Rodent Control with 1080, ANTU, and Other War-Developed Toxic Agents

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RATS have been recognized as disease carriers from an early day, and the primary rôle they play in the spread of bubonic plague, typhus fever, and many less important illnesses is well known. Public health officials and economic rodent control agencies have emphasized the importance of rat control for many years. It has been recognized that construction of rat-proof buildings and the rigid enforcement of adequate sanitation regulations are fundamentals, which must be observed to combat rodent pests effectively. As a supplement to these procedures, however, the reduction of excess rat populations is essential. It is in this phase of rodent control that most spectacular advances have been made during the past few years.

The importance of reductional control was stressed by medical officers of the Armed Forces early in the war, when it became obvious that troops would invade portions of the world where rodent-borne diseases were known to exist. Research work to discover and test new poisons was intensified when early military action by the enemy cut off supplies of red squill, thallium, and strychnine. ANTU and Compound 1080 were two of the most important discoveries. "ANTU," or "Chemical 109," were the code designations of Alphanapthylthiourea, which was the first of the newer agents to be found. ANTU was one of those fortuitous scientific "accidents" caused by the astuteness of a competent observer whose vision enabled him to recognize the value of a chance observation. At the beginning of the ANTU story, Dr. Curt P. Richter of Johns Hopkins University was studying taste psychology in rats, and he noticed that when he used PTC, phenylthiocarbamide, his experimental rats usually died. As PTC had been used safely for several years in studying taste reactions in humans, Dr. Richter was impressed by its apparent toxicity to rats. Feeding trials showed that phenylthiocarbamide was refused by rats, so it became necessary to find a chemical relative which would still be toxic, but would be more palatable. When the potential value of the thiourea compounds was explained to the Committee on Medical Research of the Office of Scientific Research and Development, it was decided that funds should be provided to follow through on the idea. Coöperation was set up between Dr. Richter and the research specialists of E. I. du Pont de Nemours and Company. A large number of substituted thioureas was synthesized, until alphanapthylthiocarbamide—or alphanapthylthiourea, as it is called more commonly—was produced. This substance was found to have the same toxicity to rats as phenylthiocarbamide, and to be much more palatable.

Extensive field trials then were

needed to test the suitability of ANTU for the control of various rodent pests. Arrangements were made with Baltimore health officials, and an extensive rat reductional program was instituted in the city. Simultaneously, the assistance of the Fish and Wildlife Service was requested, and a supply of the new poison was forwarded to Denver. Samples were distributed to workers in various parts of the country. Early reports showed that ANTU was entirely ineffective against California ground squirrels, and was only about one-thirtieth as toxic to black or Alexandrine rats as it was to Norway rats. These observations led to studies which proved that ANTU is highly specific, since it affects Norway rats more readily than it does any other species of animal. It is also more effective against adult than young Norway rats. It causes development of tolerance, since rats which have survived sublethal doses of ANTU are able to withstand subsequent amounts which are many times the acute lethal quantities. In common with many other poisons, it has the characteristic of "educating" rats which have survived small doses, against eating baits containing ANTU again. Unfortunately, it will kill dogs and is toxic in varying degrees to most carnivorous species, while being less dangerous to the herbivorous ones.

When all of these characteristics are given due consideration, the conclusion is reached that ANTU has several idiosyncrasies which must be understood before the substance can be used to best advantage, but that it has promise of becoming a very useful material. It will kill adult Norway rats at 6–8 mg./kg., and accordingly may be used effectively at 1 per cent concentration in bait. ANTU, which is a light grey insoluble powder, may be employed either mixed with ground food; dusted over cut sections of fruits, vegetables, or meats; or mixed with talc and blown into rat burrows or along rat runways. The poison is new, and there are many problems with regard to its adaptability, and to its methods of use, which remain unsolved. Dr. Richter and many of his coöperators are still studying them, however, so it is to be expected that many of these questions will be answered in the near future, and that the true value of ANTU will be demonstrated.

The discovery of Compound 1080 is an illustration of the advantages of wartime coöperation. Prior to the war, strychnine, thallium, red squill, zinc phosphide, arsenic compounds, barium carbonate, and cyanides were readily available, so the earlier search for new agents was of scientific rather than of practical importance. War changed all that, and when shortages of the more effective rodenticides appeared to be imminent, the Wildlife Research Laboratory of the Fish and Wildlife Service undertook a strenuous search for substitute poisons.

