amine hydrochloride,§ closely related structurally to Benadryl, was tested. But this compound possessed about one-fifth the antihistaminic activity of Benadryl. This compound was found to inhibit growth in a manner similar to Benadryl, but appeared to be even more potent than Benadryl itself, causing death of a large proportion of the cells in 24 hours at a concentration of 4.6 x 10^{-4} M, and producing total inhibition of growth at 2.3 x 10^{-4} M.

The lack of activity of histamine in reversing the Benadryl inhibition of *Chlorogonium* growth, and the lack of correlation between antihistaminic activity and growth-inhibitory activity in structurally related compounds appear to indicate that the growth inhibition is not related to the antihistaminic properties of the drug. The effect of Benadryl on *Chlorogonium* appears to differ from the bacteriostatic effect of antihistamines reported by Krecek *et al.*(4) and from the fungistatic effect reported by Landis and Krop(3), which were reversed by histamine, and from the bacteriostatic effect reported by De Ritis and Zanussi(1), which was reversed by a thiamin-nicotinamide mixture. Reiss and Caroline(5) have reported fungistatic effects of antihistamines which were not reversed by histamine, nor did histamine reverse the effects of Benadryl on vertebrate nervous tissue(6,7). Thus, it seems likely that the antihistaminic drugs may produce their effects by several different mechanisms.

§ Synthesized by Dr. T. A. Geissman, Chemistry Department, U.C.L.A., and tested for antihistaminic activity (guinea pig aerosol technic) by Dr. E. J. Fellows, Smith, Kline and French Laboratories, Philadelphia.

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Effects of Acute Radiation on the Adult Mammalian Central Nervous System.* (19505)

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A study in progress in this laboratory has been directed to characterize the changing metabolism of the nervous system as it develops from embryo to adulthood and to relate this to its changing radiosensitivity. Data on neurectoderm, neuroblasts and neonatal nerve cells have been reported elsewhere(1-3). In general the adult nervous system is considered to be radio-resistant, but whether it is uniformly so has not been determined.

In order to learn whether a differential of radiosensitivity exists within the adult nervous system, rats and mice were irradiated either to the head or to the whole body and the acute histopathologic changes that followed were recorded. The radiation given ranged from 50 to 20,000 r.

Materials and methods. Adult rats and

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mice of both sexes from 3 months to about one year old were given single exposures of x-rays, either total body, or to the head only with the body shielded by lead. Radiation intervals used were 50, 100, 200, 300, 400, 600, 800, 1200, 1500, 1600, 2400, 2800, 5000, 10000, 15000, and 20000 r. Both normal rats and mice and some mice bearing certain tumors were used. The tumor bearing animals were used because they offered additional material in the total body experiments, and there was no evidence that the tumors altered the radiation effects. Included in the study were additional multiple brain sections from animals previously reported as negative(4). Groups of 3 to 6 animals were used for each dose level of radiation. Rats only were used for the head experiments. X-ray factors were: General Electric Maximar therapy unit, 200 kv, 10 ma, inherent 3 mm aluminum filter, 25 cm target distance. Frequent checks were made with a Victoreen apparatus (in air). Animals were killed 6 to 48 hours after radiation except in the head experiments where the rats were in some instances allowed to survive for several days or until they died, which was usually on the 9th to 11th day. They received 1500 to 5000 r. Complete autopsies were performed, and sections made of all organs in about half of the animals, and of lymphoid tissue, spleen, muscle, bone marrow, small intestine, gonads, and nervous system only in the remainder. The nervous system was examined by multiple sections of the brain, sections of the gasserian ganglia, 2 levels of the spine including cord and associated ganglia (thoracic and lumbar), and sciatic nerve. In some of the 15,000 and 20,000 animals the thoracolumbar sympathetic chain was excised. A number of skeletal muscles were sampled in most cases. Fixation was in Bouin's or Zenker's fluids, embedding in paraffin and staining by hematoxylin and eosin usually, but also eosin-methylene-blue, Bodian protargol, phosphotungstic hematoxylin and iron hematoxylin for myelin. Comparisons were made with adult, newborn and fetal animals that were irradiated, or treated with radiomimetic drugs, sulfhydryl reagents or other forms of metabolic inhibition(1-3). Changes in the intestine, testes and hemopoietic organs served as a rough biological check on radiation.

Results. X-rays produced necrosis of several different groups of cells in the central nervous system. Those affected were oligodendroglia, neurons in parts of the olfactory brain, subependymal cells adjacent to the ventricles, especially the lateral, and rod cells of the retina.

