

REDUCTION OF MORTALITY IN SWINE FROM COMBINED TOTAL BODY RADIATION AND THERMAL BURNS BY STREPTOMYCIN*

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SEVERAL INNOVATIONS in the use of atomic weapons have somewhat altered previous evaluation of the extent to which civilian population or military personnel might be exposed to ionizing radiation, thermal trauma or a combination of these two factors. The first development is that of atomic artillery missiles which could be effectively used against local concentrations of troops. The second factor is the hydrogen bomb which, since tests are successful, will greatly extend the area over which the triple effect of the blast, burns and ionizing radiation will cause havoc.

Injuries received by the inhabitants of Hiroshima were in many cases multiple and various combinations of blast, fracture, radiation and thermal trauma were observed. Depending upon the size and type of atomic bomb, there is a zone of varying extent where a combination of radiation and thermal injury is received. From published reports dealing with the casualties at Hiroshima, it was apparent that the extent of thermal burn alone could not explain the high mortality. In an effort to investigate the therapy of this combined injury, the summation of which causes a high mortality, we decided to study the effect of antibiotic therapy on swine exposed to 400_r/2 total body radiation plus a 10 to 15 per cent flash burn.

Method. Twenty young Yorkshire swine weighing from 30 to 45 pounds were used in these experiments. They were fed Commercial hog feed† and water which is commonly used by farmers raising hogs. Both female and castrated male animals were used, since it has been shown that no particular variation due to sex is observed following total body radiation.¹ The apparatus used for radiation was a 220 KVP roentgen ray therapy machine. The animals were placed in a plywood box at a focal skin distance of 80 cm. The filter used consisted of 1 mm. Al inherent, ¼ mm. Cu inherent, and ¼ mm. Cu added. The HVL was equivalent to 1.1 mm. Cu. The dosage rate was 10_r per minute at 80 cm. as measured with a 50_r Victoreen counter. Half the total dosage of 400_r, measured in air, was delivered to each side of the hog. It was necessary to interrupt exposure for a few minutes to reverse the position of the animal so that the opposite side could be irradiated.

It is considered that exposure to gamma rays from a roentgen ray apparatus is a suitable method of studying the effect of radiation on experimental animals, even though following an atomic explosion the total dose of radiation would be received within approximately one second.¹¹ Following roentgen radiation the swine were given light ether anesthesia and exposed to a 10 to 15 per cent flash burn of the lateral as-

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† Prepared by Tougas and Tougas Limited, Montreal.

pect of the trunk. The extent of burn in each animal was calculated according to the formula of Dubois.⁴ The trunk of the animal, which had been shaved previously, was placed over an adjustable opening in an asbestos covered stand. A mixture of magnesium powder and barium peroxide was placed on an asbestos covered plate at a fixed distance of two inches from the animal. Twenty grams of the mixture were used to produce each burn and the proportions were 2.5 Gm. of magnesium powder to 17.5 Gm. of barium peroxide. A brief but intensely hot flash was created through ignition of the mixture by an electrical current conducted through a thin copper wire. It has been estimated that the maximum temperature reached was 2800°C. In every instance the thermal burn was administered as soon as possible after the exposure of the animal to radiation, and it has been concluded² that no detectable difference results from administering thermal burns before or after radiation in animals.

Prior to each experiment, the animals were weighed and a preliminary hemogram performed. Subsequent to radiation and thermal trauma, careful clinical observations were made daily as well as hemograms and a record of body weight at periodic intervals. The ten hogs that received antibiotic therapy were given 500 mg. of streptomycin intramuscularly each day, commencing one day after radiation and thermal injury and continuing for the subsequent 21 days. A complete autopsy was carried out on all animals at death or at conclusion of the 30-day period during which observations were made.

RESULTS

Control Group. In the control group the mortality was 90 per cent (Fig. 1), and occurred between the 7th and 19th days following trauma. With one exception, all animals showed marked evidence of acute radiation syndrome which included diar-

rhea, bleeding from nose and mouth and multiple petechial hemorrhages of skin and viscera (Fig. 2). Some animals exhibited an accumulation of bloody fluid in the pericardial sac, thorax and abdomen. Also noted were abdominal adhesions, massive hemorrhage into the gut and partial or complete perforation of the wall of the bowel. In all instances there was rapid loss of weight prior to death, but in the one survivor there was a gradual increase beginning 13 days after radiation.

