LIVER NECROSIS IN BURNS

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BARDEEN (1898) described "focal degeneration in the lymphatic tissues, liver and advanced parenchymatous degeneration of the kidneys" in autopsies upon five children with extensive burns. Weiskotten (1919) found focal necrosis of the liver in two of ten burn autopsies. Pack (1926), after a comprehensive review of the subject, stated that "there are no internal or visceral lesions pathognomonic of burns and scalds." Wilson (1935) attributed severe necrotic or fatty degeneration of the cells at the center of the liver lobule to the acute toxemia following severe burns. A further study of 33 cases, by Wilson, MacGregor and Stewart (1938), compared the liver lesion in burns to acute yellow atrophy.

McClure (1939), and McClure and Lam (1940) reported marked jaundice in clinical cases, with marked central necrosis of the liver in a case which failed to survive. Belt (1939) compared the midzonal necrosis of the liver found in four fatal burn cases to the liver lesions of yellow fever because of the demonstrated Councilman bodies and intranuclear inclusions. Wells (1940) was probably the first to offer objective data, suggesting that the tannic acid treatment might be the cause of liver necrosis, when he reproduced the lesion in rabbits by intraperitoneal and subcutaneous injections of tannic acid.

As a part of a study on burns projected by the National Research Council,* and carried out at the Henry Ford Hospital, further experimental study of liver damage was undertaken in an effort to determine:

1. The effect of the burn alone on the liver.

2. The effect of various types of protein coagulating chemicals, including tannic acid, on the liver.

3. The effect of burns treated with protein coagulating chemicals on the liver.

4. The effect of tannates on the liver and the significance of their identification in the urine of tannic acid treated and injected animals.

EXPERIMENTAL STUDIES

The experiments were all performed upon dogs under morphine and ether, or morphine and chloroform anesthesia. Morphine was continued for 24 to 48 hours after the procedures routinely, and longer if needed for the

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Henry Ford Hospital.

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FIG. 1.

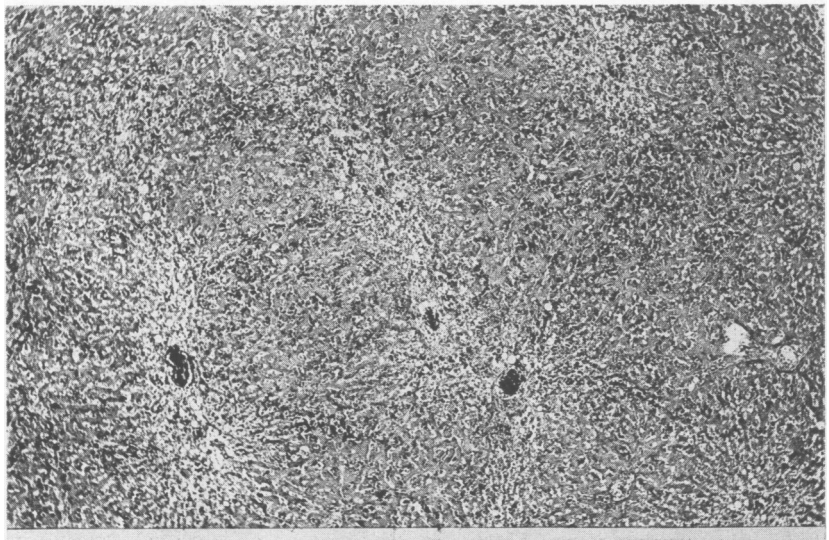


FIG. 2.

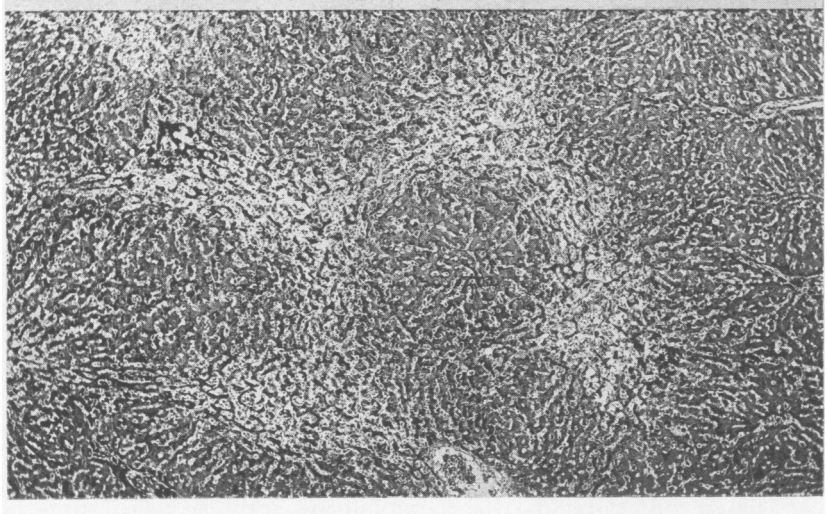


FIG. 1.—Dog. No. 3118: Photomicrograph of liver from animal in which a 60% skin burn was produced with Bunsen burner and dressed with sterile vaseline. Survival—10 days. Shows marked congestion, myelinization and necrosis at the center of the liver lobules. (Low power.)

FIG. 2.—Dog No. 3121: Photomicrograph of liver from animal in which a 60% skin burn was produced with Bunsen burner and dressed with vaseline scarlet R. Survival—9 days. Shows spotty necrosis about the center of the lobules with intense engorgement. (Low power.)

comfort of the animals. In case chloroform was used care was taken not to prolong the administration more than 15 to 20 minutes. The burns were produced with both dry heat and moist heat over 60 to 65 per cent of the body surface and were uniformly of third-degree severity.