Necrosis of retinal rod cells was seen in the 5 rats killed between 6 and 11 days but did not appear before 6 days. It was not observed in any of the animals with total body radiation (killed within 48 hours). Necrotic rod cells were seen in varying stages of disintegration, although the whole layer of these cells was sometimes destroyed, leaving only scant residual eosinophilic debris. (This strain of rats did not show congenital absence of rod cells.) In younger animals with head or total body radiation the small subependymal cells of the lateral ventricles were necrotic within 6 to 12 hours. When present in relation to other ventricles they were also affected. Necrosis was always considerable at 200 r but in both rats and mice necrotic cells were rare or absent at 50 and 100 r. These subependymal cells are small with scant cytoplasm, a compact deeply basophilic nucleus and they are indistinguishable from the immature subependymal and neuroblastic cells of this region in embryos and newborn animals(3).

In all animals with total body radiation or radiation to the head above 1200 r necrotic oligodendroglia cells were present within 6 to 24 hours after radiation. These were scattered widely in the white and gray matter but were not numerous. In a number of animals with total body or head irradiation above 1200 r there was occasional necrosis of nerve cells in the granular layers of the olfactory bulb and of larger cortical neurons in the pyramidal lobe. In no animals were necrotic cerebellar granule cells seen as sometimes happens after radiomimetic drugs. Dead oligodendroglia and nerve cells were characterized by marked reduction in cell size, poorly outlined eosinophilic cytoplasm and a strongly basophilic but blurred nucleus markedly reduced in size. Identification of necrotic oligodendroglia cells was made by seeing them,

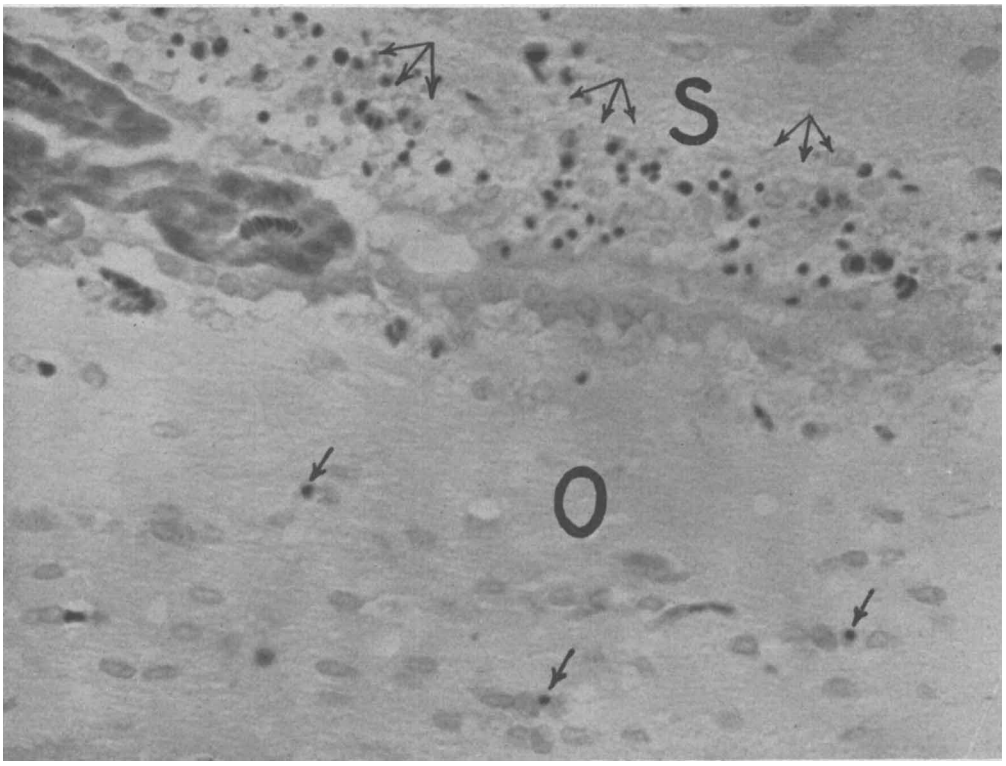

FIG. 1. Acute radiation necrosis of oligodendroglia cells (O), and subependymal cells (S). Brain of a young adult rat 6 hr after 1500 r total body irradiation. Three dead oligodendroglia cells in the corpus callosum are indicated by arrows above, and numerous necrotic subependymal cells are evident below by single or clumped masses of chromatin and indistinct cytoplasm. (Eosin-methylene blue. × 500.)

usually singly, in a row of oligodendroglia cells in such areas as the corpus callosum (Fig. 1). Necrotic satellite cells around neurons in the gray matter were presumed to be oligodendroglia by their size and shape, but in this state of destruction distinction from microglia cells was not certain. Bodian protargol and myelin stains revealed no change in the axis cylinders or myelin adjacent to regions where acutely necrotic oligodendroglia cells were observed.