The series of hemograms (Fig. 3) showed an interesting response to this combination of trauma, consisting of a moderate dose of radiation, which alone resulted in a mortality of 20 per cent and a thermal burn of 10 to 15 per cent, and which in previous experiments showed no mortality. There was a slight rise in hemoglobin for the first few days; this was followed by a definite anemia, which reached its lowest point at the 13th day. Subsequently, the sole survivor regained the previous level of hemoglobin. On the other hand, with the exception of eosinophils, which showed a rise on the second day post-trauma, all other elements of the hemogram such as the white blood cells, polymorphonuclears, lymphocytes, monocytes and stab forms showed a marked fall to low levels by the second day and from which little recovery was made throughout the period of observation.

Treated Group. The group of ten swine receiving streptomycin suffered a mortality of only 20 per cent. These two animals succumbed on the 14th and 24th days respectively. There was a remarkable difference in clinical symptoms between the treated and control groups. The treated group showed no hemorrhage from mouth or bowel and only two swine, one surviving and one dying on the 14th day, showed petechiae of the skin. There was marked loss of weight in all hogs by the fifth day, which in most cases was regained by the 13th day. In general, the extent of decrease

in the white blood cells was quite similar in both treated and control groups (Fig. 4). There was only a slight degree of recovery in the lymphocytes and polymorphonuclear

and penicillin administered parenterally both prior to and immediately following injection of P³² increased survival time and decreased mortality. Furth⁶ and coworkers

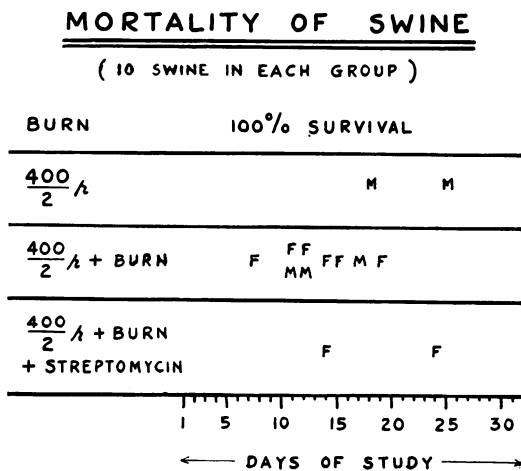


FIG. 1.—This chart shows the mortality in four groups of swine exposed to different combinations of trauma and therapy. No deaths resulted from a flash burn of 10 to 15 per cent of the body surface when no therapy was administered. The second group was exposed to 400, /2 total body irradiation. These hogs suffered a mortality of 20 per cent and also received no supportive therapy. The animals dying showed typical symptoms of acute radiation sickness. The third group received a combination of the above injuries also without supportive therapy and the mortality reached a high of 90 per cent. The fourth group received combined radiation and thermal injuries, but 24 hours after exposure, streptomycin was administered intramuscularly for 21 days. In this group the mortality fell to 20 per cent. Sex of the animal dying is represented by M for male and F for female.

leucocytes during the period of observation. On autopsy at thirty days, all survivors showed no gross pathologic changes with one exception. However, the two animals which failed to survive showed findings similar to those noted in the control group, although not quite as severe.

DISCUSSION

A number of authors have observed that administration of antibiotics to experimental animals subjected to total body radiation causes reduction in mortality. Koletsky and Christie⁹ noted that streptomycin

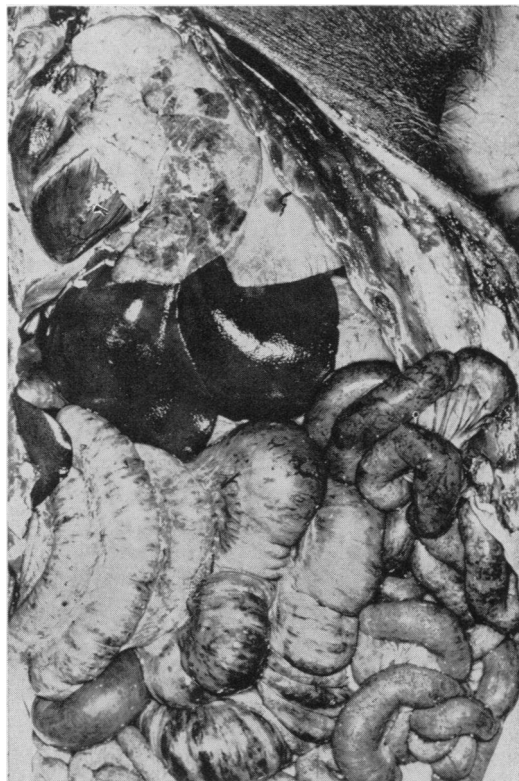


FIG. 2.—This photograph shows the appearance of autopsy of a hog dying on the 12th day, following 400, /2 to which was added a 10 to 15 per cent flash burn. There was bleeding from the nose prior to death and numerous subcutaneous hemorrhages were visible. Patchy hemorrhagic areas may be observed in the lungs, heart, stomach, large and small bowel. The thermal burn on the trunk showed numerous small granulating areas.

reported that terramycin delayed the onset and reduced the mortality in rats receiving 700, total body roentgen radiation. The same authors⁷ administered aureomycin to 12 of 24 dogs immediately after receiving 450, of whole body roentgen radiation; seven of the control and five of the treated dogs died post-radiation. Poth¹⁰ and associates treated four dogs exposed to 400, total body radiation with a combination of neomycin and sulfathalidine which was

commenced after radiation. It was found that the treated dogs survived longer than four controls. Cronkite observed that survival time was prolonged in dogs following administration of penicillin and aureomycin.

