evidence the changes in visceral function following administration of insulin are caused by stimulation of the vagus centers through the influence of hypoglycemia. Our experiments provide no additional evidence for or against that view. The occurrence of restlessness and tachycardia in dogs, convulsions in other animals, and of sweating and convulsions in the human indicates that the stimulation is general and is not confined to the vagus or the parasympathetic centers. The increased output of epinephrin which tends to counteract the fall in blood sugar may be taken as a specific indication of stimulation of thoracolumbar sympathetic mechanisms.

In such a situation the effect on the pancreas, which receives both excitatory and inhibitory innervation, could hardly be predicted. It would doubtless represent a summation of antagonistic influences and would probably be readily modified by experimental conditions such as anesthesia and operative trauma. It is not surprising, therefore, that our results in unanesthetized dogs are quite opposite to those previously reported on anesthetized, operated animals. Since they agree with the results obtained in human experiments they probably represent the normal reaction of the pancreatic secretory mechanism to the complex situation resulting from acute hypoglycemia.

The inhibitory effects of hypoglycemia were manifest in some of our experiments only as a late decrease in volume of pancreatic juice secreted in response to a constant stimulus (secretin). Babkin[1] has suggested that these effects may be due to inability of the pancreas to function normally without an abundant supply of carbohydrate for its metabolic needs. In our experiments the volume, when low, could be promptly restored to normal by slightly increasing the rate of secretin injection. The specific gravity of the juice remained high in these circumstances. Clearly the pancreas was still capable of normal function when adequately stimulated. The decreased response to secretin in these experiments could be attributed to vascular changes or to preponderance of the inhibitory innervation.

Summary and Conclusions. Specific gravity and tryptic activity of dog's pancreatic juice secreted in response to continuous injection of secretin are increased following administration of insulin. The average volume secreted during the first hour after giving insulin is not significantly affected. Inhibitory effects of hypoglycemia described as occurring in anesthetized, operated animals are not readily demonstrated in unanesthetized dogs.

15690

Some Effects of Desoxycorticosterone Acetate on Mice Irradiated with X-rays.*

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Total body irradiation with X-rays produces fatty changes in the livers of irradiated animals.[1] We have recently demonstrated that the administration of desoxycorticosterone acetate protects the livers of mice irradiated with various lethal doses of X-rays against these fatty liver changes.[2] It was noted in addition that there was a decrease in the mortality rates produced by the previously used X-ray doses. It is the purpose of this paper to analyze these phenomena

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1 Ellinger, F., *Radiology*, 1945, **44**, 241.

