THE HISTOPATHOLOGICAL CHANGES IN RATS FOLLOWING ADMINISTRATION OF PENTOTHAL SODIUM AND SULFANILAMIDE

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Since the introduction of pentothal sodium as an intravenous anesthetic agent in 1934 and of sulfanilamide as a bacteriostatic agent in 1935 a large number of clinical and experimental observations have been published regarding each of these drugs. Each one has been hailed as a great advance in its field, and there has been considerable indiscriminate use of both. Each has been shown to be toxic to some extent, even in therapeutic doses.

Sulfanilamide is detoxified by the liver and the products of detoxification are eliminated by the kidneys. Its toxic effects should therefore be most apparent in these two organs. A review of the literature lends support to this assumption. Greene and Hotz (1) describe a fatal case of acute toxic hepatitis following treatment with sulfanilamide, in which the microscopic lesion was focal periportal degeneration without leukocytic infiltration. Garvin (2) reports 5 cases of acute toxic hepatitis following treatment with sulfanilamide, of which one was fatal. In a later article (3) he concludes that sulfanilamide may be added to the list of agents capable of so damaging the liver as to produce jaundice and ascites, and yet permit recovery. Cases of acute hepatitis due to sulfanilamide are also reported by Hageman and Blake (4), Saphirstein (5), Long (6), and Bannick, Brown and Foster (7). Cline's (8) case is less clear, as it is one in which acute yellow atrophy followed the administration of sulfanilamide to a patient whose diagnosis was acute catarrhal jaundice. At autopsy the liver showed a massive breaking up of the lobules and cords, with fatty change in the cells which remained recognizable. The kidneys showed nephritis of undetermined origin.

Hageman (9) was unable to show definite pathological changes in the livers of white mice receiving 1.0 to 2.5 Gm. of sulfanilamide per kilo of body weight. After giving rabbits massive intraperitoneal injections (0.4 to 2.0 Gm. per kilo) of sulfanilamide and killing them one week later, Hawking (10) found no histological changes which could be attributed to the drug. Marshall, Cutting, and Emerson (11), using 0.16 to 0.35 Gm. per kilo for about sixty-five days, obtained similar nega-

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tive results in rats. Nelson (12) found the livers of 12 out of 20 rabbits normal after fatal (0.5 to 1.0 Gm. per kilo daily for two to ten days) doses of sulfanilamide. Changes in the others he lists as follows: slight fatty change, slight diffuse atrophy, slight central atrophy, slight to moderate vacuolar degeneration, and slight to moderate excess of bile pigment. Eighteen of the 20 kidneys which he examined showed one or more of the following changes: cloudy swelling, fatty change, presence of casts, and dilatation of the tubules. Geiling and Cannon (13) found moderate fatty change of some of the collecting tubules of dogs receiving 0.2 Gm. of sulfanilamide per kilo thrice daily for a total of eight or more doses. The same changes, but less marked, occurred in rats receiving the same dose. They found only very slight fatty change in the liver.

Marshall, Cutting, and Emerson (14) found that sulfanilamide is excreted 100 per cent in the urine after equilibrium is established. Long, Bliss, and Feinstone (15) state that patients with impaired renal function must always be observed carefully while receiving sulfanilamide, lest the drug accumulate in the tissues, and they add "The antidote for sulfanilamide is water."

The fate of pentothal in the body is less generally agreed upon than is the case of sulfanilamide. The tendency has been to assume that it is destroyed by the liver after the manner of its homologue, pentobarbital (sodium ethyl 1-methyl butyl barbiturate). Thus Hale (16) says "The short duration of the anesthesia (with pentothal) is attributable probably to a splitting of the molecule by the liver rather than to its elimination by the kidney." Marshall (17) also states that pentothal is destroyed by the liver and that its elimination is not primarily a function of the kidneys.

There is some experimental work to support this theory. Reynolds, Schenken and Veal (18) observed focal necrosis in the livers of 19 out of 20 white mice narcotized with pentothal. Cameron (19) and Cameron and de Saram (20) state that liver damage seems to increase susceptibility to barbiturates, especially to the short-acting series. Gruhzit et al (21) report that the predominating changes in all animals dying of thiobarbiturate intoxication are congestion, stasis, and hemorrhage. However, these findings may be accounted for by anoxia and are not specific for the thiobarbiturates. Vaizey (22) reports a case of toxic jaundice following the administration of pentothal sodium for a hemorrhoidectomy in a woman who had a chronic, severe anemia. He attributes the jaundice to anoxemia due to depression of respiration in an anemic patient, rather than to any toxic effect of the drug itself.