No significant changes were seen in the sympathetic ganglia. Occasional vacuoles in sympathetic neuron cytoplasm and irregular cell staining occurred but these were also observed in control material. The spinal cords were negative except for occasional necrotic oligodendroglia cells. Peripheral nerves (sciatic) were negative. Rarely was damage to skeletal muscle seen, although samples were made of diaphragmatic, abdominal, intercostal, masseter, neck organs, spinal, thigh, extrinsic eye and external ear muscles. In the diaphragms of mice and rats given 15,000 r and killed 24 hours later, necrosis with disintegration of occasional muscle fibers occurred. Bone marrow, lymphoid tissue, gut, salivary glands, testes and ovaries showed characteristic acute radiation changes depending on the dosage and interval after radiation. Changes in gut, lymph nodes, testes were evident in 24 hours at 200 r, and absent or equivocal at 100 r. Thus they were of a radiosensitivity comparable to that of subependymal cells but the variables inherent in these experiments do not justify a closer comparison.

Summary. Irradiation of rats and mice resulted in acute necrosis of scattered oligodendroglia cells, subependymal cells when present in younger adult animals, retinal rod cells, and occasional neurons in the pyramidal lobe and olfactory brain. Subependymal cells were

radiosensitive (200 r) but the other cells were not destroyed below 1200 r.

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Comparative Uptake of BR^{82} by the Hypophysis and Other Tissues.* (19506)

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Bernhardt and Ucko(1), and Zondek and Bier(2) reported that bromide was a normal constituent of the blood, that it could be detected in a variety of tissues, and that the content of the hypophysis was strikingly high. In both man and the dog hypophyseal tissue gave values of 5 to 30 mg of bromide per 100 g of wet tissue as compared to 0.5 to 1.5 mg % for the blood and most other tissues. More recently Dixon(3) and Ucko(4), using newer analytical methods, failed to confirm the existence of any preferential concentration of bromide in the hypophysis of either the ox, pig, or man. Perlman, Morton, and Chaikoff(5) employing Br^{82} could not demonstrate a high concentration of radiobromide in pooled samples of pituitary tissue from a group of 8 rats.

A selective collection of bromide by the pituitary gland would be of considerable interest because of the implication that bromine might participate in the synthesis or discharge of pituitary hormones. Moreover, a therapeutic application of radiobromine for localized radiation of the gland would be possible if the collection of the isotope greatly exceeded that attained by other tissues. In the present study a determination was made of the uptake of Br^{82} by the hypophysis and by other organs of the rat and rabbit. Any uncertainty as to the specificity or reliability of a chemical method is avoided by the use of the radioactive isotope.

Methods. Br^{82} obtained from Oak Ridge National Laboratories in the form of irradiated KBr was assayed by comparison with a Radium D plus E standard obtained from the National Bureau of Standards. Correction for the difference between the energy of beta particles of the standard and Br^{82} was accomplished by extrapolation to zero-absorption from counts obtained with a series of aluminum filters. Rate of decay was measured in order to verify the absence of appreciable quantities of K^{42} which, although present in fresh samples of KBr immediately after irradiation in the pile, rapidly disappears from the mixture because of its relatively short half-life.

Eleven rats and 12 rabbits were given Br^{82} in a dose of 0.5 to 1.0 millicurie per kilo by slow intravenous injection. The amount of KBr received averaged 28 mg/kilo and ranged from 18 to 45 mg/kilo. After 24 hours the animals were anesthetized with ether and exsanguinated by incision of the dorsal aorta. Tissue samples were weighed in the wet state. With small organs such as the pituitary, thyroid, adrenals, and ovaries, the whole gland was digested with 10% KOH and evaporated to dryness in a one-inch steel counting cup. Beta counts were obtained with a mica window Geiger counter and corrections made for self-absorption. When, as with larger organs, a sample weighing more than 0.1 g could be obtained, the activity was measured by gamma counting. This was accomplished by means

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