GROUP 1.—To determine the effect of burns alone on the liver, the lesion was immediately dressed with neutral substances, sterile vaselined gauze

in 12 instances, lanolin in two instances, and normal salt solution in two instances.

In this group, 16 animals with large skin burns were used. The duration of life following the burn ranged from 4 to 20 days. The dressings, following the Koch method, were changed infrequently, if at all. The injured skin underwent maceration in 4 to 5 days and usually was the site of infection and suppuration. At autopsy, emaciation and anemia along with local and general infection were the usual findings. Grossly, the liver was enlarged, and in those living shorter periods, congested. The spleen was usually enlarged to 2 to 4 times the normal. Metastatic abscesses, with or without hemorrhages, were frequently seen. Curling's ulcers of the duodenum were produced in 5, or 33 per cent, of this group, and will be discussed in a later communication. Microscopically, the liver lesions ranged from marked suggestion of the sinusoids, with compression of the liver cords, to varying amounts of granular, vacuolar and fatty degeneration in experiments running 4 to 10 days, while myelinization and central necrosis was seen in those surviving 8 to 10 days (Figs. 1 and 2). The central necrosis in this series is a late development and associated with intense infiltration of the affected area. Although such lesions were accompanied by depression of liver function and icterus indices up to 20, the picture was not that of acute liver insufficiency.

GROUP 2.—To determine the effect of protein coagulating chemicals on the liver these substances were injected intraperitoneally and subcutaneously, and applied as a dressing to large surfaces from which the skin had been excised in 112 animals.

A. Silver Nitrate.—In this group, 15 animals were used, and all were injected subcutaneously with 2 per cent solution while the animals were under morphine and ether anesthesia. After injection morphine sulphate was given as indicated.

These animals survived the injection from 1 to 23 days. One animal died from distemper. Four animals lived only one day, but in all these marked, acute congestion of the liver, especially about the center of the lobule, was noted. Granular degeneration and early necrosis was seen in three. Two showed central necrosis of the liver of marked degree and extensive myelinization. Thus, 5, or 33.3 per cent, showed necrosis in varying degree but only 2, or 13.3 per cent, had extensive necrosis and myelinization, and these died on the eighth and eighteenth day, respectively. Eleven of the 15 died from the effects of the injection, and 4 were sacrificed because of ulceration (Figs. 3 and 4).

B. Alum.—Nine animals were used for the subcutaneous injection of aluminum and potassium sulphate. The 10 per cent solution was sterile and used in amounts ranging from 60 to 180 cc. The injections were all done under morphine and ether anesthesia. The length of life after injection ranged from 3 to 10 days, but five animals were sacrificed because of

ulceration and infection. Microscopically, the livers showed marked congestion and engorgement, with granular, and especially vacuolar degeneration. These degenerative changes obscure the cells near the center of the lobule but do not represent necrosis of cells such as seen in other groups.

C. Sulphosalicylic Acid.—Only six animals were used in this group, partly

FIG. 3.

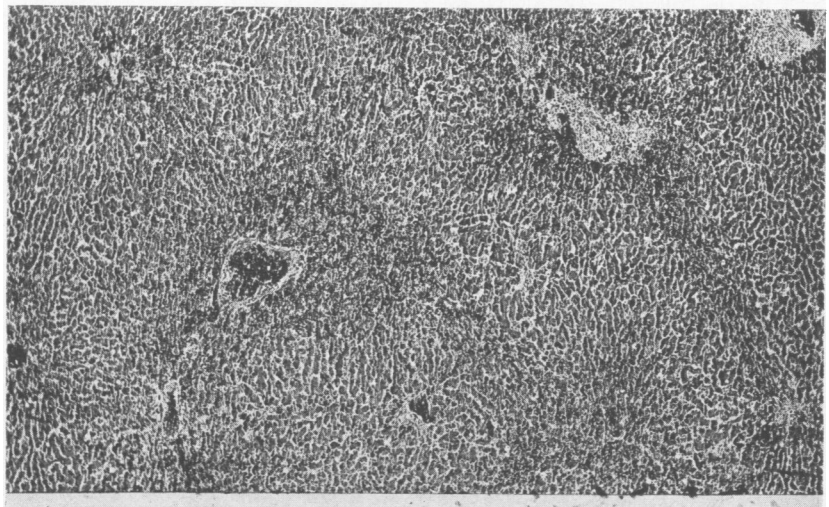


FIG. 4.

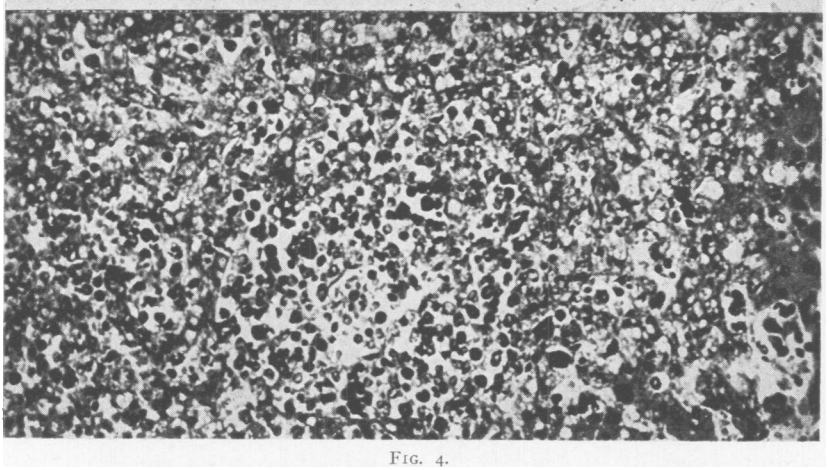


FIG. 3.—Dog No. 3126: Photomicrograph of liver from animal receiving 120 cc. silver nitrate 2% subcutaneously. Survival—5 days. Shows marked congestion, hemorrhage, and beginning necrosis at the center of the liver lobules. (Low power.)