2 Ellinger, F., *Science*, 1946, **104**, 502.

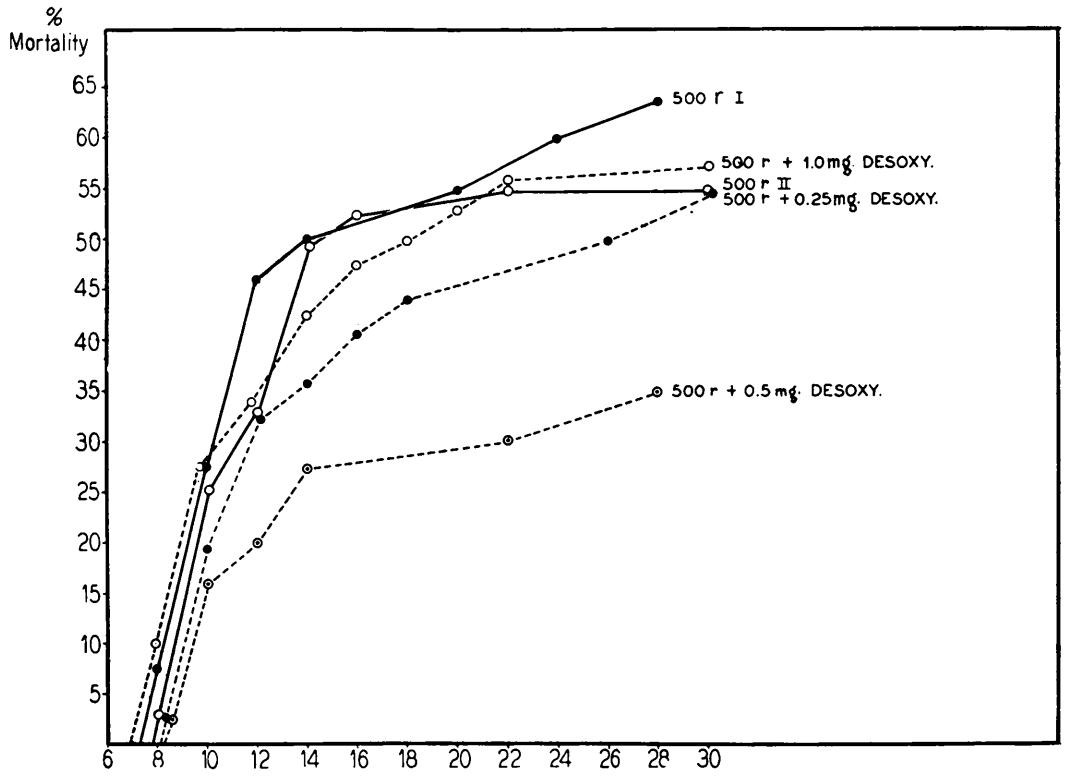

FIG. 1.

Reduction of the mortality rate produced by 500 r/air of X-rays in mice by administration of daily doses of desoxycorticosterone acetate of 0.25, 0.5, and 1.0 mg respectively. Abscissa: days after exposure to X-rays. Ordinate: % mortality.

in more detail.

Methods. A total of 166 white male Swiss mice 22 g ± 15% in weight was used, 62 of these received total body irradiation with X-rays only, while 104 animals received similar irradiation and desoxycorticosterone. All mice received 500 r/air in one exposure (HVL 0.75 mm Cu). This dose represents the LD_{50}. The technic of irradiation was the same as previously described.[3]

Daily doses of desoxycorticosterone acetate† in sesame oil of either 0.25, 0.5 or 1.0 mg were administered intramuscularly 6 times weekly over a period of 10-18 days. The total doses varied between 2.5 and 13.0 mg.

The effect on mortality rate, fat content of livers and radiation changes in other organs was studied at death of the animals. Survivors were observed 28-40 days, in some instances up to 240 days.

The fat content of livers was studied using sections stained with Sudan III, with the following grading:

0 No sudanophile fat.
\+ Traces of fat, as occasionally seen in non-irradiated livers.
++ Increased amount of fat with definite arrangement around central vessel.
+++ Considerable increase in fat.
++++ Fat making up an entire lobulus.

The arithmetical mean of these various grades of sudanophile fat was used for the quantitative evaluation of the histological changes, and called the "fat index."

Results. A graphic presentation of our experiences with various doses of desoxycorticosterone on the lethal effect produced by 500 r/air of X-rays, given as total body irradiation in one exposure, is shown in Fig. 1. It might be noted that desoxycorticosterone

[3] Ellinger, F., *Radiology*, 1945, **44**, 125.

† We are greatly indebted to Dr. E. Henderson of the Schering Co. for generously supplying us with desoxycorticosterone acetate.

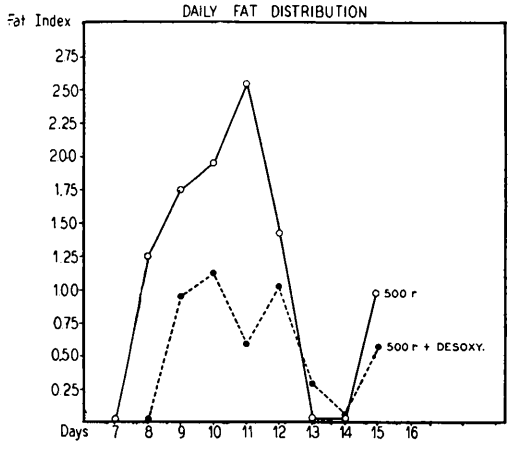

FIG. 2.

