of the vertebral arteries. Abbott, in her review, mentioned 2 of these cases, those of Knierim (1880, basilar) and Sommerbrodt (1883, vertebral). Boyd and Werblow [10] recorded a further case (vertebral) in 1938, and Walker and Livingstone [11] (case 2) the fourth (vertebral), also in 1938. In the last instance subarachnoid hemorrhage had occurred, but although the left vertebral artery showed irregular saccular aneurysmal dilatations no definite rupture was found; the patient also had infective endocarditis.

Walsh and King [12] (1942, case 4) recorded a case of rupture of an aneurysm of the anterior communicating artery confirmed by postmortem examination. Probable coarctation of the aorta was recorded on clinical examination, but there is no mention of confirmation of this diagnosis post mortem.

Lichtenburg and Gallagher [13] in 1933 reported a case of coarctation of the aorta associated with intermittent leakage of a cerebral aneurysm, diagnosed during life. Their patient, a girl aged 12, was still living after eighteen months' observation. These authors could find in the literature no record of a similar condition diagnosed in life, but a case was later recorded by Baker and Shelden [14] (1936), that of a woman of 25, and a further case by Davies and Fisher (1943), the already mentioned case of a youth aged 17. In the last case the diagnosis of subarachnoid hemorrhage was confirmed by lumbar puncture and that of aneurysm by postmortem examination thirteen months later, after the patient had died of a ruptured aorta.

SUMMARY

An active, healthy girl of 19 collapsed suddenly and died and was found at autopsy to have a ruptured cerebral aneurysm associated with coarctation of the aorta. Ten cases with similar findings have been found recorded in the literature, together with 1 case of leaking aneurysm and 4 of unruptured aneurysm, making a total of 16 cases of coarctation associated with cerebral aneurysm in which the diagnosis was confirmed post mortem. A further 3 cases are recorded but without postmortem confirmation.

10. Boyd, L. J., and Werblow, S. C.: Ann Int. Med. **11**:845, 1938.
11. Walker, J. B., and Livingstone, F. D. M.: Lancet **2**:660, 1938.
12. Walsh, F. B., and King, A. B.: Arch. Ophth. **27**:1, 1942.
13. Lichtenburg, H. H., and Gallagher, H. F.: Am. J. Dis. Child. **45**:1253, 1933.
14. Baker, T. W., and Shelden, W. D.: Am. J. M. Sc. **191**:626, 1936.

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SEVERE ADRENAL CORTICAL ATROPHY (CYTOTOXIC) AND HEPATIC DAMAGE PRODUCED IN DOGS BY FEEDING 2,2-BIS(PARACHLOROPHENYL)-1,1-DICHLOROETHANE (DDD OR TDE)

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FOLLOWING the feeding of the insecticide 2, 2-bis(parachlorophenyl)-1,1-dichloroethane, commonly called DDD or preferably TDE, to dogs for periods of one to thirty-three months there was observed on both gross and microscopic pathologic examination an unusually consistent and severe atrophy of the adrenal cortex of the type generally designated as cytotoxic. Such a lesion has not been seen in the microscopic examination of over 300 other dogs in this laboratory following the usually prolonged feeding of about fifty other chemical compounds. Some of the compounds had produced severe damage of the liver or other organs, but rarely had they affected the adrenal glands in any manner, and none had caused adrenal lesions similar to those reported here. In particular, the closely related compounds DDT (2,2-bis(parachlorophenyl)-1,1,1-trichloroethane), methoxychlor and DDT dehydrochloride when administered to dogs in the same manner as TDE did not affect the adrenal glands. As stated in a preliminary note,[1] this is a striking example of chemical specificity in the causation of damage of an organ.

MATERIALS AND METHODS

Eleven young adult dogs were fed TDE dissolved in corn oil in capsules at levels of 50 to 200 (usually 50 or 80) mg. per kilogram per working day. The dosage levels were kept constant. Seven of the dogs were mongrels and 4 were Irish terriers; 6 were female and 5 were male. Gross and microscopic pathologic examination was done on each of the 7 dogs that died and the 3 that were killed. One dog is still living and in apparent good condition thirty-eight months after the beginning of the experiment.

From each of the 10 dogs studied, hematoxylin-eosin stained paraffin sections of formaldehyde-fixed tissue were made from heart, liver, gallbladder, spleen, lymph nodes, pancreas, kidney, adrenal gland, thyroid gland, parathyroid gland,

From the Division of Pharmacology, Food and Drug Administration, Federal Security Agency.

