FLUOROACETATE POISONING

A Review and Report of a Case

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DURING the war years intensive investigations were conducted in this country with the object of discovering a more effective rodenticide than had previously been available. As a result of these studies, sodium fluoroacetate (CH_2FCOON_a) was introduced as a rodenticide and reported on by Kalmbach.[1] During this early period of investigation the laboratory number "1080" was used to represent the compound. Since then, this number has been retained and sodium fluoroacetate is often referred to by this numerical designation alone in the literature on rat extermination.[2]

This compound has gained attention recently not only because of its economic and military importance as a potent rodenticide but also because its numerous important pharmacologic properties have engaged the interest of physiologists, biochemists and neurologists, as well as pharmacologists and toxicologists.

Sodium fluoroacetate lacks one of the properties desirable in an ideal rodenticide, i. e., innocuousness for man and domestic animals. It is a potent poison for all mammals, including man, and experimental study indicates it is one of the most poisonous substances known.

Much study has been devoted to the experimental poisoning of laboratory animals with 1080, but to our knowledge no case of human poisoning by fluoroacetate has been reported. Since the introduction of

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1. Kalmbach, E. R.: "Ten-Eighty," War-Produced Rodenticide, Science **102**:232, 1945.

2. (*a*) Ormsbee, R. A.: A Summary of Field Reports on 1080 (Sodium Fluoroacetate), Report no. 163, National Research Council, Insect Control Committee, Dec. 17, 1945; (*b*) Instructions for Using Compound 1080 (Sodium Fluoroacetate) as a Rodent Poison, ibid., July 1946. (*c*) Philips, F. S.: Symposium on Advances in Pharmacology Resulting from War Research: Insecticides and

1080 as a rodenticide, cases of human poisoning have been expected. Toxicologic studies in mammals, including monkeys, were conducted, and a search for an antidote was made.[3]

Marais [4] reported that monofluoroacetic acid is the toxic principle of Dichapetalum cymosum, a toxic plant which the South African farmers call "gifblaar." He found that 1.0 to 1.5 Gm. per kilogram of body weight orally of the dried plant is a lethal dose for rabbits.

The present paper reports a case of fluoroacetate poisoning in man, together with a brief review of experimental work on fluoroacetate toxicity which may have a bearing on the medical care of subsequent cases of human poisoning by this agent.

REPORT OF CASE

N. D., a 2 year old Negro boy, was admitted to the pediatric receiving ward of the Cincinnati General Hospital, apparently moribund, about six hours after he had licked the screw top of a bottle of rat poison. There were a few crystals left from the evaporation of the clear, colorless poison solution on the bottle top which the child had removed while playing. The parents did not know whether the child had drunk any of the solution, but they had found him licking the crystals from the stopper.

Rodenticides, Federation Proc. **5**:292, 1946. (*d*) Hughes, J. H.: Studies in Deratization of Surface Vessels by Means of 1080 (Sodium Fluoroacetate), Pub. Health Rep. **62**:933, 1947. (*e*) DuBois, K. P.: New Rodenticidal Compounds, J. Am. Pharm. A. (Scient. Ed.) **37**:307, 1948. (*f*) Gratch, I.; Purlia, P. L., and Martin, M. L.: Effect of Sodium Fluoroacetate (1080) in Poisoned Rats on Plague Diagnosis Procedures: Preliminary Reports, Pub. Health Rep. **64**:339, 1949.

3. (*a*) Chenoweth, M. B., and Gilman, A.: Studies on the Pharmacology of Fluoroacetate: I. Species Response to Fluoroacetate, J. Pharmacol. & Exper. Therap. **87**:90, 1946; (*b*) II. Action on Heart, Bull. U. S. Army M. Depart. **7**:687, 1947. (*c*) Chenoweth, M. B.: Pharmacology of Fluoroacetate, Federation Proc. **5**:171, 1946. (*d*) Chenoweth, M. B., and St. John, E. F.: Studies on the Pharmacology of Fluoroacetate: III. Effects on the Central Nervous System of Dogs and Rabbits, J. Pharmacol. & Exper. Therap. **90**:76, 1947; (*e*) Spike and Dome Formation Produced in Dog's Encephalograms by Fluoroacetic Acid, A. Research Nerv. & Ment. Dis., Proc. **26**:299, 1947. (*f*) Foss, G. I.: The Toxicology and Pharmacology of Methyl Fluoroacetate (MFA) in Animals, with Some Notes on Experimental Therapy, Brit. J. Pharmacol. **3**:118, 1948. (*g*) Ward, A. A., Jr.: Convulsive Activity Induced by Fluoroacetate, J. Neurophysiol. **10**:105, 1947. (*h*) Quin, J. I., and Clark, R.: Studies on the Action of Potassium Monofluoroacetate (CH_2FCOOK) [Dichapetalum Chymosum (Hook) Engl.] Toxin on Animals, Onderstepoort J. Vet. Sc. **22**:77, 1947. (*i*) Williams, A. T.: Sodium Fluoroacetate Poisoning, Hosp. Corps Quart. **21**:16, 1948. (*j*) Possible Treatment of Sodium Monofluoroacetate (1080) Poisoning, Surgeon Circular M. Sect. Far East Command **4**:9, 1949.

