TOXIC NECROSIS AND REGENERATION OF THE ACINAR CELLS OF THE PANCREAS.*

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This piece of work was suggested by the chance finding of a mitotic figure in an acinar cell of the pancreas, a phenomenon which had been considered rare in this laboratory, although mitotic figures in the islet cells had been found quite frequently and studied with a view to learning under what conditions they occurred.

All tissues studied were fixed in Zenker's fluid and stained by Mallory's eosin-methylene blue method, in order to bring out necrotic cells, which this stain does most admirably, as is shown by the fact that the frequency and extent of necroses in the liver were not appreciated until this stain was employed. The mitotic figures were sought for with the aid of a mechanical stage and an oil immersion lens, because they are difficult to see under lower powers owing to the basophilic staining of the acinar cells.

In order to determine how frequently and under what conditions mitotic figures in the acinar cells do occur, sections of the pancreas from a series of autopsies performed here were studied with the result that one hundred such cases were collected out of some four hundred gone over. The number of mitotic figures in a section varied from one or two up to thirty-one in one instance.

The lesions in these pancreases varied from acute pancreatitis with fat necrosis to an infiltration with polymorphonuclear leucocytes, endothelial leucocytes and lymphocytes in the connective tissue. There were but seven cases of acute pancreatitis with fat necrosis, hence the cause of

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the regeneration as evidenced by the mitoses had to be sought for further, and was found in a type of necrosis not generally recognized, although quite common in the pancreas, namely, necrosis due to toxins, or toxic necrosis. This type of lesion is to be differentiated from the two other more severe and less common types which give rise to gross anatomical changes in the organ. The types of necrosis in the pancreas on an etiological basis are to be classified as follows:

1. Acute pancreatitis with fat necrosis. This is caused by the action of digestive ferments liberated from the acinar cells. What causes this liberation is not clear, although in some instances backing up of the bile due to some obstruction, usually a gall-stone in the ampulla of Vater, apparently is a factor. There has been a question as to whether necrosis precedes the liberation of the ferments, or whether the ferments are set free first, and then cause the necrosis. The latter view seems to be the correct one, as fat necrosis does not occur in the two next types where necrosis of the acinar cells is marked. The liberated ferments attack the fat tissue, causing the so-called fat necroses, and also other tissues such as the pancreatic tissue itself and muscle, with which they may come in contact. If they attack the blood vessels, hemorrhage ensues and there results the condition known as acute hemorrhagic pancreatitis. A certain number of lesions of this type are complicated by a secondary infectious process, sometimes producing gangrene.

2. Necrosis due to toxins — the type described in this paper.

3. Infectious pancreatitis. This may occur with or without abscess formation and arises:

a. By infection extending up along the ducts similar to infectious cholangitis and pyelonephritis.

b. From organisms circulating in the blood stream.

c. From extension of suppurative processes in the neighborhood.

The first and third types are generally extensive enough to give rise to clinical symptoms and even to cause death, whereas the second type would very seldom cause symptoms or death.

In toxic necrosis the pancreas grossly shows no changes. Microscopically the necrosis is found to occur in single acinar cells, groups of cells, or diffusely; the number of such lesions in a single section varies from one or two necrotic cells up to involvement of more than half the cells. The necrotic cells are invaded by polymorphonuclear and endothelial leucocytes, as in other organs, and are very quickly removed. Regeneration follows rapidly and repair is complete. Often the processes of necrosis and regeneration are found in the same section, a fact true of over one-half of the lesions collected here. These necroses are believed to be toxic in origin because of similar lesions so recognized in the heart, liver, kidney and adrenals, because of the type of infection with which they are associated and because of the form of the lesion, namely, necrosis of the acinar cells with no involvement of the connective tissue and with no demonstrable organisms present.

The cases in which toxic necroses were found most frequently were pneumonia, diphtheria, acute peritonitis and other processes due to the streptococcus and pneumococcus, — rarely to the staphylococcus aureus.