1. Nelson, A. A., and Woodard, G.: Federation Proc. **7**:277, 1948.

hypophysis, ovary (or testis) and uterus (or prostate); also frozen sections of kidney and liver were stained for fat with oil red O, and a Wright-Giemsa-stained smear of the bone marrow was made. Paraffin sections of lung and stomach and a frozen section of adrenal gland stained for fat were made from 9 dogs, and paraffin sections of thigh muscle, small intestine, colon, urinary bladder, rib bone, bone marrow and four levels of brain were made from 8 dogs. In several instances each, adrenal gland, liver and kidney were also fixed in Zenker's and/or Helly's fluid, and a Mallory type of differential connective tissue stain was made.

EFFECTS OBSERVED

Dosage of TDE, duration of feeding, etc., are given for each dog in the table. "M" in the dog number indicates that the animal was a mongrel; the others were Irish terriers. Changes resulting from treatment observed in the dogs during life were relatively slight. There was generally slight or moderate loss of weight, up to as much as 25 per cent of the initial weight. Much of this loss occurred in the last week or so of life, coincident with weakness and anorexia, which came on

Experimental Conditions for Individual Dogs

Dog	Sex	Age at Death, Mo.	Time on Experiment, Mo.	Dosage of TDE, Mg. per Kg. per Day	Weight at Start, Kg.	Weight at Finish, Kg.	Manner of Death
M-200	M	17	2	200	11.5	8.6	Died
M-198	M	16	2½	100	11.5	9.8	Killed
99-219	F	16	2½	80	9.9	7.7	Killed
M-228	M	(?)	1	80	7.0	6.8	Died
M-225	F	12	4	80	9.6	7.6	Died
M-199	M	32	20	50	9.5	9.0	Died
82-199	F	51	17	80	8.8	8.0	Died
M-201	F	38	21	50	6.5	8.3	Died
82-198	M	56	21	50	10.4	10.4	Killed
M-202	F	51	22	80	7.5	7.3	Died
99-218	F	Alive	38	50	11.0	...	.....

relatively suddenly. There were no convulsions or other neurologic symptoms. No pigmentary changes were noted.

GROSS PATHOLOGIC CHANGES

Slight or moderate emaciation was present in some of the dogs, corresponding to the loss of weight noted in these animals during life.

The adrenal glands of all the dogs, including the dog killed while apparently in good condition, were distinctly reduced in size. On section, this was accounted for by marked thinning of the cortex, which was also a deeper yellow than usual. The medulla appeared unaffected. The adrenal glands of dogs 82-198, M-201 and M-202, after formaldehyde fixation, were carefully trimmed of surrounding connective tissue and weighed; the respective combined weights were 0.50, 0.47 and 0.48 Gm. The adrenal glands of 3 control dogs of similar weight gave values of 0.82 Gm. (2 dogs) and 0.87 Gm. (1 dog) after similar treatment. Baker's [2] figures for the mean adrenal weights of dogs weighing 8.6 Kg. (average weight of the 3 TDE dogs at the time of death) are considerably higher, namely 1.14 Gm. for females in diestrus and 1.12 Gm. for mature males. The variation between different observers in the degree of careful trimming of extra-adrenal tissue, a rather time-consuming chore, is probably a large factor in such differences of weight.

2. Baker, D. D.: Am. J. Anat. **60**:231, 1937.

The liver in most instances had a moderate or marked nutmeg appearance, with a yellowish background contrasting with the dark red lobular centers. The two exceptions were dogs 82-198 and 82-199, affected respectively with slight and moderate hepatic cirrhosis, about which more will be said under "Comment."

The kidneys of several dogs showed on section prominent whitish yellow to light orange fine radial streaking of the cortices, an accentuation of the fainter streaking normally present. Apart from this, the kidneys were normal in appearance.

Organs other than the adrenal gland, liver and kidneys showed no consistent gross changes. A few incidental lesions, each occurring in only 1 dog and of uncertain relation to the treatment, will be considered together with their microscopic appearances under that heading.

MICROSCOPIC PATHOLOGIC CHANGES

Adrenal Gland.—Like the macroscopic appearance, the microscopic appearance of the adrenal gland was uniform throughout this series of dogs. Such slight variations of the microscopic picture as were present appeared to be related to the differing ages of the lesions; there was little variation in intensity.