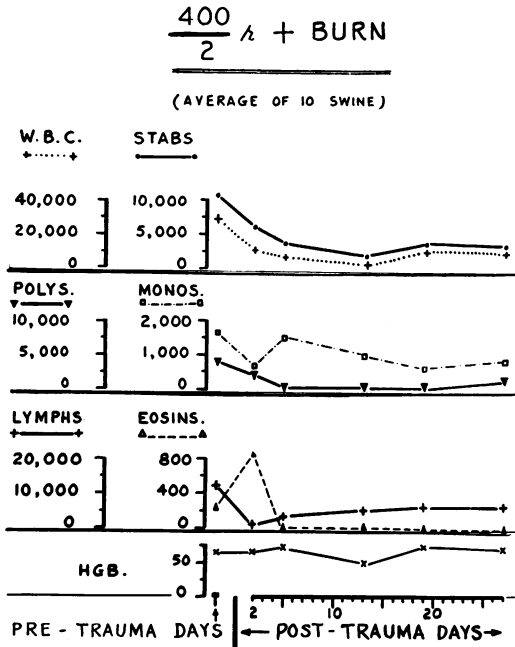


FIG. 3.—This chart presents an average of hemograms of ten swine at intervals before and after exposure to 400/2 plus a 10 to 15 per cent flash burn of the lateral side of the trunk. It may be observed that in most cases there was a rapid fall following irradiation, which in some instances was sustained throughout the period of observation and in other instances was followed by a gradual rise.

Hammond and Miller⁸ used a variety of antibiotics with good effect in irradiated mice. This included streptomycin, streptomycin with penicillin, chloromycetin, terramycin and aureomycin. The latter three antibiotics were administered orally and also parenterally in different experiments. Therapy was usually started on the first postoperative day, and continued for about three weeks. Best results were apparently obtained with streptomycin alone.

All these experiments were conducted on animals subjected only to total body radiation. Analysis of the cause of death of the inhabitants of Hiroshima has revealed that

a combination of exposure to both ionizing radiation and thermal trauma causes a high mortality. Our project was undertaken in an effort to evaluate the effect of antibiotic therapy on mortality from this combination of trauma. As far as we are aware, Brooks,

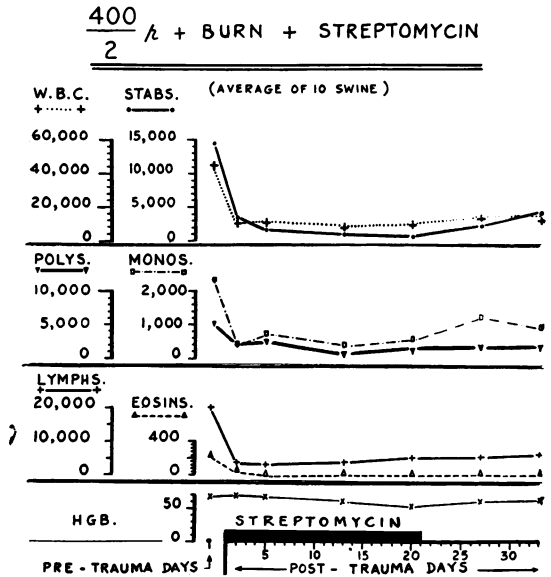


FIG. 4.—This chart presents an average of hemograms of ten swine at intervals before and after exposure to 400/2 and a 10 to 15 per cent flash burn. In this group of swine, however, 500 mg. of streptomycin was administered daily commencing 24 hours after the injury and continued for 21 days. Although eight out of ten swine survived the period of observation, it may be noted that most of the components of the hemogram show a similar trend to the group of pigs who received the same injury but no therapy. The hemoglobin showed a definite fall by the 13th day and a further decline to the 20th day. At conclusion of the experiment the hemoglobin had almost regained its original level.

Evans and associates² are the only other investigators who have reported similar studies on dogs.