The cases in which mitotic figures were found are tabulated below:

Lobar and bronchopneumonia	24
Acute peritonitis	20
Diphtheria	10
Acute pancreatitis with fat necrosis	7
Empyema and acute pleuritis	5
Acute yellow atrophy of the liver	4
Acute endocarditis and pericarditis	3
Erysipelas	3
Scarlatina (late)	2
Measles	1
Abscess of pancreas	1
Typhoid	1
Hemochromatosis	1
Amœbic dysentery	1
Suppurative processes elsewhere in the body due to the streptococcus, pneumococcus, rarely the staphylococcus aureus	17
Total	100

In view of the above facts, it was considered to be of interest to study the heart, liver, kidney and adrenal with regard to the occurrence of acute toxic lesions or mitotic figures in the cases in which mitoses were found in the pancreas. Eighty-five such cases were studied with the following results:

The heart showed acute toxic myocarditis in fifteen per cent of the cases. The liver showed necrosis or regeneration in sixty per cent of the cases; the kidney in forty-five per cent, and the adrenal in ninety-two per cent. In every case in which the heart was involved, the liver, kidney and adrenal, as far as tissues from these organs were available for study, were found to be involved. In every case in which the kidney showed involvement, the liver and adrenal also showed pathological changes; and finally, the adrenal was involved in every case in which the liver was affected. The adrenal showed such a high percentage that the pancreas was studied in another series of cases in which the adrenal was known to show lesions, with the result that the pancreas in a fair per cent showed no involvement. So, apparently, the organs should be placed in the following order as regards the frequency of toxic lesions — adrenal, pancreas, liver, kidney and heart. I find it impossible in making an analysis of the cases to determine which organ on the whole regenerates the most rapidly — as first one, then another, seems to lead. Factors such as the extent of the lesion and the general condition of the organ complicate the picture so as to render the question very difficult to decide.

The above facts emphasize once again that the lesions caused by an acute infection are by no means confined to the organ primarily involved, but that all organs suffer to some degree.

Experimental work. — But little experimental work was done owing to lack of time; it is hoped that more may be done at some future date, as the results were encouraging.

1. A male guinea-pig, weighing about three hundred grams, was kept for two hours by chloroform vapor in a state of anæsthesia varying from a light degree to a point where the

corneal reflex was lost and the breathing became slow and irregular. For one hour afterward the animal had convulsive movements. The animal was killed forty-eight hours later by rapid chloroform anæsthesia and autopsied immediately; the tissues were fixed in Zenker's fluid, embedded in paraffin, and stained by Mallory's eosin-methylene blue method. Microscopically, the liver, adrenal and pancreas all showed signs of active regeneration, the liver and adrenal, but not the pancreas, also showing remains of necrotic cells. (This line of work was suggested by similar experiments by G. S. Graham on the adrenal. Journal Medical Research, Vol. XXIX., No. 2, pp. 241–261, May, 1916.)

2. A pregnant female guinea-pig, weighing seven hundred grams, was given *per os* .70 centimeters of liquor potassii arsenitis. Five days later, the animal went into labor and gave birth to one dead fetus. She died a few hours later and was autopsied shortly afterward; the tissues were fixed and stained as in the above experiment. Microscopically the liver showed marked fatty degeneration, but no necrosis or mitoses; the pancreas, kidney and adrenals showed no necrosis, but did show signs of active regeneration, most marked in the adrenal in which mitotic figures to the number of fifteen in one high, dry field were found. It seems, therefore, that arsenic causes necrosis in the pancreas, kidney and adrenal, as well as the liver.

These two experiments confirm the findings in the human cases; namely, substances affecting the liver, kidney and adrenal affect the pancreas, and also this last-named organ has great power of regeneration.

SUMMARY.

1. Toxins which cause lesions in the heart, liver, kidney and adrenal, cause similar lesions in the acinar cells of the pancreas, which heretofore have been overlooked.

2. The acinar cells of the pancreas have great power of regeneration.

Incidentally, the observation that arsenic causes necrosis in the kidney, adrenal and pancreas as well as the liver, should be noted.

LITERATURE.