4. Marais, J. S. C.: Monofluoroacetic Acid, the Toxic Principle of "Cifblaar," Dichapetalum cymosum (Hook) Engl., Onderstepoort J. Vet. Sc. **20**:67, 1944; Chem. Abstr. **39**:4116, 1945.

Almost immediately after licking the screw top, the boy vomited, and he continued thereafter to vomit and retch frequently. Three hours after the ingestion a local physician was consulted because of persistent nausea and emesis. He prescribed a cathartic of unknown nature which the child vomited soon after administration. Vomiting and retching persisted; the child could retain no food or fluids, and about six hours after ingestion of the poison he began to have generalized convulsive movements and became stuporous. He was then immediately brought to the hospital.

The bottle of rat poison, brought by the parents to the hospital, contained several hundred cubic centimeters of a clear, colorless solution. The bottle was two-thirds full, and it was labeled in a handwritten script, "Rat Poison—1080." The nature of the poison was unknown to the parents, who had purchased it from a passing peddler two years previously.

Past History.—N. D. had previously been a healthy child. He had had a normal, full term, spontaneous delivery and an uneventful neonatal period. He had had no contagious diseases other than common colds. He had never had convulsions or any other neurologic disorder.

Emergency Therapy.—On his admission to the receiving ward, the child was in critical condition. Because of his critical state, only a cursory physical examination on admission could be done. He was in tetany, comatose and exhibiting carpopedal spasm and tetanic convulsive movements, irregular respirations and great cardiac irregularity. As an emergency measure, 0.5 Gm. of 5 per cent solution of calcium gluconate U. S. P. was given intravenously, and a continuous intravenous infusion was started with 150 cc. of isotonic sodium chloride solution U. S. P. During the administration of the calcium gluconate there were a few seconds of cardiac asystole, and thereafter the previous irregular cardiac rhythm was resumed, but at a much slower rate. The tetanic convulsive movements stopped immediately on the intravenous administration of the calcium gluconate, and the child became completely flaccid. About one-half hour later 120 cc. of milk containing 3 Gm. of added calcium chloride U. S. P. was administered by gavage, but shortly thereafter the boy vomited 80 cc. of this. Only at this time was it possible to make a more thorough physical examination.

Results of Physical Examination.—His temperature was 97.4 F. (rectum); the pulse rate was irregular, 40 to 50 per minute, and respirations were 26 per minute.

The boy was a well developed and well nourished Negro child in deep stupor, completely flaccid, with no muscle spasm. Convulsive movements had stopped. The skin was clear, and no lymphadenopathy was present. The eyes were deviated upward and to the right. The pupils were round and equal and reacted normally to light. Cardiac action was irregular and slow, and there was a soft apical systolic murmur. Blood pressure in the right arm with the child recumbent was 94 systolic and 70 diastolic (with a 2 inch [5 cm.] cuff). Respirations were shallow and somewhat irregular. The lungs were clear to percussion and auscultation. There was now no carpopedal spasm, and no Chvostek sign could be elicited. Deep reflexes were hypoactive, and the Babinski response was positive.

Therapy and Course.—The 150 cc. of isotonic sodium chloride solution was followed by administration of 2 Gm. of calcium gluconate in 700 cc. of 5 per cent dextrose solution by slow intravenous drip during the next twelve hours. A few hours after his admission the child became responsive and appeared to recognize his father. He continued to vomit most of the milk given in the receiving ward by gavage. Four hours after his admission a generalized tonic-clonic convulsion lasting several minutes occurred and was followed by deep postconvulsive coma from which

the patient could not be aroused. One hour later he became slightly responsive again, grunted and appeared to recognize his father but could not speak or sit up. After one hour he again had a generalized tonic-clonic convulsion and thereafter remained comatose during the entire night.