The adrenal cortex was strikingly reduced in width, being in all instances no greater than about half the usual thickness, while in the extreme examples the thickness was about one-fifth the normal (figs. 1 *B*, *C* and *D*). The normal structure was highly disorganized (figs. 2 *A*, *B* and *C*). The zona glomerulosa was the best retained of any of the cortical zones, but it showed at least slight (in the dog killed while in apparent good health) and often marked changes in the form of loss of outline of the zone and of enlargement, rounding and foaminess of the individual cells. The zona fasciculata was shortened, the individual cords were irregular, and the cells showed the same types of alteration as did those of the zona glomerulosa. The zona reticularis had essentially vanished. Because of the loss of glandular cells from the inner portion of the cortex, there was usually an appearance of fibrosis in the juxtamedullary region, looser in the earlier examples and denser in the later ones. However, collagen stains of the Mallory type showed that most of this apparent fibrosis could be accounted for by condensation of the preexisting stroma.

Cortical inflammatory or necrotizing phenomena were never massive, but enough were present to suggest a slow, continuing process of damage with at least some coincidental attempt at repair. More of these changes were seen with the shorter than with the longer periods of survival. In the outer part of the cortex particularly, individual cells or small groups of cells showed fragmentation or pyknosis of the nuclei and/or oxyphilia or partial loss of the cytoplasm. At the same time small, undifferentiated cells appeared to be enlarging and differentiating into cortical cells. Other histologic features indicating a process other than simple atrophy were the irregularities of size and shape already noted in the individual cells and cell cords, and a mild degree of mobilization of small mononuclear and rare polymorphonuclear cells. No unquestionable mitotic figures were seen, and nothing even resembling adenomatoid hyperplasia was present. In the dogs surviving for the longer periods, the innermost cortical cells became even foamier and more like macrophages in appearance than previously and contained in addition to much lipoid material a small amount of finely divided, light brown pigment.

Vascular abnormalities in and around the adrenal glands were looked for and were absent. In frozen sections the content of sudanophilic material and of doubly refractile material in such cortical cells as remained was not diminished. The adrenal medulla was uniformly uninvolved and gave its usual chromaffin reaction

with fixatives containing potassium bichromate. Accessory cortical tissue is rare in dogs and was not noted in any location in this study.

Liver.—Moderate or severe fatty degeneration was present in the liver of every one of the 10 dogs except the one killed while in apparently good condition. Moderate centrolobular atrophy and more or less centrolobular congestion were generally present; the congestion was apparently secondary to the atrophy of hepatic cells, since elsewhere in the body evidences of chronic congestion were absent. Present in from one third to two thirds of the dogs were slight

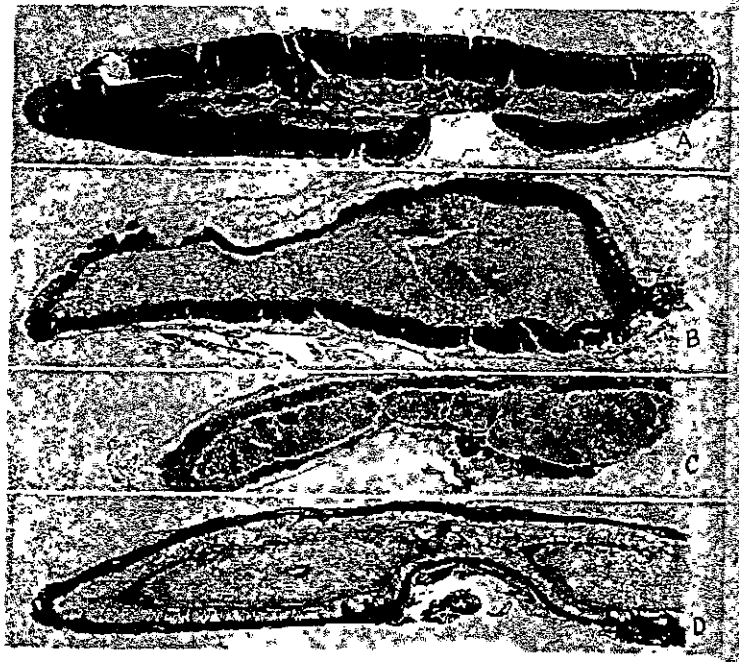

Fig. 1.—*A*, frozen section of an adrenal gland of a control dog of the same weight as the average of those fed TDE; stained with oil red O and counterstained with hematoxylin; low magnification. The magnification of B, C and D in this figure is greater than that of A.