The works of Aschoff, Kaufmann, Orth, Ribbert, Opie and Heiberg were consulted, and no reference to regeneration of the acinar cells of the pancreas was found with the exception of mention in the " Pathologische Anatomie " of Aschoff, under the head of " Die chronische produktif Pankreatitis," of regeneration of the islet and acinar cells in this condition with the formation of adenomatous masses (analogous to similar changes in the lobules of the liver) leading to the process known as " Pankreaszirrhose."

[I wish to express my great indebtedness and gratitute to Dr. F. B. Mallory for his many helpful suggestions and advice, and for his teachings, without which this piece of work would not have been possible.]

DESCRIPTION OF PLATES XIX. AND XX.

(The photomicrographs were made by Dr. F. B. Mallory.)

PLATE XIX., FIG. 1. — Late scarlatina; acute pleuritis and pericarditis; septicæmia (? of streptococcus). Section of pancreas showing toxic necrosis of acinar cells with an exudate of polymorphonuclear and endothelial leucocytes. x250.

FIG. 2. — Similar lesion from same pancreas under oil immersion lens. x1000.

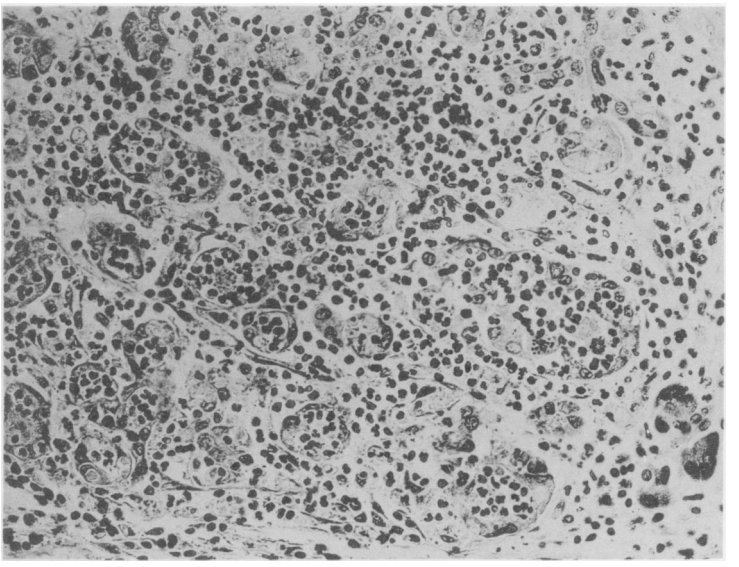
PLATE XX., FIG. 3. — Diphtheria. Pancreas. Focal toxic necrosis of acinar cells with an exudate of polymorphonuclear and endothelial leucocytes. x500.

FIG. 4. — Bronchopneumonia. Pancreas. Field showing one normal and six necrotic acinar cells. In the upper part of the field, two necrotic cells are contained within endothelial leucocytes, whose crescent-shaped nuclei can be made out. The normal cell is in the lower, right central part of the field. x1000.

FIG. 5. — Lobar pneumonia. Pancreas. Mitotic figures in two acinar cells. x1000.

FIG. 6. — Diphtheria. Pancreas. Mitotic figure (diaster) in an acinar cell in the neighborhood of a focal toxic necrosis. x1000.

FIG. 7. — Acute pancreatitis with fat necrosis. Pancreas. Mitotic figure (diaster) in an acinar cell. The lumen of the gland contains polymorphonuclear and endothelial leucocytes, and some necrotic cell débris. x1000.