The nature of the rat poison the child had ingested was unknown. Since there was still the possibility that the poison contained arsenic, BAL (2,3-dimercapto-propanol) was administered intramuscularly at four hour intervals, 3 mg. per kilogram of body weight—the child's weight was estimated at 10 Kg.—for a total of five doses. Its use was then discontinued because analyses failed to reveal any arsenic or heavy metals in the rat poison.

Because it was strongly suspected from his gastric symptoms and tetany on his admission that the patient had fluoride poisoning, 1 Gm. more of calcium gluconate was administered through the constant intravenous drip, and thereafter no further calcium therapy was given.

On the day following his admission the child was limp and unresponsive. Breathing was regular. The gag reflex was present; deep tendon reflexes were active and equal. There was no stiffness of the neck. At frequent intervals, however, tonic convulsions occurred, during which the child occasionally groaned. At times spasticity persisted for several minutes, remaining longer on one side than on the other. His eyes wandered about; the pupils remained round, regular, equal and reactive to light. The child did not respond to painful stimuli until they were of severe intensity and then only groaned, showing no withdrawal response. The heart rate was 96 per minute. Cardiac rhythm remained irregular, with exaggerated sinus arrhythmia and many dropped beats, occasional periods of asystole or of complete arrhythmia (fibrillation) and infrequent runs of what appeared to be paroxysmal tachycardia. Intervals of normal rhythm occurred. Atropine U. S. P. was administered intramuscularly in a dose of 0.125 mg. which was repeated in fifteen minutes, twenty-one hours after his admission; this therapy was followed by a period of regular cardiac rhythm, with a pulse rate of 180 per minute.

The cardiac rhythm and the quality of cardiac sounds continued to change frequently during the first three days in the hospital. Tonic convulsions lasting several minutes occurred many times every hour—sometimes about every ten minutes for many successive hours. During the tonic convulsive spasms the pupils dilated and remained inactive to light. Between seizures the pupils were miotic and responsive to light. No carpopedal spasm or Chvostek sign could be demonstrated.

On the third day in the hospital the tonic convulsions gradually subsided, but the child remained comatose. Respirations were regular and shallow, but no cyanosis was present. The pulse became regular, with periods of pronounced sinus arrhythmia. In the afternoon the boy suddenly had a long period of apnea while a new constant intravenous infusion was being started. Artificial respiration was performed for three minutes, with an oxygen mask over the child's face, before his breathing was again resumed spontaneously. Later that day a second period of apnea occurred, during which artificial respiration was again required. In the interval respiration had become regular. A mechanical respirator was kept in readiness in the event of a third such episode, but its use was not required. In the evening the boy was noted to whimper on painful stimulus and to be slightly more responsive than previously.

On the fourth day the child remained unresponsive, with shallow, slow respirations (14 per minute). Administration of amobarbital (amytal®) had been stopped.

There was no cyanosis. His eyes wandered less but became divergent, and his pulse was full, with decided sinus arrhythmia. He lay stuporous and totally flaccid. No further tonic convulsions occurred.

In the evening of the fourth day—one hundred hours after ingestion of the poison—the child began to open his eyes and look about. He tried to talk but was unable to articulate. He could neither sit up nor reach for objects but appeared quite alert. During the course of a few hours a remarkable change in consciousness and responsiveness occurred. On the fifth and sixth days he rapidly regained all his motor ability, slowly lost his drowsiness and became articulate. On the evening of the sixth day he was clinically well. He was able to sit up and to play, and, according to his father, he could speak and perform as well as he could before his illness.

The constant intravenous infusion was continued until the morning of the fifth day, when the boy was finally taking fluids orally. Total fluid intake intravenously on the second, third, fourth and fifth days was 850, 1,450, 2,100 and 1,700 cc., given as 5 per cent dextrose solution except that 100, 200, 300 and 200 cc. of isotonic sodium chloride solution was administered on each of the successive days.

The boy was discharged well from the hospital on the eleventh day.