B, frozen section of an adrenal gland of dog M-225; same stain as in *A*. Note the great reduction in the width of the cortex (darker portion).

C, frozen section of an adrenal gland of dog M-201; same stain as in *A*. Note the great reduction in the width of the cortex (darker portion).

D, frozen section of an adrenal gland of dog 82-198; Mallory connective tissue stain. Note the small amount of fibrous tissue between the markedly narrowed cortex and the medulla as compared with the larger amount in the capsule. It is apparent that any cortical fibrosis present is chiefly relative, from loss of parenchyma.

periportal fibrosis, slight proliferation of small bile ducts, slight portal lymphoid cell infiltration and portal macrophages containing small amounts of hemosiderin. Only in the dog surviving for the shortest period, thirty-four days, was there definite necrosis of hepatic cells.

Kidney.—The kidney was unaffected by TDE except that the average fat content of the tubular epithelium was about double the normal. In our experience this is a fairly common and nonspecific reaction of the dog kidney to toxic agents. Glomeruli and blood vessels were unaltered, and no "spontaneous" nephritis was present.

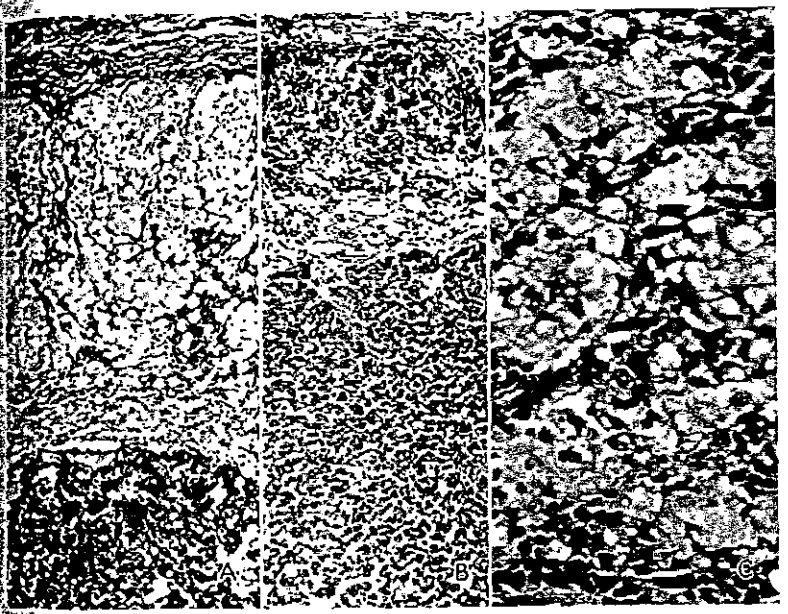

Fig. 2.—*A*, section of an adrenal gland of dog M-198; hematoxylin-eosin stain; medium magnification. Note the foamy appearance of the remaining cortical cells and the marked narrowing of the cortex. The edge of the medulla occupies the lower third of the print.

B, section of an adrenal gland of dog 82-198; same stain and magnification in *A*. Note the even greater narrowing of the cortex, now only a thin rim. About half the thickness of the medulla is shown below.

C, portion of adrenal cortex of dog 90-219, showing the foamy appearance of the remaining cortical cells, and smaller cells of various types as described in the text; high magnification.

Bone Marrow.—The marrow showed slight changes, of the type often seen accompanying death from toxic substances. With some inconsistencies, there were on the average a slight increase in the myeloid-erythroid ratio, a reduction in the number of mature granulocytes and a slight shift to the left in the myeloid line,

the metamyelocytes and myelocytes being increased in number. These changes were judged from inspection of both sections and smears; counts were not made. In at least 2 dogs, it was thought, the erythroid elements were decreased in absolute number.

Incidental Lesions.—As mentioned in connection with the gross description, there were a few lesions, each occurring in but 1 dog, which were of uncertain relation to treatment or at least not in causative relation to the adrenal lesions. To save space, only the diagnoses will be given here. Each of the lesions was visible grossly as well as microscopically. The lesions were moderate subacute focal myocarditis in dog M-200, marked erythrophagia of recent appearance in the mesenteric lymph nodes of dog M-198, a small amount of recent mucosal hemorrhage in the neck of the urinary bladder of dog M-228, a moderate amount of recent hemorrhage of the stomach mucosa in dog M-201, focal papillary proliferation of the prostatic epithelium in dog 82-198 and massive pyometra in dog M-202. The total amount of parasitism in this group of dogs was relatively small.

