BIOCHEMISTRY

New Disease Attack

Idea of "lethal synthesis" suggested as line for attack upon disease germs. Body may make seemingly harmless chemicals deadly to disease organisms.

➤ A NEW line of attack upon disease germs by "lethal synthesis" is suggested by Prof. R. A. Peters, F.R.S., biochemist at Oxford University, Oxford, England.

Prof. Peters believes investigation should be conducted with a view to discovering seemingly harmless chemicals which, as a result of enzyme action in the body, may be converted into quite different chemical substances which would be deadly to disease organisms.

He based his faith in this line of attack on recent discoveries made by himself and his colleagues that conversion of a harmless chemical into a quite deadly one does take place in at least one instance.

The chemical they investigated was fluoroacetic acid, the poisonous principle in the shrub *Dichapetalum cymosum,* a notorious killer of cattle and sheep in the Pretoria and Transvaal regions of South Africa, and also poisonous to man. The poison has a delayed effect especially upon the nervous system or upon the heart.

What puzzled Prof. Peters' group of researchers was that fluoroacetic acid by itself failed to inhibit or poison any of the body's essential enzymes when enzyme and chemical were put together in a test tube. It was only when taken into the body that extremely small quantities of the fluoride compound became toxic.

The first real clue to what was happening in the body was the discovery that when an animal suffering from fluoroacetate poisoning was killed and its body tissues analyzed they were found to contain much greater concentrations than normal of citric acid—a product in the body's vital energy-producing tricarboxylic acid cycle (nicknamed "tri-cycle" by Prof. Peters).

The kidneys were the most affected, containing about 80 times the normal quantity of citric acid. The liver and cancer tissues seem to be exceptions.

From this observation the investigators reasoned that in the body the fluoroacetate was being converted into some other chemical, now believed to be fluorocitric acid, which jammed the "tri-cycle." This caused a slowing and even stoppage of metabolism, resulting in illness or death.

It would appear that the jamming occurs at that point in the "tri-cycle" at which citric acid, one of the chain of compounds in the cycle, is due to be converted into the next compound, cisaconitate, by the body enzyme aconitase.

The fluoroacetate is probably converted by enzyme action to fluorocitrate, which is sufficiently like citric acid to tie up the aconitase and keep it from doing its normal job of converting citric acid to cisaconitate. This throws a monkey-wrench into the "tri-cycle" works, without the normal functioning of which life can not carry on.

Prof. Peters and his co-workers succeeded in extracting the compound synthesized by the body from fluoroacetate and have shown that it is poisonous to the enzyme aconitase outside the body as well, thus clinching their case. They can now isolate it in relatively pure form by passing solutions of it through resin columns.

Since the fluoroacetate is not poisonous until it is changed into another compound by a body enzyme, it is considered an example, the first of its kind, of "lethal synthesis," or the manufacture of a deadly substance from a harmless one by the body.

If other chemicals could be found which, though harmless in themselves, could be converted by the body into substances which would poison the enzyme systems of disease germs, this would open up a whole new field of chemotherapy. Prof. Peters believes the facts of the fluoroacetate case justify serious investigation into this new approach.

As a sidelight to his work, Prof. Peters pointed out in his Royal Society presentation, its possible application to medico-legal cases. Toxicologists might find the citric acid content of tissues a useful index in cases of suspected fluoroacetic acid poisoning.

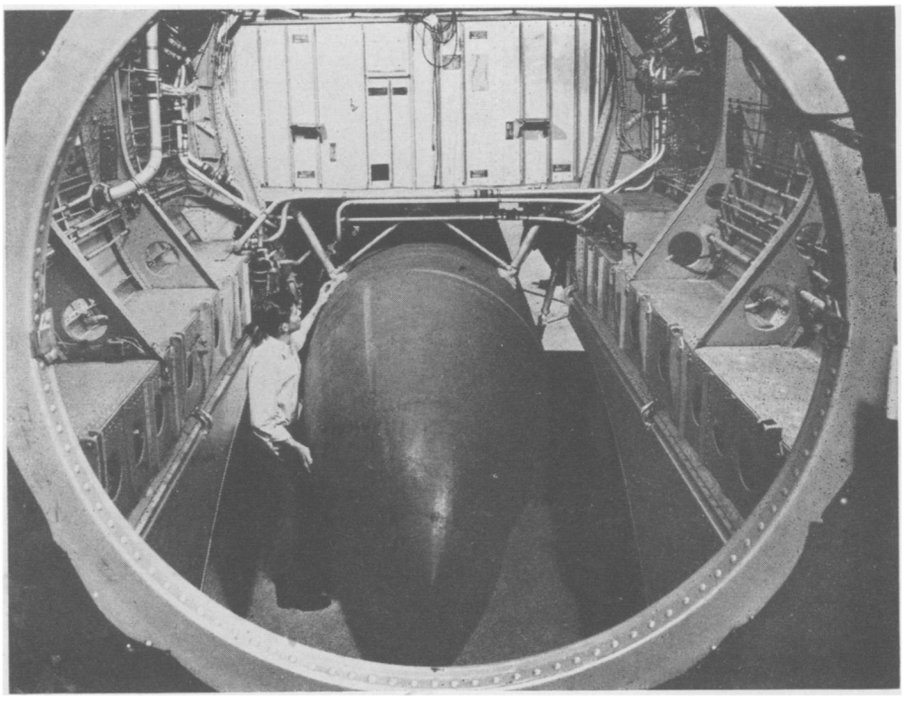
However, as the citric acid concentration begins to fall soon after death, it could only be used as proof of poisoning when immediate autopsy was possible.

Prof. Peters humorously dropped the hint that, if anyone was contemplating using fluoroacetic to poison his mother-in-law, he had better pick a Saturday to do it. By the time the coroner's office opened on Monday the citric acid evidence would be gone.

Science News Letter, July 7, 1951

On This Week's Cover

➤ LINED UP ready to begin the long journey to Korea, the Bell H-13D helicopters shown on the cover of this week's SCIENCE NEWS LETTER will fill a vital role for our fighting forces. Helicopters of this and other types have evacuated more than 5,000 wounded from the battlefront as well as performed other valuable tasks.



GIANT AERIAL BOMB—Shown for the first time, cradled in the bomb bay of a B-29, is the giant 44,000-pound aerial bomb. It is so large that it partially hangs out of the plane.