Laboratory Data.—Electrocardiograms were taken on the second, third, fourth and seventh days, but none were recorded during the periods of most serious arrhythmia. They revealed in all tracings a pronounced sinus arrhythmia. The P-R interval was 0.10 second and the QRS complex was 0.06 to 0.07 second, with the rate varying between 90 and 130 per minute on the respective recordings. One record revealed many premature ventricular contractions. On the third day, prominent T waves in leads I, II and IV were noted, with a Q-T interval of 0.34 second, and the S-T segment was elevated in all leads. On his discharge the electrocardiogram was normal.

During the hospitalization, results of four hemoglobin determinations ranged between 11.0 and 11.2 Gm. per hundred cubic centimeters and red blood cell counts between 4,000,000 and 4,300,000. The white blood cell count on his admission was 9,900, with 71 per cent neutrophils, 26 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. During the remainder of the course in the hospital, the white blood cell count ranged between 7,100 and 8,900, with 61 to 65 per cent neutrophils. Four uninalyses gave normal results, with no cells, casts or albumin, acetone or sugar present. On the third day serum chemical values were: 91.2 milliequivalents of chloride per liter, 6.4 mg. of phosphorus, 25 mg. of nonprotein nitrogen and 6 Gm. of total protein, per hundred cubic centimeters. Alkaline phosphatase measured 8.4 Bodansky units. On the fourth day, blood urea nitrogen was 21.1 Gm. per hundred cubic centimeters and chloride was 92.2 milliequivalents per liter.

Roentgenograms of the chest, skull and long bones all showed a normal appearance on the day before his discharge from the hospital, and teleroentgenograms of the chest revealed a normal cardiac shadow.

Lumbar puncture was performed on the second day, and an initial pressure of 170 mm. of water was noted. Dynamic pressure was normal, and 10 cc. of clear, colorless cerebrospinal fluid was removed. A cell count on this fluid revealed no red blood cells and 6 white blood cells per cubic centimeter, all lymphocytes. The Wassermann reaction of the fluid was negative. There were 28.8 mg. of protein and 111 mg. of sugar per hundred cubic centimeters and 118.6 milliequivalents of chloride per liter.

The bottle of rat poison was brought to Dr. Francis F. Heyroth, of the Kettering Laboratory of Applied Physiology of the College of Medicine of the

University of Cincinnati, for analysis. Analysis was performed to ascertain what poisons were in the "Rat Poison—1080," since it may well have been a crudely compounded mixture instead of pure 1080, as the label implied. No heavy metals or arsenic was found. Analysis for total fluorine revealed 1.35 Gm. per liter (0.135 per cent fluorine). Decomposition (at a temperature somewhat above 300 F.) of the residue on evaporation of the solution indicated the probable presence of an organic compound. Sodium fluoride would not melt with decomposition. Steam distillation of the acidified solution yielded some fluorine-containing material in the distillate.

Two twenty-four hour specimens of urine collected on the third and fourth (1,500 cc.) and fourth and fifth (450 cc.) days of the child's illness were analyzed for fluorine content: 0.32 and 0.63 mg. of fluorine per liter, respectively, was found, and these values were within the limits of normal controls. However, the toxicity of sodium fluoroacetate is so great that it is unlikely that a case of poisoning by 1080 could be proved or disproved by analysis of the urine.

Follow-Up Observations.—One year after his discharge from the hospital, the boy, now 3 years old, appeared normal and healthy. Mental and physical development had proceeded normally, and there had been no further convulsions or other symptoms of neurologic disorder. Results of physical examination were within normal limits, with a pulse rate of 120 and prominent sinus rhythm; the size and shape of the heart were normal to percussion. Blood pressure was 94 systolic and 60 diastolic. Cardiac sounds were of good quality, and no murmurs were present. Neurologic examination gave entirely normal results.

Follow-up laboratory studies revealed a hemoglobin concentration of 11.5 Gm. per hundred cubic centimeters. White blood cells numbered 7,700, with 24 per cent neutrophils and 76 per cent lymphocytes. Basal urea nitrogen was 9.7 mg. per hundred cubic centimeters. Urinalysis showed nothing abnormal. The Wassermann reaction was negative. The electrocardiogram revealed a rate of 115 per minute, a P-R interval of 0.12 second and a Q-T interval of 0.32 second, with sinus arrhythmia, sinus tachycardia and occasional premature ventricular contractions.