FIG. 4.—Dog No. 3041: Photomicrograph of liver from animal receiving 100 cc. 2% silver nitrate subcutaneously. Survival—18 days. Shows central necrosis of liver lobule with intense myelinization. (Medium power.)

because the pathologic changes in the liver and other organs were minimal and partly because the sites of injection opened spontaneously and drained. Even the animals receiving from 120 to 140 cc. of 3 per cent solution, and surviving 7 to 10 days, showed congestion with early necrosis in two, and myelinization in one animal.

D. Zinc Peroxide.—In this group only five animals have been used to date. All were given subcutaneously suspensions of sterile ZnO_2 in sterile water; in the first instance 200 cc. of 7 per cent, and the other four 110 cc. of 22 per cent. These animals survived from 6 to 15 days. Three showed clinical jaundice with icterus indices from 15 to 35. Two showed central necrosis, while all showed congestion coupled with granular and vacuolar degeneration. The jaundice seen in this group is out of proportion to the necrosis seen in the liver but corresponds with the rapid weight loss and short duration of life.

E. Ferric Chloride.—Ferric chloride is one of the chemicals used as a tanning agent in the treatment of burns, hence it was included in this study both for subcutaneous injection and as a dressing for burned areas.

Thirteen animals were used for subcutaneous injection, 11 receiving from 100 to 175 cc. of a sterile 5 per cent solution, and two receiving 110 and 120 cc., respectively, of a sterile 10 per cent solution. Ten of the 13 died in from 1 to 5 days, and three were sacrificed after becoming moribund in 2 to 5 days. At autopsy, there was extensive greyish-yellow coagulation necrosis at the site of injection and extending around either side to the abdomen, associated with marked edema and blood extravasation. The hemorrhagic tendency was also seen at times in the pericardium and intestines. The liver was usually enlarged, mottled and dark red in color. Microscopic sections showed marked acute congestion with hemorrhage in seven animals and central necrosis in five, or in 38 per cent. This incidence of necrosis is somewhat higher than with tannic acid but the extent of the necrotic areas tends to be less. Hemorrhage, with and without necrosis, is more striking with ferric chloride than with tannic acid (Fig. 5).

F. Gallic Acid.—It has been suggested, from time to time, that gallic acid is toxic for the animal organism, at least that it is more toxic than tannic acid. This has been given as a reason for insistence on using only freshly prepared tannic acid solutions in the treatment of burns. Gallic acid, as a sterile 7.5 per cent solution, has been used five times for subcutaneous injection in amounts ranging from 110 to 150 cc. Microscopically, the livers of these animals showed principally acute congestion, hemorrhage and compression of the liver cells.

G. Quebracho Tannin.—Only four animals were used in this series because of the scarcity of material. The material used was the crude tannin* made up in a solution roughly comparable to the 7.5 per cent tannic acid, as far as the tannin content is concerned. This solution was injected subcutaneously in amounts ranging from 90 to 150 cc. The animals survived for periods ranging from 8 to 18 days. Clinical jaundice occurred once and, microscopically, central necrosis of the liver was found in two animals. Although this group is small it suggests that crude quebracho tannin has the same, or greater, possibilities for tannate absorption as tannic acid.

* Furnished by Parke, Davis & Co.

FIG. 5.