Influence of treatment with desoxycorticosterone on the appearance of sudanophile fat in the livers of irradiated mice. Abscissa: Days after exposure to X-rays. Ordinate: Arithmetical mean of the arbitrary grades of sudanophile fat (fat indices) for each day.

decreases the lethal effect of this X-ray dose.

From our previous studies it was inferred that there might be a quantitative relationship between the dose of desoxycorticosterone and the decrease in mortality rate produced by the X-rays.

Our data on the influence of desoxycorticosterone on the mortality rate have therefore been broken down into 3 groups for a closer analysis of this phenomenon: (a) mice receiving 0.25 mg daily (36 animals), (b) mice receiving 0.5 mg daily (34 animals), (c) mice receiving 1.0 mg daily (34 animals). Furthermore, the total data concerning the mortality rate produced by irradiation of mice with 500 r/air not treated with desoxycorticosterone has been divided into 2 groups: 500 r I and II consisting of 35 and 27 animals respectively, in order to demonstrate the variation in the mortality rate of solely irradiated mice. The graph demonstrates a slight variation in the mortality curves of the 2 groups of mice which received irradiation only. Administration of daily doses of 0.25 mg of desoxycorticosterone decreases the lethal effect of the X-ray dose beyond the variation observed in untreated irradiated mice. The decrease in mortality rate is still more marked in the group of mice which received 0.5 mg of desoxycorticosterone daily. The administration of 1.0 mg, how-

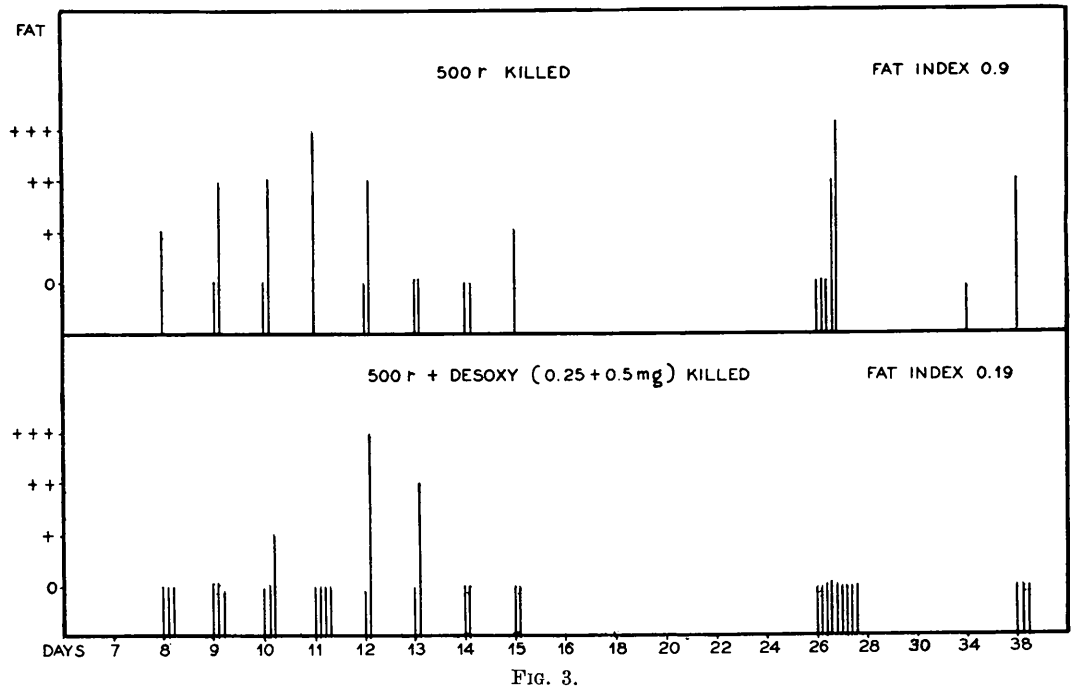

FIG. 3.

A comparison of the fat content of livers in solely irradiated and irradiated and desoxycorticosterone treated animals killed at various days, also indicates reduction in the content of sudanophile fat in the desoxycorticosterone-treated group. Each column represents the findings in one mouse. Abscissa: Days after exposure. Ordinate: Arbitrary grades of sudanophile fat.