COMMENT

The circumstances surrounding the present case are confusing. Two years before the poisoning, the patient's parents had bought from a neighborhood peddler an old pint (473 cc.) whisky bottle filled with a clear solution, clearly labeled in freehand script, "Rat Poison—1080." The poison had been employed with success against rats near the home, but the bottle—still two-thirds full—had been left in a cupboard. Not until Dr. Francis F. Heyroth identified the label as referring to sodium fluoroacetate were we familiar with the nature of the poison in the flask. Subsequent study at the Kettering Laboratory proved the solution to contain fluorine in a concentration of 0.135 per cent, with no arsenic or heavy metals present. The fluorine was present largely in the bound, organic form, but some inorganic fluorine was also detected. This is not surprising, for in the preparation of sodium fluoroacetate contamination with fluoride ions occurs unless special precautions are taken. For this reason careful pharmacologic studies of experimental poisoning have usually been performed with methyl

fluoroacetate, but the toxicity of both sodium fluoroacetate and methyl fluoroacetate is dependent on the fluoroacetate part of the molecule and on equimolar dosage is identical. Fluoroethanol [2a] and fluoroacetphenylhydrazide (fanyline)[5] have also been studied, and their toxicity is found to depend on the fluoroacetate which is produced in the body from these compounds. The present patient was known only to have licked crystals of fluoroacetate from the screw top of the bottle, and, if he had drunk any liquid, he could not have taken more than a few cubic centimeters. From the analysis of total fluorine, the pint bottle could contain only about 1.5 Gm. of sodium fluoride (3 mg. per cubic centimeter), if all the fluorine were present in the form of the fluoride ion. There is no possibility that the child could have obtained more than a few milligrams of sodium fluoride per kilogram of body weight, and this would have been too small a dose to account for his illness. If the fluorine were all present as 1080, there would have been 7.11 Gm. of the poison per liter, or 7.11 mg. per cubic centimeter. Ingestion of the crystals from the evaporation of a few cubic centimeters of such a solution or of a few cubic centimeters of the solution itself could well account for the child's illness. He undoubtedly obtained relatively pure sodium fluoroacetate with little contaminating ionic fluoride. He could easily have obtained many milligrams of the 1080, but the exact dose he received is unknown. Thus, although complete isolation and characterization of the material in the flask of "Rat Poison—1080" are not available, circumstantial evidence points strongly to the fact that we are here dealing with a case of pure sodium fluoroacetate poisoning.

The clinical picture closely paralleled that seen in experimental poisoning in laboratory animals, and the total recovery without sequelae is what would be expected from observations of those few animals which have survived poisoning severe enough to produce signs and symptoms.

EXPERIMENTAL TOXICOLOGIC STUDIES

Chenoweth and Gilman [3a-c] and Chenoweth and St. John [3d,e] extensively studied the pharmacologic aspects of fluoroacetate. They investigated its effects on 11 species of mammals, on chickens and on frogs. They reported no pharmacologic similarity between the action of fluoroacetate and that of other monohalogen derivatives of acetic acid. Poisoning with this compound is totally different from that produced by the fluoride ion. In fluoroacetate the fluorine is tightly bound in a fluorine-carbon linkage which can be split only by harsh treatment, such as pyrolysis in a free flame or exposure to hot sulfuric acid with potassium

5. Karel, L.: The Rodenticide Activity of Fluoroacetphenylhydrazide ("Fanyline") and Its Oral Toxicity to Several Species, J. Pharmacol. & Exper. Therap. **93**:287 (July) 1948.

dichromate. These authors divided the mammalian species studied into four groups, this classification depending on the nature of the response to the poison: group I (rabbit, goat, horse, spider monkey): no central nervous system action observed, death being always due to cardiac effects with ventricular fibrillation; group II (cat, pig, rhesus monkey): both cardiac response and central nervous system affected, death usually resulting from respiratory failure during convulsions, but occasionally from ventricular fibrillation; group III (dog, guinea pig): epileptiform convulsions, with death due to cessation of respiratory activity; central nervous system primarily affected and no cardiac abnormalities observed; group IV (rat, hamster): atypical response with respiratory depression and delayed bradycardia; ventricular fibrillation rare.

Chickens exhibited both central nervous system and cardiac effects and frogs only central nervous system effects, with convulsions followed by flaccid paralysis and, in those which survived, complete recovery.