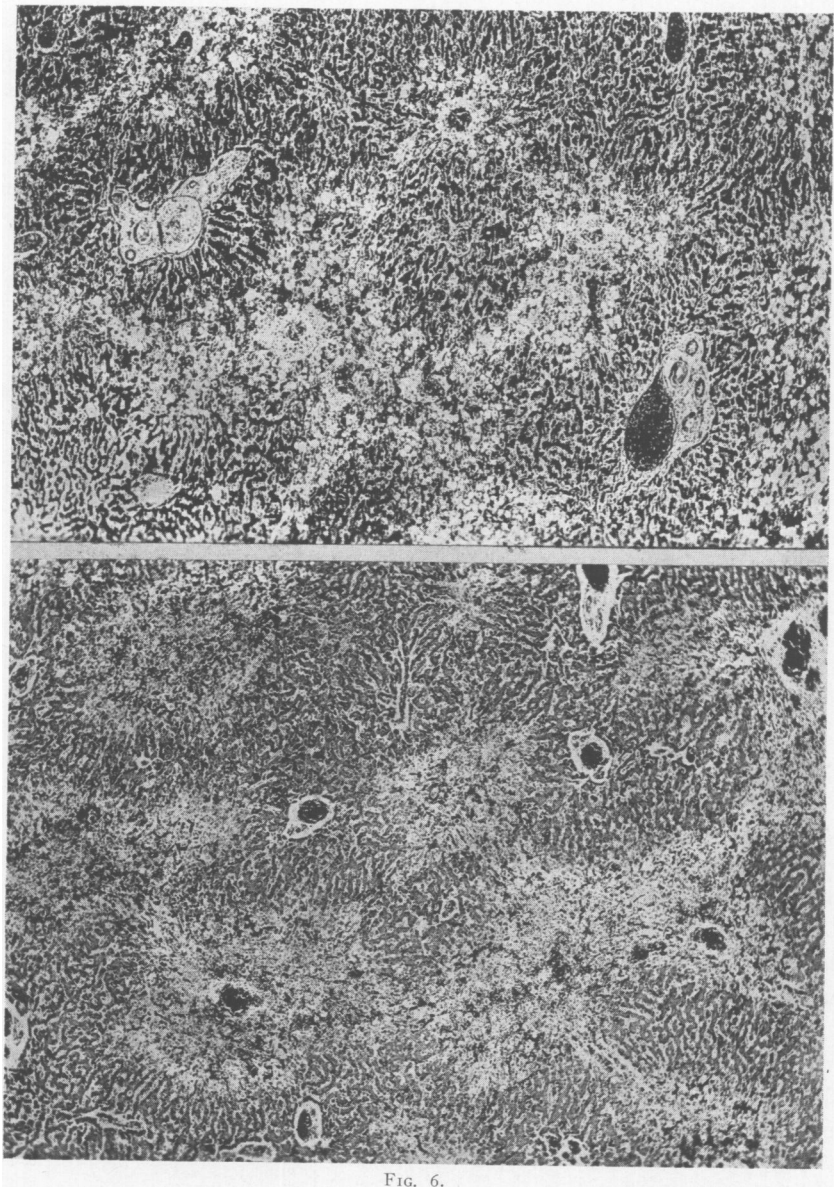


FIG. 6.

FIG. 5.—Dog No. 3160: Photomicrograph of liver from animal receiving 120 cc. of 10% ferric chloride subcutaneously. Survival—3 days. Shows extensive necrosis, fatty infiltration, and hemorrhage involving approximately one-third of the liver tissue. (Low power.)

FIG. 6.—Dog No. 3124: Photomicrograph of liver from animal receiving 150 cc. of 7.5% tannic acid subcutaneously. Survival—3 days. Shows very extensive central necrosis of liver lobules with hemorrhage. (Low power.)

H. Tannic Acid (used as intraperitoneal and subcutaneous injection).—In this group there are 41 experiments, each including the injection of sterile 7.5 per cent tannic acid solution. Six intraperitoneal and 33 subcutaneous injections were done. The intraperitoneal route was abandoned because of

the violent peritonitis produced and the short duration of life; however, central necrosis of the liver was seen twice, or in 33.3 per cent. With subcutaneous injections the dose ranged from 60 to 200 cc., depending upon the size of the animal. These injections were all done while the animals were under ether anesthesia, and were made at several points. The length of life after injection ranged from 2 to 16 days.

Autopsy showed extensive coagulation necrosis at the sites of injection and extending down the sides around the abdomen, especially with the larger doses. In five instances, 7.5 per cent tannic acid neutralized to p_H 7.4 with sodium bicarbonate was used subcutaneously, and the resulting coagulation and edema was comparable to that from the usual tannic acid at p_H 3.5.

None of the animals living less than two days showed necrosis of the liver, but marked acute congestion at the center of the lobule associated with granular and vacuolar degeneration predominated. In the 25 animals living 2 to 16 days, central necrosis of the liver was seen six times, or in 25 per cent, and extensive fatty degeneration twice, or in 8 per cent (Figs. 6, 7 and 8).

I. Tannic Acid Jelly (as dressing for areas from which skin was excised). —A group of three animals from which skin areas 20 x 20 x 16 inches were excised, had the denuded area dressed with sterile 7.5 per cent tannic acid jelly. These animals lived from 10–16 days. At autopsy, infection and suppuration was present in the wounds. Microscopically, the livers showed congestion, fatty degeneration and myelinization, but no central necrosis.

Analysis of the lesions obtained by the injection of these seven different chemical coagulating agents shows that the three most commonly used in the treatment of burns are the same ones responsible for the liver damage, namely, silver nitrate, ferric chloride and tannic acid.

The liver damage associated with the injection of silver nitrate developed relatively late and was accompanied by intense myelinization. Clinical jaundice and liver insufficiency were not produced with silver nitrate.

The liver damage occurring after the injection of ferric chloride was acute and hemorrhagic. The incidence was 38 per cent as compared with 25 per cent for tannic acid in the dosage-range used. Clinical jaundice was seen only twice in this group.

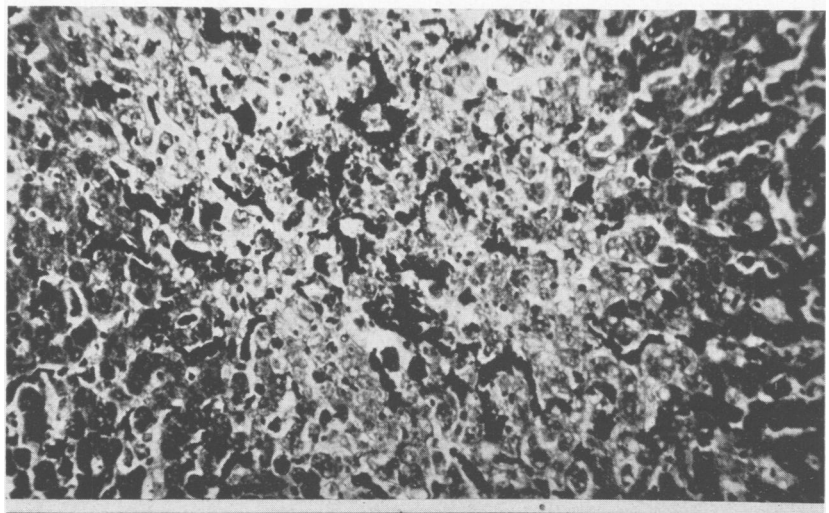
Central necrosis of the liver occurred in 33.3 per cent of animals receiving intraperitoneal injections of tannic acid and 25 per cent of animals receiving subcutaneous injections. The necrosis of the liver was produced more promptly and was more extensive than with the other coagulating chemicals. Clinical jaundice was seen on the fourth day and was progressive unless measures to combat it were instituted. The jaundice was accompanied by refusal of food, loss of weight and strength, vomiting, bloody stools, and coma.