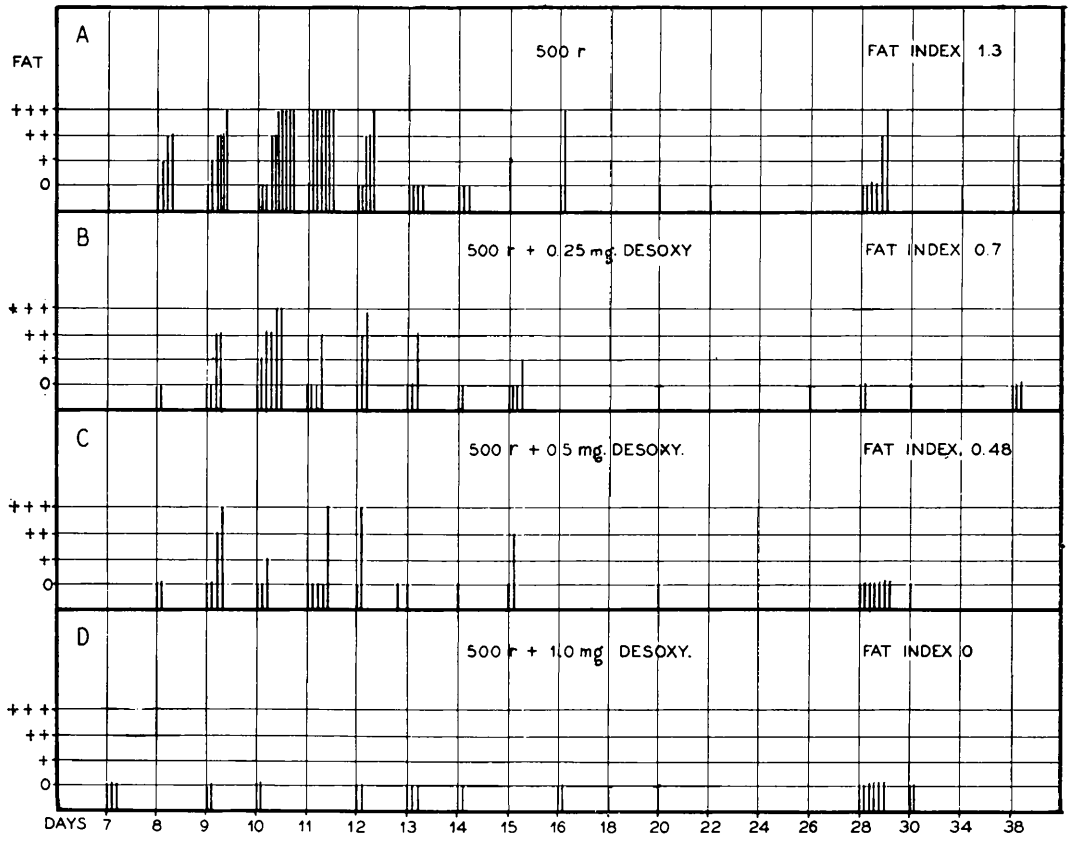

FIG. 4.

Analysis of the influence of the size of the daily dose of desoxycorticosterone acetate on the appearance of sudanophile fat of the livers of irradiated mice, indicates a graded effect of desoxycorticosterone.

ever, does not change the mortality rate. The mice receiving the largest daily doses evidently were suffering from an intoxication produced by these large amounts of desoxycorticosterone, which manifested itself in a ragged fur, sometimes loss of fur and considerable emaciation of the animals.

Our observations concerning the liver changes found in both the untreated irradiated and the irradiated and desoxycorticosterone-treated mice are presented in Fig. 2. This graph shows that the decrease in mortality rate produced by the administration of desoxycorticosterone is accompanied by a marked and statistically valid decrease in the formation of sudanophile fat in the livers of irradiated and desoxycorticosterone-treated animals.

Fig. 2 confirms previous observations[1] that the occurrence of sudanophile fat in irradiated livers proceeds in waves with peaks at various times after cessation of irradiation.