The lethal dose for 50 per cent of the various animals (LD_{50}) in milligrams per kilogram of body weight was quite different: dog 0.06, rabbit 0.2 to 0.25, guinea pig 0.35, pig 0.4, cat 0.5, goat 0.5, horse 0.5 to 1.75, hamster 2.5 to 5.0, rhesus monkey (Macaca mulatta) 4.0, rat 5.0, spider monkey (Ateles geoffroyi) 14.0, chicken 15 and frog 300. LD_{50} for man has been estimated at 5 mg. per kilogram of body weight.

In these studies the route of administration was found to be unimportant, the lethal doses being the same for all routes. Latent periods before the appearance of symptoms after intravenous injection of methyl fluoroacetate of one to two hours were always observed, and even with huge doses these latent periods did not disappear.

The rhesus monkey was carefully studied, and poisoning in this species was treated by various means in an attempt to find an antidote. One hour after injection of 10 mg. per kilogram of body weight of methyl fluoroacetate, Chenoweth and Gilman observed occasional premature ventricular contractions; two hours after injection T waves in the electrocardiogram were accentuated, and a few minutes later convulsions, heralded by blinking, nystagmus, twitching of facial muscles, defecation and some salivation, occurred. After the jerking, symmetric tonic convulsion, the animals remained conscious for a short while and persistent changes in the T waves of the electrocardiogram and alterations in the pulse rate and heart sounds were noted. A second convulsion occasionally occurred. Four hours after injection, pronounced alteration in T waves in the electrocardiogram and a 50 per cent pulse deficit were present, and one-half hour later ventricular fibrillation occurred. Quinidine, papaverine and sodium para-aminobenzoate were used as possible antidotes for ventricular fibrillation without effect. The only effective therapy was intracardiac administration of procaine hydrochloride and cardiac massage, which in many instances produced

reversal of an episode of ventricular fibrillation to a normal contraction, but in only 2 cases were animals permanently saved by this method, since recurrent attacks of fibrillation eventually became irreversible.

Fluoroacetate poisoning was studied in the cat by Chenoweth and his associates [3a-e] and by Ward.[3g] After 0.5 to 2.0 mg. per kilogram of body weight of fluoroacetate was given intravenously, the symptoms, after a latent period of one hour, were ushered in with sudden retching and vomiting, salivation, pupillary dilatation, micturition, hyperpnea, hyperexcitability and a myotonic convulsive state, with flexion of the forelegs in a posture resembling carpopedal spasm. Occasional violent myoclonic convulsions developed, with intervening periods of flaccidity, and their frequency increased from about one every ten minutes until a status epilepticus without flaccidity prevailed. Death was usually caused by depression of the respiratory center. In a few cases animals were tided over an apneic period with artificial respiration.

In the rhesus monkey convulsions were ablated or averted by sedative doses of pentobarbital sodium U. S. P. (15 to 20 mg. per kilogram of body weight) given intravenously, while in the cat convulsions occurred even when the animal was completely anesthetized with pentobarbital sodium (35 mg. per kilogram of body weight intraperitoneally) before injection of the fluoroacetate.

Quin and Clark,[3h] in studying the poison of "gifblaar" (potassium fluoroacetate) in sheep and rabbits concluded that it was a cardiac poison affecting the conducting mechanism, thus leading to partial or complete heart block.

Thus, from the experimental work with animals, an array of responses has been obtained which encompasses completely the clinical picture seen in the present case of human poisoning. In spite of the lack of electrocardiographic records during the moments of maximal cardiac irregularity, premature ventricular contractions and totally irregular rhythm were noted. Accentuated T waves appeared in the electrocardiogram. Preliminary retching and vomiting, followed by carpopedal spasm and, later, by convulsive episodes with intervening flaccidity, and periods of myotonic convulsions with interspersed violent myoclonic convulsions occurred much as they were described in experimental poisoning in the cat. Episodes of complete respiratory cessation during the convulsive period, quite similar to the apnea described in many animals (particularly the pig), occurred twice in the present case and may have ended fatally had artificial respiration not been employed. Recovery, as it was with experimental animals, was complete without sequelae. From the present case it appears that the human species falls into Chenoweth and Gilman's group II (cat, pig, rhesus monkey) with both cardiac and central nervous system effects.

No electroencephalographic records were made during the child's illness. Ward [3g] studied the central nervous stimulation produced by fluoroacetate and observed local, rhythmic seizure discharges in subcortical structures at the time severe tonic seizures were present in the animals (cats). He concluded that the major locus of action is subcortical and that the cortical petit mal type of response (spike and dome waves of high voltage at a rate of 3 per second) in the electroencephalogram observed by Chenoweth and St. John,[3d,e] and also occasionally by Ward himself, was of secondary importance. Ward found no clear correlation of the electrical activity of the cortex with the paroxysmal activity in the thalamus, hypothalamus or reticular formation of the pons.

