paraldehyde narcosis. Animals in coma resulting from the administration of the drug (1.5 cc. per Kg. of body weight) were promptly aroused to a standing position, without development of convulsions, by intravenous injection of 50 mg. of metrazol per Kg. of body weight. However, the metrazol did not accelerate the removal of paraldehyde from the blood. Picrotoxin was much less effective, it being necessary to give this drug to the point of moderate convulsions before the animals could be aroused, and even then they were unable to stand up.

The clinical use of metrazol in paraldehyde narcosis has been briefly noted by Burstein and Rovenstine (21).

Clark and Morrissey (22) have reported that insulin and glucose accelerate the oxidation of alcohol. (Compare, however, with Mirsky and Nelson (23).) A similar study in our laboratory of the effect of these agents in paraldehyde narcosis yielded negative results with regard to the rate of disappearance of the paraldehyde from the blood. No analeptic effect was demonstrable.

SUMMARY

Paraldehyde has been generally recognized as a relatively safe drug, and it is perhaps for this reason that it has been so little investigated. Information concerning its fate in the body is meager and conflicting, and practically nothing is known concerning the concen-

trations of paraldehyde attained in the blood and tissues during narcosis; nor have the occasional instances of paraldehyde poisoning, some with fatal outcome, been adequately explained. Hypersusceptibility to paraldehyde, though seemingly rare, is nevertheless a problem which deserves serious consideration. While it is conceivably due to a multiplicity of unknown factors, there is experimental evidence that the ability of the liver to destroy paraldehyde is of outstanding importance in determining the intensity and duration of paraldehyde narcosis. In animals with hepatic insufficiency the concentration of paraldehyde remains at a high level for a longer period, disappearance of the drug from the blood is prolonged, and a greater amount is excreted by the lungs. Similar relations hold in man; in fact, the response to small doses of paraldehyde may serve as an index of liver function. The hypnotic effect of paraldehyde is more marked in patients with liver disease than in normal individuals. Doses ordinarily given for obstetrical analgesia and amnesia seldom produced a blood paraldehyde concentration of more than 30 mg. per cent. Metrazol effectively antagonizes paraldehyde narcosis, but does not influence the concentration of paraldehyde in the blood.

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MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS, INC.

STOUFFER'S RESTAURANT, 3 E. 57TH STREET, NEW YORK CITY

February 13, 1941—8 P.M. Dinner—7 P.M.

1. President's Address.
   By Ralph M. Tovell, M.D., Hartford Hospital, Hartford, Conn.
2. Case Report: Anesthetic Complications, Bellevue Hospital—3 minutes.
   By Mary Lou Byrd, M.D., Bellevue Hospital, New York City.
3. Laboratory and Clinical Fields for Investigation of New Anesthetic Agents—30 minutes.
   By Henry K. Beecher, M.D., Massachusetts General Hospital, Boston, Mass. Discussion to be opened by E. A. Rovenstine, M.D., New York City.
4. Certain Physiological Principles Underlying Resuscitation and Oxygen Therapy—50 minutes.
   By Albert R. Behnke, M.D., U. S. Naval Medical School, Washington, D. C. Discussion to be opened by Alvan L. Barach, M.D., New York City.

Subscription to dinner $2.00 per plate, proceeds of which will go to the British Anesthetists Fund. Funds are to be administered by the Associated Anesthetists of Great Britain and Ireland. Members of the medical profession are also invited. Members are urged to donate new or used equipment which will be sent to the British Anesthetists through the "Bundles for Britain," whose office is located in the Squibb Building, 745 Fifth Avenue, New York City.