Recognition of this fact raises the question, whether the observed reduction in the occurrence of sudanophile fat in the irradiated and desoxycorticosterone-treated animals might not be due to the fact that death in these animals occurs at later dates, where the manifestation of sudanophile fat is less pronounced.

To answer this question animals have been killed at various dates after irradiation in both groups. Fig. 3 shows our observations. The data, though not statistically relevant, appear significant, showing a marked reduction in the amount of sudanophile fat in the desoxycorticosterone-treated group, when compared with the finding in the untreated irradiated mice. The fat indices are 0.19 and 0.9 respectively.

In Fig. 4, finally, data on the effect of desoxycorticosterone on the appearance of

sudanophile fat are arranged according to the size of the daily doses of desoxycorticosterone. Section A of Fig. 4 shows the results in the untreated irradiated mice. Section B in those which received 0.25 mg of desoxycorticosterone daily, Section C of those which received 0.5 mg and Section D of those which received 1.0 mg daily. The fat indices are 1.3, 0.7, 0.48 and 0.00 respectively.

The trend of Fig. 4 corresponds to the observations concerning the influence of various daily doses of desoxycorticosterone on the mortality rate. It is very interesting to note that the administration of daily doses of 1.0 mg are able to suppress the appearance of sudanophile fat in the livers completely, although these doses do not reduce the mortality rate.

No significant changes in the effect of the X-ray on spleen and bone marrow was observed with any of the used doses of desoxycorticosterone.

Discussion. The data presented in this paper confirm the previously described protective action of desoxycorticosterone acetate against X-ray-induced liver changes. They establish a parallelism between the reduction in sudanophile liver fat and the decrease in mortality rate in the irradiated and desoxycorticosterone-treated animals.

The analysis of the phenomena presented reveals that both effects within certain limits are dependent on the size of the daily dose of desoxycorticosterone.

The observation of a graded action of desoxycorticosterone with respect to its protective power against X-ray-induced liver damage, seems to indicate a definite antagonistic effect to the processes leading to the appearance of sudanophile fat in the liver.

We have recently adduced the evidence[1] which makes it highly probable that the occurrence of fatty changes in the livers of irradiated animals is the result of an indirect action of the rays by release of tissue breakdown products, histamine-like in character, most probably histamine itself.

Since desoxycorticosterone is known to counteract certain histamine effects[4] it appears highly probable that its protection against radiation-induced liver changes is based on this known histamine antagonism.

In favor of this explanation of the effect of desoxycorticosterone is the observation that desoxycorticosterone leaves the radiation effects on spleen and bone marrow unchanged. These effects are considered as predominantly the result of the direct destructive action of the X-ray in these tissues.[3]

The evidence presented in this paper indicates the possibilities of closer analysis of radiation effects by pharmacological means.

Finally, these data provide a pharmacological basis which justifies the use of desoxycorticosterone in the treatment of radiation sickness, a general intoxication of the irradiated patient, caused by the release of tissue break-down products. While our data indicate in a general way the usefulness of desoxycorticosterone for the treatment of radiation sickness, these observations should not be interpreted as indicating optimal doses for therapeutic purposes.

Summary. 1. A reduction in mortality rate of mice irradiated with X-ray by the use of desoxycorticosterone acetate has been demonstrated. 2. The reduction in mortality rate has been correlated with the protective action of desoxycorticosterone against radiation-induced liver changes. 3. It has been shown that reduction in mortality rate and protection against radiation-induced liver changes are dependent, within limits, on the size of the daily dose of desoxycorticosterone. 4. It has been suggested that the graded effect of desoxycorticosterone is possibly due to an antagonism to the indirect action of the X-rays which consists in the release of histamine-like substances from the irradiated tissues. 5. The data presented are proposed as a pharmacological basis which justifies the clinical use of desoxycorticosterone in the treatment of radiation sickness.

The author wishes to express his gratitude to Dr. A. L. L. Bell, Director of the Department of Radiology, Long Island College of Medicine, for his kind interest in and support of these investigations.

Valuable technical assistance has been rendered by Miss Jean Bernstein.

[4] Swingle, W. W. and Remington, J. W., *Physiol. Rev.*, 1944, **24**, 89.