On the other hand, Scheifley and Higgins (23) found that although partial hepatectomy in rats caused marked prolongation of anesthesia with pentobarbital, it had no effect on the action of pentothal sodium. Also, Adams (24) says "it has been observed clinically that patients who
have hepatic damage appear to require as much of the drug (pentothal) to produce narcosis as do those patients who have no hepatic damage."

In spite of the lack of conclusive evidence it is commonly said that there may be danger in giving pentothal to a patient who has been treated recently with sulfanilamide. Hewer (25) described the production of sulfhemoglobinemia following the simultaneous use of two sulfur-containing preparations. Adams (26) states that a thiobarbiturate is not felt to be a safe anesthetic when the patient has been receiving another sulfur-containing drug, such as sulfanilamide. Lundy (27) mentions that previous treatment with sulfanilamide may possibly be considered as a contraindication to pentothal sodium, and recommends evipal for such cases. Adriani (28), using 0.5 to 1.0 Gm. of sulfanilamide per kilo per day for three days, came to the conclusion that the administration of barbiturates subsequent to sulfanilamide therapy seems to render rats more easily anesthetized, this being especially true of the thiobarbiturates, and he suggests that the combination of sulfanilamide and barbiturates may be unwise in human therapy.

King (29), however, found no correlation between the degree of sedation with nembutal and sodium amytal and previous dosage of sulfapyridine or sulfanilamide in clinical patients with pneumonia. Long, Bliss, and Feinstone (15) state that barbiturates, arsenphenamine and other drugs except saline cathartics may be given in conjunction with sulfanilamide as indicated.

The present study was undertaken to determine the toxic effects of pentothal sodium upon the liver and kidneys subsequent to sulfanilamide therapy. The animals used in our experiments were white Wistar rats between the ages of 6 weeks and 3 months having an average weight of about 150 grams. They were given sulfanilamide intraperitoneally in dosage of 0.15 Gm. per kilo of body weight per day. This dose was chosen as being comparable to that recommended by Long and Bliss (30) for human therapy. At the end of seven days they were given an anesthetic dose of pentothal sodium intraperitoneally. The criteria of anesthesia were inability of the rat to move from its side when placed there, and abolition of the pain reflex when the tail was pinched with a hemostat. This usually required from one to 3 minims of a 5 per cent solution of the pentothal. The animals remained in this condition for periods ranging from a few minutes to one hour or more. Eighty-eight rats were treated in the manner described above; 20 others were given only pentothal sodium, one to 3 minims of a 5 per cent solution; another group of 16 rats was given sulfanilamide 0.15 Gms. per kilo per day for seven days, but no pentothal. Seventeen untreated rats were used as controls. The animals were killed by a blow on the head one-half to six hours after receiving pentothal sodium, except for 36 of the rats which had had sulfanilamide; 18 of these were killed twenty-four hours after being given pentothal and 18 were killed forty-eight hours after having been anesthetized with pentothal. When no pento-
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that was given the rats were killed twenty-four hours after the last dose of sulfanilamide. Sections were made and studied by one of us (M. H.) after the liver and kidneys had been fixed in 10 per cent formalin. They were numbered in code so that the pathologist did not know which were the controls nor what drug or drugs each animal had received.

The gross anatomical changes in all animals were insignificant. The histopathological findings consisted of (1) cloudy swelling, which in some fields had advanced to vacuolar or hydropic degeneration with disruption of the cords of hepatic cells or of the tubular epithelium of the kidneys; (2) hyaline droplet formation in certain tubules of the renal epithelium; (3) early nuclear changes—pyknosis and karyolysis—in the hepatic and renal epithelium showing the most advanced parenchymatous changes.

The accompanying tables list in order of increasing severity the histopathological changes noted in the various groups. Table 1 shows the pathological findings in 17 normal rats; Table 2, the findings in 16 rats given a therapeutic dose (0.15 Gm. per kilo) of sulfanilamide; Table 3, the pathological findings in 20 rats given anesthetic doses of pentothal sodium; and Table 4, the histopathological findings noted in 88 rats which were given sulfanilamide and later pentothal sodium.