Other Structures.—The spleen contained a possibly slight excess of hemosiderin over the small amount normally present. Except for the incidental possibilities mentioned in the previous paragraph, lymph nodes, heart, gallbladder, lungs, pancreas, stomach, intestines, urinary bladder, thyroid and parathyroid glands, ovaries, uterus, testes, prostate, voluntary muscles, brain and hypophysis were not affected by TDE, and in all these structures the microscopic appearance was that seen in normal young adult to middle-aged dogs.

COMMENT

From the chemical point of view the adrenal lesion described is a remarkable example of chemical specificity as related to damage of an organ. From the pathologic point of view the considerable morphologic resemblance to human Addison's disease of the idiopathic or cytotoxic type raises the question of the possible position of various chemicals in the etiology of the human condition. However, we simply state the latter possibility and do not wish to stress it. We do not infer that human beings rather heavily exposed to TDE, e. g., pest control operators, are necessarily liable to adrenal damage. In all probability, some people react to a toxicant more in the fashion of a rat than a dog, and other people do the opposite. Since man is now exposed to an ever increasing number of chemicals, it becomes of some importance to determine the similarities and differences of human and animal reactions to these chemicals.

Perhaps first a brief mention of the proper name for the pathologic process seen in these dogs may be appropriate. We have labeled it "severe cortical atrophy" with the alternative designation of "cytotoxic" to agree with the more common name for the similar morphologic picture seen in man. The process is certainly not a simple type of atrophy such as may occur in certain other organs during slow starvation or in the adrenal gland itself following hypophysectomy or treatment with adrenal cortex extracts. Actually, it seems to be a slow necrosis with a certain amount of simultaneous attempt at repair, and the histologic features indicating this have already been stated. Other

names for this type of adrenal lesion of man are given by Weiner.[3] In a recent and detailed discussion Friedman[4] used the term "adrenocortical contraction."

Spontaneous disease of the adrenal cortex of a type histologically comparable to certain forms of Addison's disease seen in man apparently does not occur in animals, judging from a reasonably thorough search of the literature. Such a condition, on the basis of subtotal vascular occlusion, has been produced by the experimental surgical procedures of Rogoff,[5] principally in cats. We have seen no previous reports of its having been produced in animals on the basis of chronic toxicosis except to a limited degree in guinea pigs by Humphreys and Donaldson,[6] who used a German preparation of the type of suramin sodium U. S. P. We do recognize that less severe atrophies of a more simple type have been produced on such a basis and that severe acute damage of the adrenal gland has been produced by a variety of methods. Implication of chemical toxicants in human Addison's disease seems limited to the aforementioned German proprietary drug (germanin or Bayer 205).[7]

We have done no blood chemical, hematologic, hormonal or metabolic studies on the dogs reported on in this paper.

Only 2 of the dogs had been used in previous toxicity experiments. Strangely enough, these were the only 2 that showed cirrhosis of the liver grossly and microscopically; the condition was pronounced in dog 82-199 and of lesser degree in dog 82-198. A year and a half previously these 2 dogs had finished an eight months' course of feeding of 100 mg. of 3-methyl-4-(4-diethylamino-1-methylbutylamine)-7-chloroquinoline (SN 6911, an antimalarial drug) per kilogram per day, apparently without effect. (Two other dogs given the same course of feeding of this drug had shown only minor alterations of the liver on microscopic examination; these dogs, however, were mongrels, while the 2 later given the TDE were purebreds).

Bronchopneumonia or other infection as a contributing cause of death was essentially absent; the one exception was dog M-202, which died of pyometra nine days after being mated.

The animal toxicity studies of TDE (DDD) reported in the literature include those of Lillie and associates[8] and Haag and associates.[9] The former studied 8 rabbits treated for periods up to

3. Weiner, H. A.: Am. J. Path. **12**:411, 1936.
4. Friedman, N. B.: Endocrinology **42**:181, 1948.
5. Rogoff, J. M.: Arch. Path. **38**:392, 1944.
6. Humphreys, E. M., and Donaldson, L.: Am. J. Path. **17**:767, 1941.
7. Wells, H. G.; Humphreys, E. M., and Work, E. G.: J. A. M. A. **109**:490, 1937.
8. Lillie, R. D.; Smith, M. I., and Stohlman, E. F.: Arch. Path. **43**:127, 1947.
9. Haag, H. B., and others: Indust. Med. **17**:477, 1948.

thirty-nine days and stated that "the adrenal glands were regularly normal, with lipid depletion of the glomerular zone in 2 of 7." In 2 rats dying acutely, there was "some fatty degeneration of medulla cells in the adrenal glands." Haag and co-workers included the adrenal glands among the organs studied histologically when they exposed dogs, rabbits and rats to this toxicant by a variety of routes, but reported no lesions in them. The dogs had dust atmosphere and spray atmosphere exposure. Unpublished studies of rats, mice, rabbits and 2 monkeys of the Division of Pharmacology of the Food and Drug Administration have shown no adrenal damage from TDE.