GROUP 3.—To determine the effect of burns dressed with protein coagu-

lating chemicals on the liver, these chemicals were applied as dry dressings and as wet dressings to large skin burns in 31 animals.

A. Experiments with Skin Burns Treated with Tannic Acid Prepara-

FIG. 7.



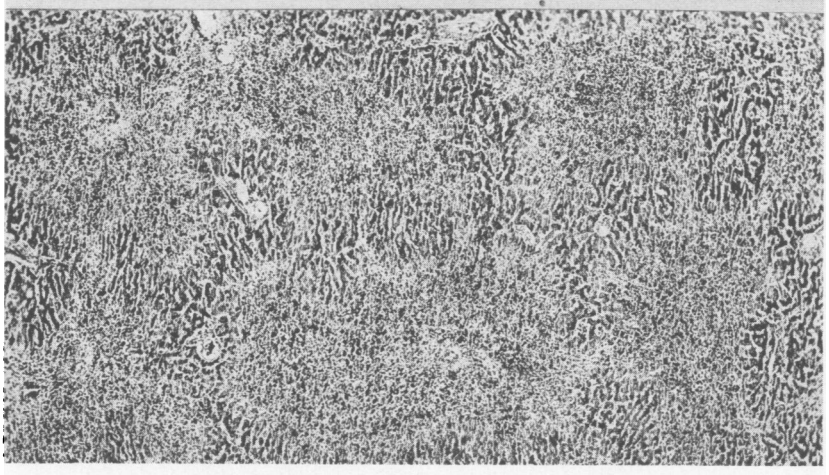


FIG. 8.

FIG. 7.—Dog No. 3124: Photomicrograph of liver from animal receiving 150 cc. of 7.5% tannic acid subcutaneously. Survival—3 days. The large lighter zone at the center shows complete lysis of liver cells with engorgement of the sinusoids and central vein. (Medium power.)

FIG. 8.—Dog No. 3161: Photomicrograph of liver from animal receiving 150 cc. of neutral tannic acid 7.5% subcutaneously. Survival—2 days. Central zone is necrotic, the liver cells being represented only by amorphous blue-staining material. The liver cells at the periphery also show degeneration so that they do not stain well. (Medium power.)

tions.—In the group of 24 animals, skin burns covering the entire back and sides were produced, ranging from 60 to 65 per cent of the body surface. In ten instances the burns were produced with a Bunsen burner and 14 times with a steam jet. The length of life was from 2 to 27 days. Clinical jaundice, with icterus indices ranging from 20 to 58, was seen in three animals,

or 12 per cent, and all these had a wet dressing with the tannic acid preparation. The urine from the animals with wet dressings was unusually dark in color and gave strongly positive tests for tannates.

Autopsy showed third-degree burns and good tanning in all, including those treated with neutral solution; but with the wet dressings the skin was macerated and usually suppurating. There was marked subcutaneous edema, especially over the abdomen, as in Dog No. 3170 (Fig. 9). Here it was noted that the edema fluid was blackened by the tannic acid, although the animal lived only 24 hours, suggesting that the tannate was absorbed especially when this plasma was reabsorbed. Metastatic abscesses of the kidneys were present in some cases. Central liver necrosis was present twice and central degeneration twice. In only one instance (Dog No. 3076) was necrosis associated with a dry dressing, and in this instance crude quebracho tannin was used as a spray (Fig. 10).

One animal, Dog No. 3142, with a fire burn, and a wet dressing of plain 7.5 per cent tannic acid jelly, passed blood from the intestinal tract for 24 hours preceding death, and was found to have a large Curling's ulcer, with blood clot attached, in the first portion of the duodenum.

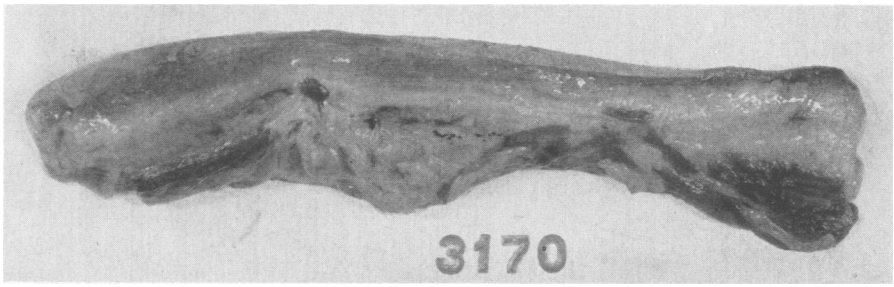


FIG. 9.—Dog No. 3170: Had burn produced with steam jet covering 60% of the body surface, to which a wet dressing of 7.5% tannic acid jelly was applied. Survival—1 day. Shows penetration of the tannic acid dressing 1 cm. into the edematous subcutaneous tissue beneath the burn.

B. Experiments with Skin Burns Treated with 5 per cent Ferric Chloride. In this group 5 per cent sterile ferric chloride solution was used to dress and tan large burned areas of about 60 per cent of the body surface. Two burns so treated were produced with the Bunsen burner and three with the steam jet. This solution produced a good tanning in both types of burns after four to six applications over a 12- to 24-hour period—fully equal to that produced by tannic acid. Three animals had dry dressings and lived from 7 to 16 days before being sacrificed while still in good condition. Two in which wet dressings were applied died after 8 and 11 days, respectively. These two were the only ones in this series showing significant lesions in the liver, Dog No. 3141 showing extensive central necrosis with hemorrhage, and Dog No. 3145 showing marked fatty infiltration and congestion (Fig. 11).

