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MEDICAL DEPARTMENT

Division of Pathology

Long Term Effects of Various Small Doses of I^{131} in Rats

Progress is satisfactory.

Boron, Slow-Neutron-Bombarded, Brain Tumors

Material is being prepared for publication.

Histological and Radioautographic Studies of Iodothiouracil-Treated Rats

Progress is satisfactory.

(J.T. Godwin)

Histological and Radioautographic Studies of Titanium and Germanium with Incorporated Isotopes

Additional material has been submitted for histological study. (J.T. Godwin and H.C. Dudley*)

Long Term Effects of 400 μc of I^{131} in Long-Evans and Sprague-Dawley Rats

Progress is satisfactory. (J.T. Godwin and C.J. Shellabarger)

Studies on the Thyroidal Uptake of Astatine in the Rat

It has been demonstrated that rats previously treated with thiouracil exhibited a larger thyroidal accumulation of astatine than control rats. Star-shaped groups of alpha tracks were found only in radioautographs of thyroid glands from thiouracil-treated animals. (C.J. Shellabarger and J.T. Godwin)

Effect of Thiodiphenylamine on the Rat Thyroid (6300)**

Thiodiphenylamine has been compared with thiouracil in regard to 1) the depression of thyroidal accumulation of I^{131} and 2) the stimulation of hypertrophy and hyperplasia of the thyroid. Thiodiphenylamine was slightly less potent than thiouracil in depressing I^{131} uptake but did not appear to cause thyroid hyperplasia or hypertrophy which accompanied thiouracil. Further studies are being made to estimate the antithyroid potency of this drug in terms of thiouracil. (C.J. Shellabarger)

(6300)

EFFECTS OF TRIIODOTHYRONINE ON TADPOLES. C.J. Shellabarger and J.T. Godwin. Endocrinology 54, 230 (1954). Abstract.

D-L-Triiodothyronine and D-L thyroxine were effective in shortening the body length of tadpoles immersed in these compounds for 10 days. An estimation of relative potency indicated that triiodothyronine was approximately 3.5 times as effective as thyroxine.

*Guest of the Medical Department from U.S. Naval Hospital, St. Albans, N.Y.
**For explanation of these numbers, see Foreword.

(6300)

THE EFFECTS OF THYROXINE OR TRIIODOTHYRONINE ON THE CHICK THYROID IN THE PRESENCE OR ABSENCE OF TSH. C.J. Shellabarger and J.T. Godwin. Am. J. Physiol. 176, 371 (1954). Abstract.

Either thyroxine or triiodothyronine inhibited the expected response to thyroid-stimulating hormone (TSH) of an increase in thyroid weight and thyroid cell height in the 2.5-day White Leghorn cockerel. Neither thyroxine nor triiodothyronine affected thyroid weight or cell height in birds that received no TSH. This was interpreted as evidence that thyroxine or triiodothyronine acts directly on the thyroid gland to inhibit its response to TSH. When I^{131} uptake was studied, neither thyroxine nor triiodothyronine interfered with uptake when given with TSH. These thyroid hormones suppressed radioiodine uptake in birds that received no TSH. This was interpreted as evidence that the pituitary secretes minute amounts of TSH which are sufficient to effect I^{131} collection, yet do not produce discernible changes in thyroid weight or cell height, and that this pituitary TSH secretion can be inhibited by either thyroxine or triiodothyronine.

Division of Bacteriology and Virology (6300)

Virulence of Irradiated Type III Pneumococci

An investigation of the virulence of Type III pneumococcal cells exposed to gamma radiation is in progress. Preliminary studies show that the nonviable cells in a radiated population are avirulent for mice; in vivo recovery from radiation damage has not been demonstrated. The cells which survive radiation damage possess the same high degree of virulence for mice as nonirradiated cells.

Both normal and irradiated (sublethal) mice have been used for the experimental work. The irradiated mice were injected with radiation-exposed cells at a time when the white blood cell count was determined to be very low. This was done to minimize the possibility of rapid removal of the radiation-damaged cells from the peritoneal cavity by phagocytosis. The results in sublethal irradiated mice were the same as those obtained in nonirradiated mice. (R.M. Drew)

Tetanus Antitoxin Formation by Intraocular Transplants of Thymus Tissue

A series of experiments is being carried out to compare tetanus antitoxin formation by intraocular transplants of thymus tissue taken from donor mice sensitized when 7 days, 10 weeks, and 6 months of age. (R.D. Stoner)

Increased Sensitivity of Mice to Anaphylactic Shock After Cobalt-60 Gamma Radiation

Work is being continued on the enhancing effect of ionizing radiation upon the anaphylactic response in mice sensitized with tetanus toxoid. Preliminary work indicates that mice sensitized with pertussis vaccine, phase I, demonstrate increased susceptibility to anaphylaxis when challenged 7 days after gamma radiation. (R.D. Stoner)

A METHOD FOR ERADICATION OF THE MITE, "MYOCOPTES MUSCULINUS," FROM LABORATORY MICE. R.D. Stoner and W.M. Hale. J. Econ. Entomol. 46, 692 (1953). Abstract.