When invasion forces encountered rat-borne tsutsugamushi disease, the importance of this project was emphasized and the Office of Scientific Research and Development provided sufficient funds to accelerate this work. Close coöperation was set up with research units of chemical industry, certain army laboratories, and various committees of the OSRD. Several hundred compounds known to possess toxicity in themselves, or to contain molecular configurations suspected of being toxic, were obtained for tests. Finally, Division 9, National Defense Research Committee of the OSRD, sent 10 chemicals to the Fish and Wildlife Service laboratory at the Patuxent Refuge, where preliminary toxicities were being run. One of these ten was given the invoice number "1080."

Stomach tube tests showed that "1080" and one or two others of this batch of chemicals were highly toxic,

so they were forwarded to Denver for further examination. Compound 1080 was found to be the only one of the ten meeting all of the requirements, and, the first of the several hundred chemicals tested, to show evidence of becoming a satisfactory poison.

As the first reports reached the OSRD, it appeared that 1080 might be the new poison which had been sought by Service forces and public health agencies for fighting rodent-borne diseases. The need for haste in testing 1080 was obvious, and the OSRD set up a Rodent Control Subcommittee to expedite that program. To supplement the field testing being done by the staff of the Wildlife Research Laboratory of the U. S. Fish and Wildlife Service, whole-hearted coöperation was obtained of the U. S. Public Health Service, the Surgeon General's Office of the Army, the Bureau of Medicine and Surgery of the Navy, the U.S.A. Typhus Commission, the Chemical Warfare Service, the University of Chicago Toxicity Laboratory, the British Commonwealth Scientific Office, the Texas State Department of Health, the Pan American Sanitary Bureau, and many others. Thus, it was possible to get world-wide studies with 1080 under way.

The results of all of this work have been most revealing. As a poison for the control of certain pests, Compound 1080 has no equal. It is highly effective against all species of rats; it is satisfactory for the control of mice; it gives phenomenal control of prairie dogs, California and other ground squirrels, and gives promise of being useful on other species on which it has not been tested. In short, 1080 is so generally and highly toxic that it is too dangerous for general distribution.

Whereas ANTU is reasonably safe for the inexperienced layman to use, 1080 has been proved to be a tool for only the most expert and careful specialist. To the pharmacologist familiar with strong poisons, the toxicity of 1080 is almost unbelievable. Table 1 illustrates that point.

TABLE 1

Toxicities of Sodium Fluoroacetate (1080)

Animal	*Route of Administration*	*Approximate LD 50%*
Dog	IV *	0.1–0.2 mg./kg.
Coyote	IP Less than	0.2 mg./kg.
Rabbit	IV	0.3 "
Pig	IP	0.3 "
Cat	IP	0.3 "
Calif. ground squirrel	Fed	0.3 "
Black-tailed prairie dog	Fed	0.3 "
Guinea pig	Fed	0.3–0.4 mg./kg.
Field mouse	Fed Less than	0.5 mg./kg.
Bobcat	IP Less than	0.67 "
Goat	IM	0.7 "
Rat (black species)	ST	1.0 "
Rat (Norway)	ST	3.0– 4.0 mg./kg.
Monkey (Rhesus)	IV	5.0– 7.5 "
Monkey (Spider)	IV	10.0–12.0 "
Chicken (Rhode Island Red)	Fed	6.0– 7.0 "
Frog	SC	1000.0–2000.0 "
Horse (British data)	Not given	1.0 mg./kg.

* Experiments at Edgewood Arsenal have indicated that the route of administration has a minor effect on the toxicity of 1080. Consequently, it was considered permissible to compare the results obtained by intravenous injection (IV); stomach tube (ST); intraperitoneal injection (IP); subcutaneous injection (SC); and intramuscular injection (IM); with those determined by feeding.

The comparative toxicities of 1080 to dogs, cats, and rats foreshadows one of the most serious disadvantages of this poison. Because of their greater sensitivity, dogs and cats are killed by eating sick or dead rodents killed by 1080. This means that pets must be removed from areas where this poison is exposed, and must be kept away until all bait and all carcasses have been picked up.

In fact, there is only one advantage appearing on the list of toxicities given above, and that is that primates are less susceptible to 1080 than are most of the lower animals. That makes it possible for us to assume that there is a relative degree of resistance in humans.