### TABLE 1

**Histopathological Findings**

<table>
<thead>
<tr>
<th>Liver</th>
<th>Kidney</th>
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<tbody>
<tr>
<td>1. Negative ............................................. 7</td>
<td>1. Negative ............................................. 6</td>
</tr>
<tr>
<td>2. Cloudy swelling ...................................... 4</td>
<td>2. Cloudy swelling with precipitate in tubules ............. 5</td>
</tr>
<tr>
<td>3. Area of nuclear degeneration and regeneration with cloudy swelling .......... 6</td>
<td>3. Tubular vacuolization and degeneration .................. 2</td>
</tr>
<tr>
<td>5. Chronic glomerular nephritis ...................... 1</td>
<td>5. Chronic glomerular nephritis ...................... 1</td>
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<tr>
<td>17</td>
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### TABLE 2

**Histopathological Findings**

<table>
<thead>
<tr>
<th>Sulfanilamide</th>
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<table>
<thead>
<tr>
<th>Liver</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1. Negative ............................................. 4</td>
<td>1. Negative ............................................. 3</td>
</tr>
<tr>
<td>2. Early fatty degeneration ......................... 3</td>
<td>2. Cloudy swelling ....................................... 7</td>
</tr>
<tr>
<td>3. Mild toxic changes ................................. 5</td>
<td>3. Cloudy swelling with karyolysis in tubules ............. 4</td>
</tr>
<tr>
<td>4. Toxic changes, cells swollen, and granular. Many pale nuclei, pyknosis, vacuolar degeneration .......... 3</td>
<td>4. Cloudy swelling with moderate advanced early degenerative changes in tubules ...................... 1</td>
</tr>
<tr>
<td>5. Very marked toxic change with degeneration and beginning necrosis .......... 1</td>
<td>5. Early glomerulonephritis ...................... 1</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
</tr>
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At this point it should be mentioned that the early degenerative changes described are not specific for the drugs used in this experiment. It should also be pointed out that we expected to find only early changes in those animals which were sacrificed within six hours after the administration of the pentothal sodium. This was done with the idea of avoiding regeneration or recovery from the immediate toxic effects, in which we were primarily interested. We are aware that the maximum pathological changes in chloroform poisoning are seen twenty-four
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hours after the administration of the anesthetic, and that the possibility of similar delayed damage with pentothal has not been ruled out. However, a group of 18 rats which were permitted to survive for twenty-four hours after receiving pentothal sodium and 18 others which were killed after forty-eight hours showed no more pathology than those which were killed at the end of six hours.

In the first group of animals we thought that we were able to distinguish the normal or control animals showing changes from those showing parenchymatous degeneration in the liver and kidneys produced by drugs. But on a larger series of rats the same degenerative changes were found in the controls as in the rats given sulfanilamide, pentothal sodium, or both drugs. There is no correlation between the degree of degeneration, the dosage of the drugs and the period of time the pentothal was allowed to act, or the amount of liver damage as compared to the kidney damage in the same animal.

From the results which we obtained in the study of the toxicity of pentothal sodium in conjunction with therapeutic doses of sulfanilamide it would seem that there is no cumulative toxic action on the livers and kidneys of white rats due to the administration of these two drugs. The slight changes that were seen might have been produced by either the sulfanilamide or pentothal sodium alone and were often similar to the early degenerative changes seen in the control rats.

We cannot conclude from this data that the administration of pentothal sodium following sulfanilamide therapy is entirely without danger, since the effects of the two drugs upon the organism as a whole and particularly upon the cerebral and medullary centers must be considered before reaching such a conclusion.

REFERENCES


Physician-anesthetists desiring certification whose practice is not limited exclusively to anesthesiology should obtain information from the Committee on Fellowship of the American Society of Anesthetists, Inc., E. H. Eliasberg, M.D., Secretary, 275 Central Park West, New York City.

If the practice of physician-anesthetists is limited exclusively to the specialty, they may be eligible for certification by the American Board of Anesthesiology, Inc., Paul M. Wood, M.D., Secretary, 745 Fifth Avenue, New York City. It is suggested that possible applicants read the statement of the American Board of Anesthesiology, Inc., in the Journal of the American Medical Association, which statement is appearing in alternating current issues.