In this group large skin burns were actually treated with tannic acid and ferric chloride preparations. Here, conditions similar to those present in the handling of clinical burns were reproduced. Clinical jaundice with icterus

FIG. 10.

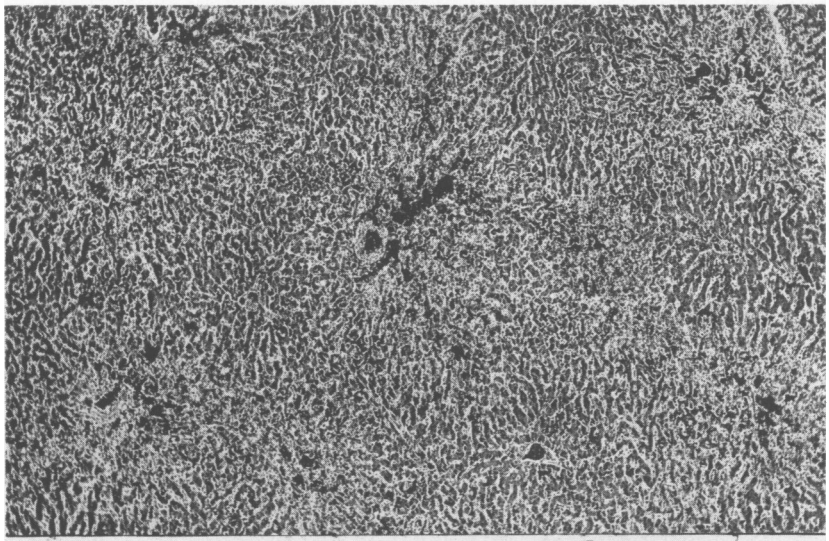


FIG. 11.

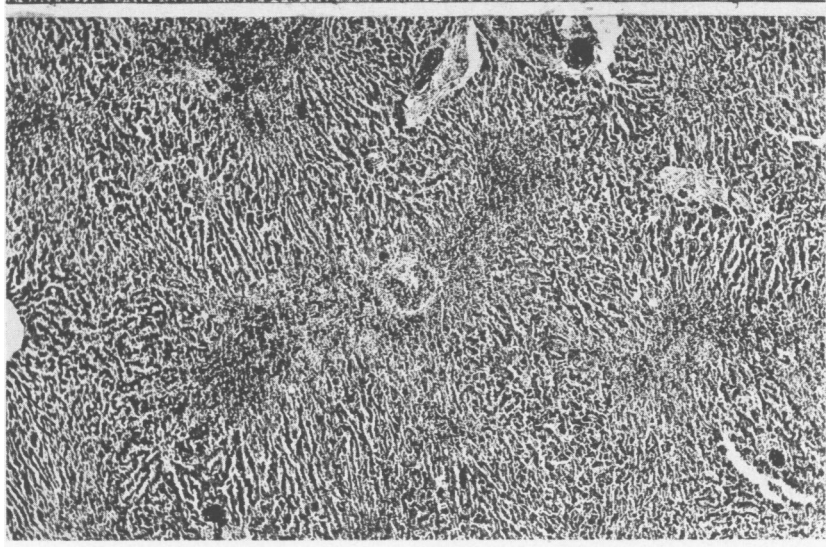


FIG. 10.—Dog No. 3176: Photomicrograph of liver from animal in which a burn was produced with steam jet covering 60% of the body surface, to which a wet dressing of 7.5% tannic acid in cetyl alcohol base was applied. Survival—11 days. Shows marked congestion and hemorrhage with central necrosis. (Low power.)

FIG. 11.—Dog No. 3141: Photomicrograph of liver from animal in which approximately 60% burn was produced with steam jet and dressed with 5% ferric chloride jelly. Kept wet with pliofilm covering. Survival—8 days. Shows marked engorgement of blood vessels with necrosis and hemorrhage at the center of the lobule involving approximately 40% of the liver tissue. (Low power.)

indices ranging from 20 to 58 was seen in three animals, or 12 per cent, all of which had wet dressings rather than the usual drytanned eschar. Central necrosis and degeneration was found in four, or 16 per cent. Only one of these had a dry dressing, and that consisted of crude quebracho tannin applied as a spray.

On the basis of these findings, wet dressings and baths of tannic acid will give us the highest incidence of liver necrosis and should be avoided, as pointed out by Davidson in his original contributions.

GROUP 4.—To determine the effect of tannates on the liver, blood plasma was precipitated with tannic acid, twice washed, and injected subcutaneously. Alkaline sodium tannate solution p_H 9 was injected intravenously. Tannates and gallates excreted in the urine were identified.

It had been assumed that tannic acid with a p_H of 3 combined with proteins formed an insoluble compound which would be inert in the body. However, such compounds were prepared using blood plasma as the source of protein and the twice washed precipitate was injected subcutaneously in 100 to 120 cc. amounts of the 50 per cent suspension. Two of the four animals injected showed early central necrosis of the liver, suggesting at least that the material was absorbed and was toxic for the liver (Fig. 12). Following this experiment it was observed that tannic acid was absorbed into the edematous subcutaneous tissues beneath the burned tanned skin for a distance of 1.5 cm., as evidenced by the brownish-black discoloration. Then the dark brownish urine excreted by both the animals injected subcutaneously with tannic acid preparations and those burned and dressed with the same preparations, were shown to contain tannates, as identified by Dr. V. Schelling. Neutralized tannic acid and quebracho tannin used for subcutaneous injection and dressings excreted relatively large amounts of tannates and gallates.

