Fat Deposits in the Kidney in Chronic Intoxication of the Dog by Hexachlorocyclohexane

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We have found that chronic intoxication of dogs by the γ isomer of hexachlorocyclohexane (HCH) results in abnormal intracellular deposits of fat in most tissues and organs. This intoxication was obtained by repeated intramuscular injections of 10–30 mg of γ HCH in 10% oily solution per 1000 g of body weight, to a total dose of 130–475 mg/kg. The dogs died or were killed 7–44 days after the first injection.

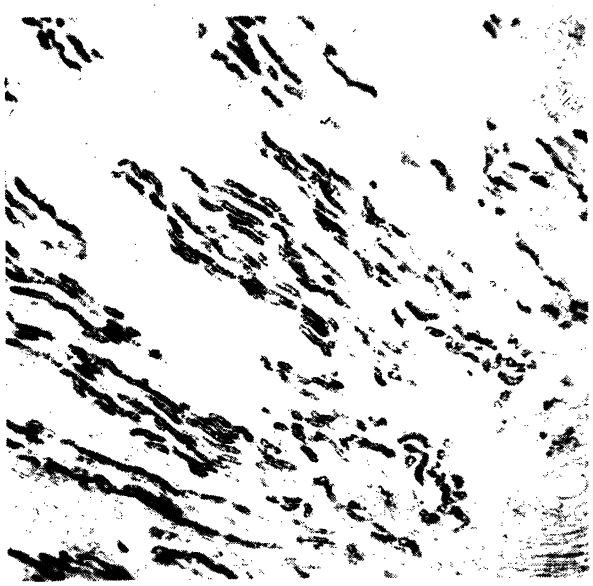

FIG. 1. Intracellular fat deposits in terminal parts of proximal convoluted tubules of the kidney, in a γ HCH-treated dog. Stained with Sudan black; magnification 22 ×.

The fat deposits are most marked in liver, striated muscle, nerve cells, and kidneys. They appear quite clearly in frozen sections of formaldehyde-fixed material, stained with general fat stains such as Sudan black or scharlach red.

Intracellular fat deposits in the kidney are limited to the proximal convoluted tubules (Fig. 1), the other tubules being practically free of fat droplets. Even in the proximal tubules, there is a precise distribution of the deposits, which may be formed by very big droplets. Whereas the glomeruli have a normal appearance and the initial parts of the tubules show only scattered and rare droplets, the terminal straight parts of the proximal tubules, or medullary segments of these tubules, contain numerous intracellular droplets. Some extracellular fat droplets are also to be seen in the lumen of these tubules. There is no cell destruction or any alteration in nuclear structure, even in those parts of the tubules that are filled up with fat. The outer zone of the medulla shows no fat deposits. When the deposits in the proximal convoluted tubules are very rich, the lumen of the terminal parts of the collecting tubules and of the papillary ducts of Bellini may contain some fat and also some hyaline globules and cylinders. In the same animals, the epithelium of the calyces and the kidney pelvis may contain intracellular droplets.

Ureter, urinary bladder, urethra, and Littre's glands are free of fat deposits. In the male, one may sometimes see fat droplets in the epithelial cells of the prostatic portion of the urethra. This seems to be correlated with the abnormal amount of fat granules in the prostatic and Cowper's glands.

Treatment by the δ isomer of HCH produces the same distribution of fat deposits in the kidney, but they are in smaller amount. We have noticed no fat droplets in the kidney following intramuscular injections of big amounts of oil and DDT.

Our experiments allow us to conclude that this specific intracellular fat deposit in the kidney is bound to the still unelucidated biochemical lesion induced by hexachlorocyclohexane.

A Simple Apparatus for Multiple Uniform Intravenous Injections[1]

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In the course of carrying out a study of total body water[2] on a large series of subjects, a simple method for the intravenous administration of precisely 50 ml of fluid was devised.

The apparatus consists of single unit (unit I, Fig. 1) calibrated to contain 50 ml. This unit is filled from a Baxter infusion bottle through the inlet (A). The inlet side-arm empties completely, thus eliminating any error from trapped air bubbles.

A two-way stopcock is provided for the outlet, allowing any excess of fluid (over the calibration mark) to be eliminated via the waste outlet (C).

The injection fluid is then delivered through the tubing (B). The reservoir of injection fluid (antipyrine solution, 1 g in 50 ml) was analyzed only once for each 20 subjects, as compared with 20 separate analyses when 50-ml syringes and separate 50-ml solution bottles were used for each subject.

A separate piece of tubing, with a glass adapter and needle attached, is autoclaved as a unit (II), and changed for each subject. In this manner, the hazards from injecting refluxed blood to successive subjects are eliminated.

[1] The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

[2] Using the "antipyrine technique" of Messinger & Steele.