Several studies of the biochemical mechanism underlying the toxicity of fluoroacetate have been made. Bartlett and Barron [6] advanced the hypothesis that fluoroacetate is a competitive inhibitor for biochemical reactions in which acetate takes part. Liebecq and Peters [7] recently further investigated this hypothesis and observed that an additional hypothesis was necessary: Fluoroacetate is transformed into another substance which is inhibitory to the tricarboxylic cycle, thereby causing accumulation of citrate. Neither group of workers observed a single enzyme reaction inhibited by fluoroacetate to explain the fact that this substance stops carbohydrate oxidation in the tricarboxylic acid cycle.

CONCLUSIONS

Human poisoning with fluoroacetate further reflects the species differences in the clinical picture presented which many other mammals with experimental poisoning have previously revealed. Cardiac and central nervous system effects are both important, the central nervous system effects predominating. This renders the clinical picture somewhat similar to that observed in the cat, pig and rhesus monkey, but most like that in the cat.

No antidote is available for the poisoning, but sedation with barbiturates offers a possible means of combating the convulsions. Because of the danger of respiratory depression and cessation, a respirator should be kept on hand and artificial respiration started immediately if prolonged apnea appears.

One cannot be certain whether the calcium therapy given early in the clinical course really influenced the outcome of the present case or

6. Bartlett, G. R., and Barron, E. S. G.: Effect of Fluoroacetate on Enzymes and on Tissue Metabolism: Its Use for Study of Oxidative Pathway of Pyruvate Metabolism, J. Biol. Chem. **170**:67 (Sept.) 1947.

7. Liebecq, C., and Peters, R. A.: The Toxicity of Fluoroacetate and the Tricarboxylic Acid Cycle, Biochem. Biophys. Acta **3**:215 (April) 1949.

not. However, the notable relaxation from the tonic tetany-like state in which the patient was admitted and the immediate improvement associated with administration of calcium gluconate (intravenously) warrant its use again in any future cases.

Should ventricular fibrillation occur, the experimental experience of Chenoweth and Gilman with monkeys warrants the intracardiac use of procaine hydrochloride and cardiac massage.

It should constantly be remembered that supportive and symptomatic therapy alone is available; however, if the patient is carefully observed and emergencies handled as they appear, complete recovery without sequelae is possible.

SUMMARY

Sodium fluoroacetate, commonly called "1080," has obtained widespread use since the war as a potent rodenticide. Because of its varied pharmacologic properties and biochemical interest, it has become increasingly important in laboratory studies. Experimental poisoning in laboratory animals was studied during and since the war by many workers, but no previous report of a case of human poisoning is known to us.

A case of poisoning with what was probably relatively pure sodium fluoroacetate in a 2 year old Negro child is reported. Cardiac and central nervous system symptoms predominated, as in experimental animals, but the child recovered completely without sequelae.

The clinical picture presented by this case is briefly compared with that seen in experimental poisoning, and the literature on fluoroacetate poisoning is briefly reviewed.

NOTE.—Since this paper was submitted for publication, we have noted in an article by Hutchens and his associates [8] reference to a case of this poisoning in a child (from a personal communication to the authors by Dr. Eleanore R. Wright) whose convulsions were controlled with pentobarbital sodium and who was also given ethanol. The child survived. These workers reported decreased mortality due to fluoroacetate poisoning in mice, guinea pigs and rabbits treated with 10 per cent solution of ethanol in isotonic sodium chloride solution given subcutaneously within ten minutes of injection of the poison. The mechanism of competitive inhibition of acetate reactions suggested this form of therapy. Its value in human cases is unknown.

Dr. Francis F. Heyroth and Dr. Henry W. Ryder, of the Kettering Laboratory of Applied Physiology, Cincinnati, assisted with the case here presented.

Children's Hospital, Boston (Dr. Gajdusek).

8. Hutchens, J. O.; Wagner, H.; Podolosky, B., and McMahon, T. M.: The Effect of Ethanol and Various Metabolites on Fluoroacetate Poisoning, J. Pharmacol. & Exper. Therap. **95**:62, 1949.