It is apparent from our results that streptomycin administered 24 hours following exposure to a combination of external body radiation and thermal burns will markedly reduce mortality. Freidman and Warren⁵ showed that radiation of the intestine resulted in a damaged mucous membrane which was especially susceptible to ulceration, and Chrom³ has pointed out

that there is almost a constant bacteremia, with organisms of the colon aerogenes group following experimental radiation death.

We believe that streptomycin may have had a beneficial effect by reducing the extent of secondary infection and hemorrhage of the gastro-intestinal tract. It is most likely, moreover, that the evidence of bac-

antibiotic, by reducing infection, ulceration and necrosis of tissue, may thereby decrease the incidence of hemorrhage. It was quite evident, moreover, that the areas of second degree burn in the treated swine healed more rapidly than in the control group, and this may similarly be attributed to control of secondary infection by streptomycin (Figs. 5 and 6).

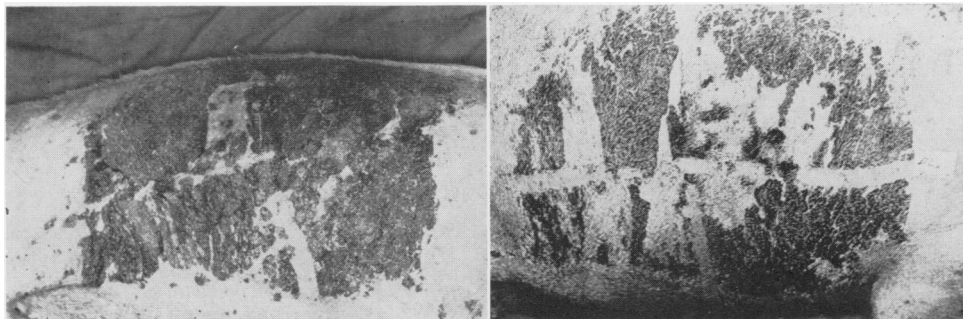


FIG. 5.—This photograph shows the appearance of a burned area nine days later with the eschar partly separated. The darker areas represent patches of second degree burns with granulation tissue exuding plasma. This photo shows the average response in the group of swine who received $400_r/2$ and a 10 to 15 per cent burn without supportive therapy. Multiple skin petechiae may be observed about the burned area. These were scattered over the entire body surface.

FIG. 6.—This photograph reveals the stage of healing which was typically observed in the group of swine who were exposed to $400_r/2$ plus a 10 to 15 per cent flash burn and streptomycin therapy after the first day. It is apparent that healing has been most rapid in this group.

teremia, frequently observed during the height of post-radiation syndrome in various species of experimental animals following total body radiation, was also markedly reduced.

Although a hemorrhagic diathesis exists following total body radiation which has been attributed to direct effect upon vessel walls, thrombocytopenia, production of a heparin-like substance in the blood and other factors, nevertheless it was remarkable that of eight survivors of ten swine receiving streptomycin, only one showed petechiae, while seven hogs in the untreated group showed skin petechiae during the 30-day observation period. At autopsy, only one of the surviving streptomycin treated hogs showed scattered petechial hemorrhages of the lungs. This suggests that the

SUMMARY

1. Twenty young hogs received $400_r/2$ total body radiation plus a 10 to 15 per cent thermal burn. Of these, ten received 500 mg. of streptomycin daily, commencing 24 hours after trauma and continued for the subsequent 21 days. Clinical symptoms, body weight and blood hemograms were recorded at frequent intervals following injury. Colored photographs were used to record the appearance and rate of healing of thermal burns and the gross appearance of the organs upon autopsy.

2. Under the conditions of our experiment, exposure of young swine to $400_r/2$ resulted in a mortality of 20 per cent. On the other hand, a 10 to 15 per cent flash burn caused no mortality. However, combining these two types of trauma resulted

in a marked synergistic effect so that the mortality increased to 90 per cent. It was found that administration of streptomycin parenterally, commencing 24 hours after injury and continuing for the subsequent 21 days, reduced the mortality to 20 per cent.

3. Following external body radiation, there were marked changes in the intestinal tract which resulted in ulceration, necrosis, hemorrhage, bacterial invasion of the intestinal wall and probably septicemia. Apparently this sequence of events contributed substantially to other factors which are thought to occur, such as anemia, suppression of bone marrow, production of heparin-like anticoagulants, or abnormal production of certain enzymes which often result in death of the animal.

4. Early and adequate treatment with streptomycin will contribute to reduction of mortality in swine following exposure to a moderate amount of total body radiation combined with a flash burn. Healing of second degree burns is accelerated.

5. Administration of streptomycin did not stimulate recovery of the blood-forming tissues as indicated by close similarity in the hemograms of treated and control groups of swine.

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