A method is described for eradication of the Listrophorid mite, Myocoptes musculinus, from laboratory mice by means of di-(p-chlorophenyl) methylcarbinol (DMC). It was found that 0.2 percent DMC in 50 percent alcohol was satisfactory as a Myocoptes miticide. The mice were submerged in the DMC solution and scrubbed about the ears,

eyes, and mouth with a cotton pad saturated with the solution. Four-week-old mice and three- to five-month-old breeding mice have been treated with DMC. Breeder mice were treated before mating and twice during pregnancy at five-day intervals with no adverse effects upon the newborn litter. Additional control measures for maintenance of the mite-free mouse colony are reported.

Division of Biochemistry (6300)

The Absorption and Metabolism of Glycerides

Triolein labeled in the glycerol moiety was synthesized from C^{14}-glycerol and oleyl chloride. Approximately 90 mg of triolein per 100 sq cm of body surface area were administered via stomach tube to rats which had been fasted 24 hr. The respiratory $C^{14}O_2$ was collected. At the end of 1, 2, 4, or 8 hr, the animals were sacrifieed and the lipides were extracted from the stomach, the stomach contents, the small intestine, the contents of the small intestine, the contents of the large intestine, and the liver and plasma. From the radioactivity found in $C^{14}O_2$ and lipides, the absorption and lipolysis of the administered glyceride were estimated. At the end of 5 hr, 40 to 75 percent of the lipide was absorbed. During the first hour of absorption, 9 to 17 percent of the administered triolein underwent complete lipolysis to oleic acid and glycerol. At the end of the second hour, 30 to 55 percent of the absorbed fat had been completely split. By the end of 4 hr nearly all the triolein had been absorbed while the extent of lipolysis was the same as that at 2 hr. (L.I. Gidez)

Metabolism of Lysine

The protein collagen contains a unique amino acid, hydroxylysine. By feeding carbon-14-labeled lysine, it was possible to demonstrate that the carbon chain of hydroxylysine is formed from lysine. An examination of the juice pressed from rat skin, a tissue rich in collagen, has failed to reveal a significant amount of free hydroxylysine. A possible explanation is that hydroxylysine is formed after the synthesis of the peptide chain of collagen has begun. This has raised the general question of whether or not an oxidative attack on the free ϵ-amino groups of lysine peptides is possible. Such a possibility is consistent with the observation reported in the literature that α-amino adipic acid, rather than ϵ-amino-α-keto caproic acid, appears to be one of the primary products of lysine oxidation. The oxidation of a peptide of lysine is now being studied. (F.M. Sinex)

Micro Chambers for Van Slyke-Neill Manometric Blood Gas Apparatus

Two modified micro chambers have been developed for the Van Slyke-Neill manometric gas apparatus. These chambers should prove useful in the determination of oxygen, carbon dioxide, and plasma amino acids in blood. The gas volume may be read at 0.05, 0.1, or 0.2 cc. The quantity of blood required for the determination of oxygen or carbon dioxide has been reduced from 1 ml to 0.05 ml. (D.D. Van Slyke, J. Plazin)

Division of Physiology (6300)

Enzymes in Vascular Physiology

A specific submicro method has been developed which now makes possible the direct assay of cholinesterases. The procedure is based on chromatographic separation of the

acetic acid released during the hydrolysis of acetylcholine. The free acetic acid is measured by means of direct microtitration following microdiffusion in a Conway unit. This permits the measurement of at least 1/100 of the activity measurable by classical techniques. The present "microness" and precision of 5 percent appear to be subject to further refinement by means of the use of radioactive acetylcholine. The method makes possible the investigation of effects of relatively small doses of irradiation administered in vivo. (G.C. Cotzias and I. Serlin)

Radiopotassium Early Kinetics in the Circulation (6300)

A study of the early kinetics of radiopotassium (K^{42}) exchange in the normal intact dog is being made. Several organ systems, including kidney, liver, heart, brain, and muscle, are being studied by a continuous simultaneous measurement of K^{42} blood activity in the vascular influx and outflux of the organs named. Measurements of organ blood flow and nonradioactive serum K levels are also being made. These curves of activity, following injected "slug" and constant rate infusions of 100 to 150 μc of K^{42}, are obtained during and for the initial four minutes after injection. The data indicate that K^{42} is lost extremely rapidly through the capillary bed in all the organs studied, that there are two vascular mixing components and at least two extravascular mixing components in the early equilibration, and that all organs studied seem to incorporate a large fraction of the injected K^{42} intracellularly in very rapid fashion. (H.L. Conn, Jr.)

Measurement of Portal Blood Flow by Utilization of the Hepatic and Lienal Extraction of Radioactive Colloids (Indirect Fick Equation) (6300)

Work is continuing and being broadened to include uptake of colloidal radioactive materials in various tissues. (H.L. Conn, Jr.)