Detection of Tannates in Urine. —Tannates excreted in urine are demonstrated by the bluish-black color with ferric chloride. Since, however, gallic acid, a hydrolysis product of tannic acid, gives the same color, a more specific reagent is required. Sanin's reagent (Merck's Index, 5th edition, p. 808) fulfills this requirement. It gives a white precipitate with tannic acid but no precipitate with gallic acid.

Some urines which gave a positive ferric chloride reaction did not precipitate with Sanin's reagent, indicating that gallates were present in these urines. The kidney, according to Sieburg and Mordhorst, does not possess an enzyme system that is capable of splitting tannins. However, the liver, according to these authors, might be the site where splitting of tannins occurs.

Attempts were made to use Folin and Denis phenol reagent for a more quantitative evaluation of tannates in urine. All urines which gave a positive ferric chloride reaction developed a blue color with this reagent after treatment with silver-lactate-NaCl-HCl. However, the color developed was different for each urine and could not be matched adequately with the color of the standard prepared from tannic acid.

Although neutralized tannic acid proved quite effective in the coagulation of proteins, both *in vitro* and *in vivo*, alkaline sodium tannates with p_H 9 failed to coagulate proteins so that it became possible to inject such solutions directly into the blood stream of both rabbits and dogs without immediate

or delayed reaction. Two dogs of 7 and 8 kilos were given 15 cc. of 7 per cent sodium tannate solution intravenously. These animals excreted brownish urine containing tannates, and showed a rapidly deepening jaundice at the end of 48 hours. One animal died in 48 hours in deep coma, with

FIG. 12.

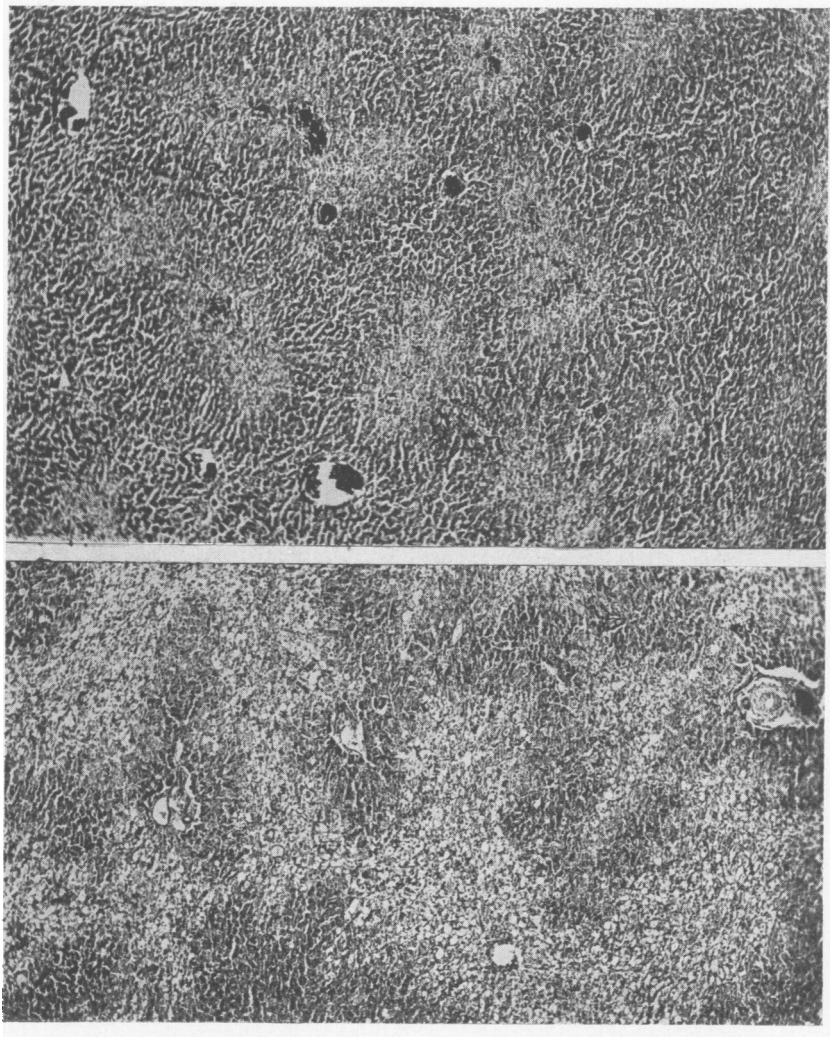


FIG. 13.

FIG. 12.—Dog No. 3137: Photomicrograph of liver from animal receiving 100 cc. of twice washed protein tannate subcutaneously. Survival—3 days. Shows extensive central necrosis of liver lobule. (Low power.)

FIG. 13.—Dog No. 3193: Photomicrograph of liver from animal receiving 15 cc. of 7% sodium tannate solution intravenously. Survival—3 days. Clinical jaundice marked. Icterus index 140. Shows vacuolar degeneration and necrosis of liver cells about the centers of lobules. (Low power.)

an icterus index of 140 (Fig. 13). The second lived a week, with increasing jaundice, marked listlessness, and refusal of food. Autopsy of these animals showed a small, brownish-green liver that was flabby and soft and friable

on section. The usual lobulation could not be made out. Microscopically, there was acute central necrosis of 50 per cent of the liver tissue.