The high suceptibility of rodents makes it possible for a very small amount of the poison to be used in bait, and as a consequence, normal baits containing 1080 are not extraordinarily dangerous to humans. In Table 2, the strongest concentration of 1080 recommended in any standard formula is used.

This is the mixture of ½ oz. of 1080 in 1 gallon of water. Rat food baits use 1 gm. of 1080 per lb. (1 oz./28 lb.) and field rodent formulas use only 1 or 2 oz. per 100 lb. of grain. These baits would be less dangerous to man because of the weaker concentration of poison than would be true of the water mix. It is of interest to compare the relative danger from baits containing several of the common poisons in the concentrations that these are commonly prepared.

In interpreting this table, one important factor must be considered. There is no known antidote for this new poison, and its rapid absorption makes the use of first aid measures effective for only a short time after the poison is swallowed. Much work has been done to find an effective treatment for 1080, and the following suggestions are offered by the Chemical Warfare Service.

TREATMENT IN CASES OF ACCIDENTAL POISONING WITH 1080

Treatment is limited to the use of emetics, and the poison must be eliminated within a few minutes if the absorption of dangerous quantities is to be prevented. Make the patient vomit at once by tickling the throat with the finger, or give ½ teaspoonful of powdered mustard in a cup of warm water. Give a dose of Epsom salts as a purge. Call a physician at once and give him the following information:

For the Physician—Compound 1080 affects the myocardium and the central nervous system. In primates the effect on the heart is the primary cause of death. Pulsus alternans appears first, followed by premature systoles and ventricular fibrillation. The central nervous system reaction is shown by epileptiform convulsions. Following treat-

TABLE 2

Toxicities to Man of Rodent Bait Prepared with Common Poisons

Poison	*Accepted Lethal Dose to Man mg./kg.*		*Concentration Used in Baits*	*Ounces of Bait Containing a Lethal Dose for a 150 lb. Man*
Arsenous acid (As_2O_3)	1.5–15.0	3%	(1 part in 33 parts)	0.12–1.22 oz.
Strychnine	1.0	0.3%	(1 " " 320 ")	0.8 oz.
Sodium fluoroacetate (1080)	5.0	0.4%	(1 " " 256 ")	3.15 "
Thallium sulphate (Tl_2So_4)	20.0	1.5%	(1 " " 65 ")	3.2 "
Zinc phosphide (Zn_3P_2)	40.0	2.0%	(1 " " 50 ")	4.9 "
Barium carbonate ($BaCo_3$)	800.0	20.0%	(1 " " 5 ")	9.9 "
Alphanopthyl thiourea (ANTU)	Unknown	5.0%	(1 " " 20 ")	Probably very large

ment to remove the poison, place the patient at complete rest. Control the CNS excitement by careful use of barbiturates having a moderate duration of action, such as sodium amytal. Little else can be done to arrest the cardiac symptoms.

This summary would be incomplete without reference to two chemicals discovered in Germany during the war. The first of these was *p*-dimethylaminobenzene diazosulfonic acid, sodium salt. This substance was moderately toxic and was reported to be rather effective in the control of rats in Germany. The other was 2-Chloro-4-dimethylamino-6-methylpyrimidine, called " Castrix "—obviously for convenience. This chemical was a great deal more toxic, and was said to be an excellent substitute for thallium. Adequate supplies of these materials have not been made available as yet to workers in the United States, but arrangements have been completed to obtain reasonable lots of both poisons for study. Enough work has been done, however, to justify the belief that neither will be superior to 1080 in efficiency, and that " Castrix," at least, will also be highly dangerous. There is no expectation that either one will be a substitute for 1080, as far as efficiency is concerned, but there is a chance that both may be used more generally with less danger to pets and children.

The conclusion which must be reached from the review of the developments of the past few years is that new discoveries often come in groups. It is no longer fantastic to hope that toxic agents which will be effective only against the rodent pests may be found soon. It is much more logical now to look forward to a world in which man will be able to keep his communities free of rats, than it was before ANTU, 1080, and the other new control agents were discovered. A strong research program in rodent control will continue to be a definite adjunct to permanent improvement in the economic welfare and in the public health, and will be useful in proportion to the degree in which its discoveries are put to use by local and national agencies.