SUMMARY

Ten dogs were studied grossly and microscopically after being fed the insecticide TDE (also called DDD; chemically, 2,2-bis [para-chlorophenyl]-1,1-dichloroethane) at levels of 50 to 200, usually 50 or 80, mg. per kilogram per day for periods of one to thirty-three months. In every one there was a high grade of adrenal cortical atrophy of a cytotoxic type. The adrenal cortex was from one half to one third or less of its usual thickness, and microscopically there was much distortion of the normal structure with alteration of the normal cellular appearances. The adrenal medulla showed no changes.

Of some dozens of compounds fed to over 300 of our dogs, none except TDE has caused adrenal cortical atrophy, even though several have caused severe hepatic damage; few have affected the adrenal gland in any way, even though they differed chemically from TDE as little as the presence of a single additional chlorine atom in the molecule.

In other animal species studied by ourselves and others TDE caused little if any adrenal damage.

Males and females, purebred and mongrel dogs, were affected alike. In addition to the adrenal gland the liver was uniformly affected, the principal lesion being fatty degeneration. The kidneys contained a greater than usual amount of fat. Among other structures the hypophysis, the testis or the ovary, the pancreas, the thyroid gland and the parathyroid gland of every one of the 10 dogs were examined, and none of these structures showed any effect attributable to TDE.

Morphologically, the condition in the adrenal gland of the dog has considerable resemblance to that observed in the adrenal gland of man in some instances of Addison's disease of the idiopathic or cytotoxic type, but we are not stressing either the morphologic resemblance or any idea of a specific chemical cause of the latter. The effect of TDE on the dog adrenal gland is, however, a striking example of chemical specificity in the causation of organic damage.

HEPATIC LESIONS PRODUCED BY LEAD IN RATS FED A HIGH FAT DIET

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ALL FORMS and degrees of damage of the liver have been described in lead poisoning: fatty infiltration or degeneration, hepatic cell degeneration with nuclear changes, fibrosis with lobular atrophy, and cirrhosis, among others.[1] Nevertheless, authors do not agree on the importance and the constancy of the hepatic injuries produced by lead.

In their book, Cantarow and Trumper [1b] concluded: "Despite the fact that hepatic cellular damage does not occur consistently in clinical or experimental lead poisoning, there seems little doubt that under certain conditions lead is at least able to contribute to the development of such damage which if protracted may eventuate in cirrhosis of the liver."

In 21 cases of acute lead poisoning in which the patients were children, Blackman [2] found inclusion bodies in the liver cells, many abnormal nuclei with or without inclusions, and occasional necrotic cells. In the majority of cases there was evidence of destruction of a few periportal liver cells together with slight chronic inflammatory reaction and scarring in each portal area. He also found somewhat similar hepatic lesions in rats given lead carbonate with drinking water.

On the other hand, rats fed a standard diet and poisoned during periods of three weeks to twenty-four months failed to show any conspicuous damage of the liver.[3]

The occurrence of hepatic lesions in lead-poisoned rats fed a high fat diet induced us to study the subject further. The results are presented in this paper.

From the Instituto de Biología y Medicina Experimental.

1. For a review of the literature see: (*a*) Schmidt, P.: Bleivergiftung, Berlin, Urban & Schwarzenberg, 1930; (*b*) Cantarow, A., and Trumper, M.: Lead Poisoning, Baltimore, Williams & Wilkins Company, 1944.

2. Blackman, S. S., Jr.: Bull. Johns Hopkins Hosp. **58**:384, 1936.

3. (*a*) Finner, L. L., and Calvery, H. O.: Arch. Path. **27**:433, 1939. (*b*) Fairhall, L. T., and Miller, J. W.: Pub. Health Rep. **56** (pt. 2):1610, 1941. (*c*) Chiodi, H.: Unpublished Data.