Rabbits of 3 and 4 kilos were given 8 cc. of the 7 per cent sodium tannate solution into the marginal ear vein. No jaundice was detected either clinically or at autopsy, but all succumbed in two to six days. Microscopically, the livers showed more marked central necrosis than those of the dogs receiving this solution. Only a fringe of liver cells remained at the periphery of the lobule while the centers were necrotic and hemorrhagic (Fig. 14).

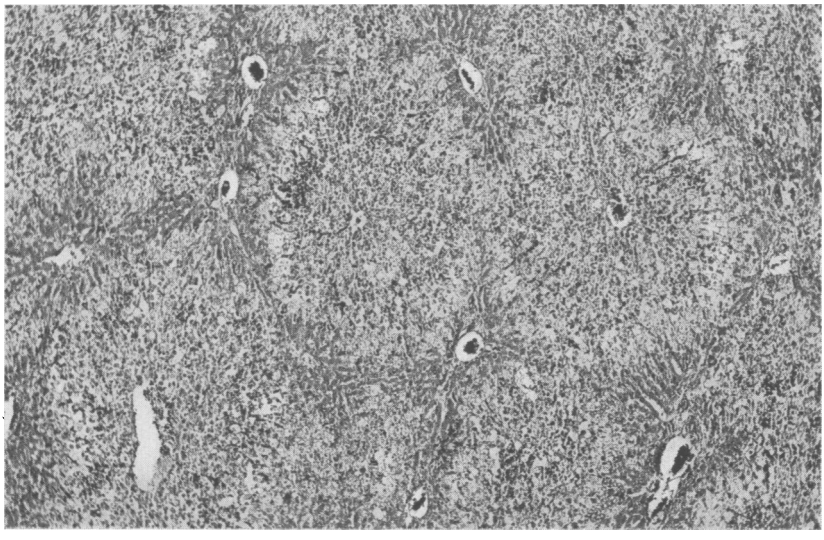


FIG. 14.—Rabbit No. 3195: Photomicrograph of liver from animal receiving 7 cc. of a 7% sodium tannate solution intravenously. Survival—24 hours. Shows complete lysis of the cells of the liver lobule with the exception of a fringe about the periphery. (Low power.)

The production of liver necrosis by the subcutaneous injection of washed tannates and the intravenous injection of alkaline sodium tannate solutions demonstrates the etiologic importance of tannates in the pathogenesis of this lesion. Further the identification of relatively large amounts of tannates and gallates in the urine excreted by animals burned and treated with tannic acid preparations, as well as in the urine of those injected with tannic acid subcutaneously, shows that these tannates are absorbed from the site of treatment or injection into the blood stream. This fact being established, it is clear that the liver cells may be destroyed just as they are when tannates are injected intravenously.

SUMMARY AND CONCLUSIONS

1. Large experimental burns result in marked engorgement of the sinusoids of the liver, especially about the central veins, and compression of the liver cells in this area.

2. Acute compression of the liver cords is followed even in the groups treated with sterile vaseline and sterile salt solution by granular, vacuolar

and fatty degeneration. With longer survival, especially if infection either in the form of pneumonia or suppuration of the burned area occurs, actual necrosis of liver cells at the center of the lobule, with myelinization, may be seen.

3. Introduction of any of the coagulating agents mentioned, either as a dressing for a burned or denuded area, or as a subcutaneous injection, increased the incidence of degeneration and necrosis of liver cells, with or without hemorrhage.

4. Oddly enough, the three coagulating agents that have been used in the treatment of burns are the only ones that have, in this work, increased the danger of clinical jaundice and liver insufficiency. These chemical agents are in order of importance: Tannic acid; ferric chloride; and silver nitrate.

5. Tannic acid used as a wet dressing for burns has produced clinical jaundice in the dog in 12 per cent and central necrosis of the liver in 16.5 per cent. In only one instance was liver necrosis seen associated with the dry tanning of a burn, and in this crude quebracho tannin was used.

6. Tannic acid used as a subcutaneous injection in a series of 25 animals has produced liver necrosis in 25 per cent. With intraperitoneal injection, in a series of six, liver necrosis was produced in two, or 33.3 per cent.

7. Quebracho tannin and tannic acid neutralized with sodium bicarbonate in a small series were more potent than tannic acid in the production of liver damage.

8. Animals having burns treated with wet dressings of tannic acid or tanning preparations and those receiving subcutaneous injections of these preparations, excrete relatively large amounts of tannates and gallates in the urine. These groups have the highest incidence of liver necrosis.

9. Sodium tannate of p_H 9 does not coagulate protein readily and may be given in amounts of 10 to 20 cc. of the 7 per cent solution daily without reaction. Such injections in four rabbits and five dogs have resulted in the consistent production of liver necrosis in both groups with clinical jaundice and death in the dogs.

10. The excretion of tannates in the urine of animals receiving wet dressings or injections of tannic acid, coupled with the fact that these animals along with those receiving tannates intravenously have a high incidence of jaundice and liver necrosis, shows the etiologic relation of these tannates to the liver lesions.

11. Silver nitrate used in 2 to 10 per cent sterile aqueous solution subcutaneously, produces extensive necrosis and edema at the site of injection, with some degeneration, hemorrhage, and necrosis of the liver. However, clinical jaundice has not occurred, and death could not be charged to the grades of liver damage seen.

12. Ferric chloride used in 5 to 10 per cent sterile aqueous solution subcutaneously, produces marked necrosis, edema, and hemorrhage at the site of inoculation. Clinical jaundice does occur, and the extensive central

necrosis and hemorrhage in the liver must be listed as one of the causes of death. A single animal with a wet dressing of ferric chloride on its 60 per cent burn died on the eighth day and showed liver necrosis, with hemorrhage.

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