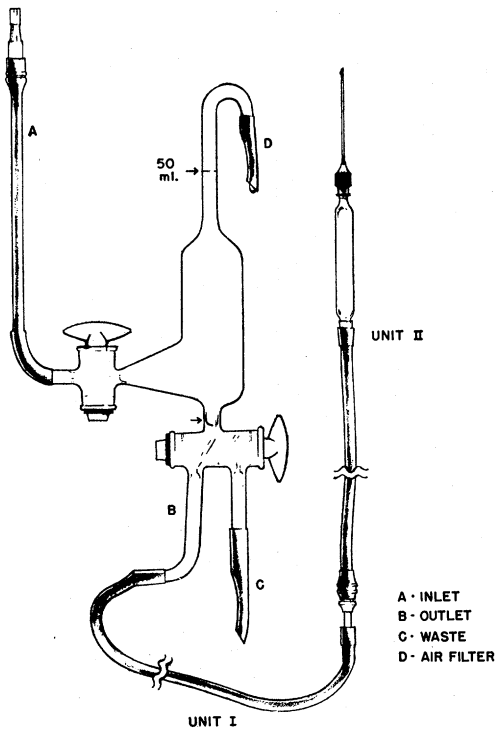

FIG. 1. Multiple sterile infusion apparatus.

The two stopcocks are greased with "high vacuum" grease supplied by Dow Corning Co. This silicon lubricant withstands temperatures over 200° C and may be repeatedly autoclaved without deterioration.

By means of this setup, the difficulty attending the sterilization of a large number of syringes was by-passed, and it was felt that the volume of injection fluid could be more accurately controlled. Using a No. 20 gauge needle, the injection time for 50 ml ranged between 4 and 5½ min. This apparatus was used successfully on over 50 subjects without a single untoward reaction.

Plasma Concentrations of *p*-Aminosalicylic Acid (PAS) Increased by *p*-(Di-*n*-propylsulfamyl)benzoic Acid

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PAS is being applied increasingly to the treatment of tuberculosis, the daily dose being 8–16 g. The amount of this dose is based on patients' ability to tolerate PAS medication, not on the belief that it represents the optimal dose; indeed, some workers believe that 20 g per day would be desirable (*3*). Therefore, an agent capable of enhancing the plasma concentrations of PAS would be worthy of attention, for although a direct relationship between plasma concentrations of PAS and therapeutic effect has not been established, this relationship, within limits, can be anticipated.

It was shown (*4*) that carinamide reduces the renal clearances of PAS to glomerular filtration rate, supposedly by inhibiting tubular excretion of PAS. But the suggestion was made that the same elevation in plasma concentrations of PAS produced by inhibiting the excretory function of the tubules would be observed if a form of PAS, less readily cleared by the renal tubules, was presented to the kidney for excretion. The concept that the catabolism (conjugation) of PAS may be altered in such a way as to slow its elimination gains support from the demonstration that carinamide acts upon an enzymatic conjugase system (*1*). A new compound *p*-(di-*n*-propylsulfamyl)benzoic acid, Benemid,[2] also has been shown to influence an enzymatic conjugation system that tentatively is regarded as related to the reversible inhibition of the excretion of penicillin and *p*-aminohippurate (*2*). The possibility that Benemid might inhibit the conjugation of PAS, and thereby retard its elimination from the body, prompted this investigation.

Seven patients with tuberculosis whose renal functions were unimpaired as determined by microscopic examination of the urine, blood urea nitrogen determinations, and phenolsulphonphthalein excretion tests were chosen for this investigation. In the fasting state, each patient was studied on three occasions: (A) after a single 4-g oral dose of PAS[3] (administered as NaPAS in aqueous solution); (B) after a 4-g oral dose of PAS and a single 2-g oral dose of Benemid; and (C) after a 4-g dose of PAS that was administered subsequent to premedication for 24 hr with 0.5 g of Benemid every 6 hr. The test doses of PAS were administered when the patients were in the fasting state, and blood samples for plasma determination of PAS were drawn at ½, 2, 4, 6, and 8 hr after administration of PAS. Plasma determinations of PAS were done by the method of Way (*5*).

The mean plasma concentrations[4] for the three periods of study were for treatment A, 1.00 mg PAS/100 ml blood; for treatment B, 1.71 mg/100 ml; and for treatment C, 2.63 mg/100 ml. These means were determined with a standard error of ±0.20 mg/100 ml, and the 95% confidence limits are ±0.44 mg/100 ml. Thus, treatment B gave significantly greater plasma concentrations of PAS than treatment A ($P < 0.05$), and treatment C gave plasma concentrations of PAS significantly

[1] The authors wish to express their thanks to Drs. Charles A. Heiken and Peter A. Theodos, chiefs of service of the Department of Chronic Diseases of the Chest, Philadelphia General Hospital, for the privilege of studying patients on their services. The technical assistance of Mrs. Alice E. Pitt is gratefully acknowledged.

[2] Benemid is Sharp and Dohme's trademark for *p*-(di-*n*-propylsulfamyl)benzoic acid. Tentatively, the compound has been given the nonproprietary chemical name "probenecid."

[3] Supplied through the courtesy of Sharp and Dohme, Inc., in the form of Propasa, an effervescent tablet of PAS that permits formation of NaPAS immediately prior to administration of the drug.

[4] The ½- and 2-hr plasma concentrations were eliminated from the statistical analysis because these samples were drawn during the period required for PAS from the single oral dose to be absorbed and distributed in the body fluids.