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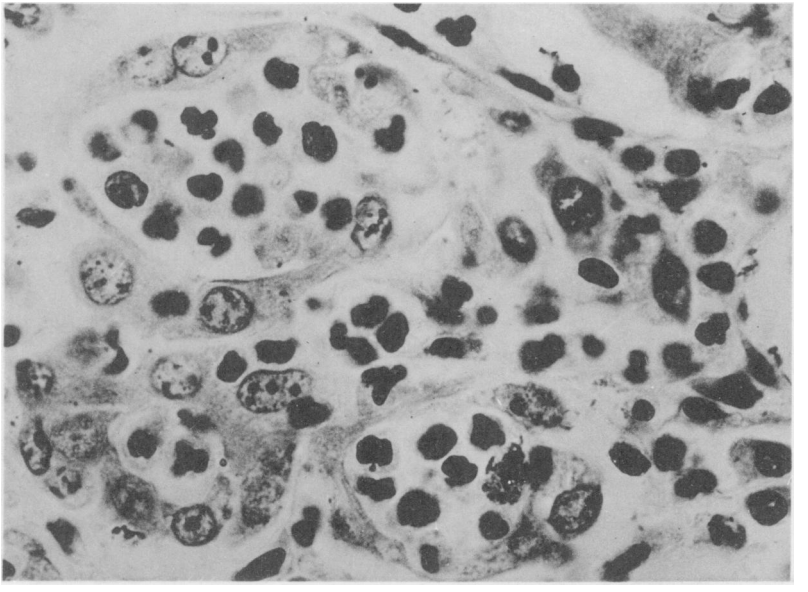

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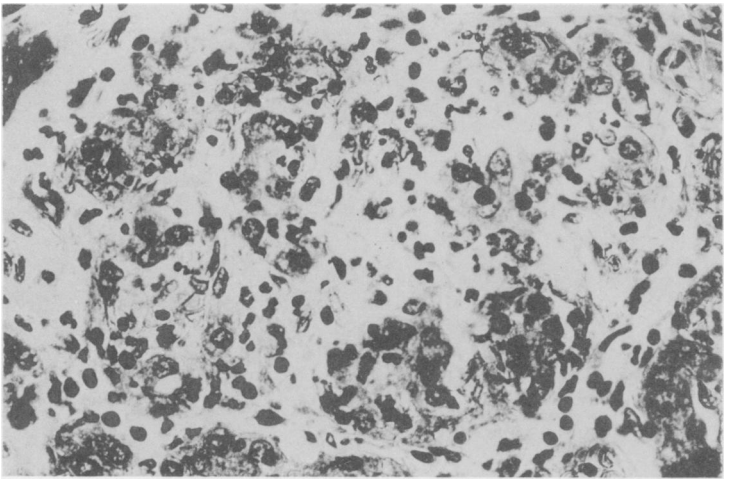
F. Parker Jr

Toxic necrosis.



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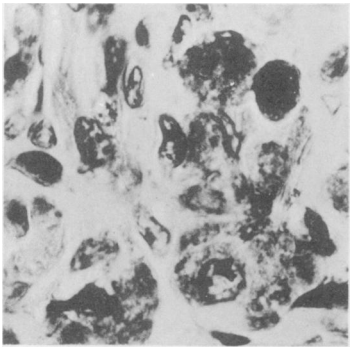

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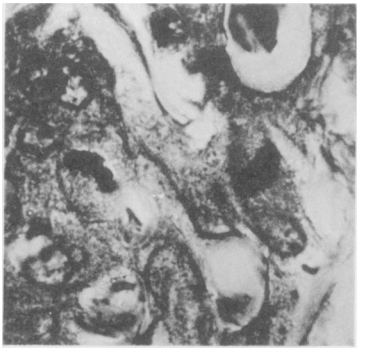

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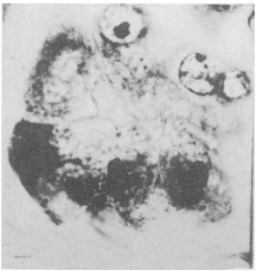

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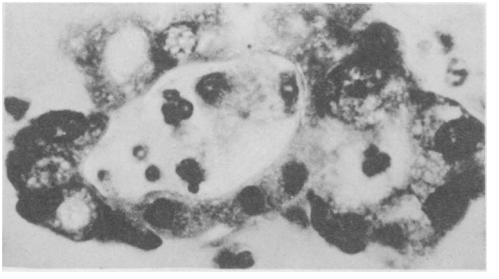

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