Boron and Lithium Toxicity in Mice (6300)

Preliminary intravenous acute toxicity studies were made employing several boron and lithium derivatives in an infection-free, parasite-free population of 4- to 6-week-old Swiss strain of albino mice. (O.D. Easterday and L.E. Farr)

Bone Cancer Treatment with Radiogallium (6300)

Ga^{72} has been administered for palliation to six patients, three suffering from multiple myeloma and three from multiple osseous metastases secondary to carcinoma of the breast. No palliative effect has been observed in two of the multiple myelomas; the third shows at present moderate symptomatic improvement. Of the carcinomas of the breast, one has shown rather marked symptomatic improvement, one questionable improvement, and the third has been treated too recently for evaluation of the results of therapy. Tracer studies of Ga^{72} with varying amounts of carrier have been undertaken in the hope that it will be possible to predict dosage to the blood with a given quantity of radioactive isotope. These studies have not been concluded. (W. Wolins and H.C. Dudley)

Ion Transport Across Cell Surfaces (6300)

The effects of pH on sodium and potassium transport across the human red cell membrane in vitro are being investigated. Studies to date have shown that at pH 6.0 all unidirectional fluxes and rate constants are reduced markedly compared with physiological pH (7.4), but especially those in the direction of (necessarily) active

transport. Potassium influx and sodium outflux decreased fifteen to twentyfold, potassium outflux twofold, and sodium influx four to fivefold. Selective potassium uptake and sodium output still took place, but were greatly diminished. Potassium influx was no longer concentration independent, but increased sixfold with a twenty-fivefold increase in external concentration. At pH 5.0, all selectivity was virtually abolished and potassium influx was related linearly to external concentration.

At these pH levels, a marked reduction in red cell glycolysis occurs. Relationships of cation transport at decreased pH levels to cation transport under other conditions producing similar reductions in red cell glycolytic activity are being studied.

Studies directed toward the further definition of the kinetics of cation transport under optimal conditions for active transport have been initiated. (E.T. Dunham)

Xenon Anesthesia (6300)

The cooperating research team from the State University of Iowa carried out a series of experiments with the chief objective of determining the desaturation characteristics of xenon in various organs of interest. Continuous blood levels of xenon saturation upon initiating and terminating xenon administration were obtained by means of catheterization techniques. (H.L. Conn, Jr. and E.E. Stickley in collaboration with S.C. Cullen,* C.B. Pittinger,* R.M. Featherstone,* and L. Levy*)

Slow Neutron Beam Therapy (6210)

Extensive measurements have been made of the component radiations at the new medical treatment facility with shutter open and shutter closed. The uniformity of the neutron field in the arrangements for both tumor treatment and mouse colony exposure has been checked. Improvements in methods of handling the subjects have been developed. (E.E. Stickley)

Radioautographic Analysis for Boron in Tissue (6300)

Exposures to thermal neutrons have been made with tissues in the normal and boron-treated states mounted on nuclear emulsion plates. The results are being analyzed to determine the location and concentration of boron in tissue on a cytological scale. (P.B. Kruger** and E.E. Stickley)

Biological Titration of the Medical Facility of the Reactor (6210)

A preliminary experiment was conducted in the new medical facility of the BNL reactor to determine an approximate LD50 in terms of exposure time, with an infection-free, parasite-free population of 4- to 7-week-old Swiss strain of albino mice. The exposures were made under conditions of no filter, bismuth filter, lithium fluoride filter, and variation in exposure time. (O.D. Easterday)

NEUTRON CAPTURE THERAPY WITH BORON IN THE TREATMENT OF GLIOBLASTOMA MULTIFORME. L.E. Farr, W.H. Sweet, J.S. Robertson, C.G. Foster, H.B. Locksley, D.L. Sutherland, M.L. Mendelsohn and E.E. Stickley. Am. J. Roentgenol. Radium Therapy Nuclear Med. 71, 279 (1954). Abstract.

1) The feasibility has been shown of the use of a nuclear reactor to provide a neutron souce for B^{10} capture therapy of glioblastoma multiforme.

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2) A series of 10 patients were treated, of whom five received a single radiation, one received two radiations, two received three radiations, and two received four radiations. Multiple radiations were in general given at 5- to 6-week intervals.

3) Temporary amelioration of clinical symptomatology suggestive of retardation of tumor growth was seen to occur after 8 of 21 capture therapy efforts, questionable improvement after 6 of the remaining 13 efforts, and no detectable change after 7 of the treatments. Only one of five patients receiving multiple treatments registered no improvement at any time.

4) Periods of observation of up to six months, during which patients received up to four capture therapy procedures, have revealed no serious complications of this therapy. A detailed pathological report of tissues obtained from these patients is being published elsewhere.

5) Further extensive exploration of neutron capture therapy is warranted.

(6210)

SLOW NEUTRON DEPTH DOSE MEASUREMENTS. E.E. Stickley. Am. J. Roentgenol. Radium Therapy Nuclear Med., in press. Abstract.

Slow neutron flux density measurements have been taken through plastic, gel, and liquid phantoms made to simulate the neutron-sensitive characteristics of tissue. Foil activation technics were employed, using the radioactivity induced in gold and indium. Irradiations were made at the nuclear reactor port used for experimental neutron capture therapy process. In vivo intracranial flux measurements made during the therapeutic experiment are compared. Calculated values of the induced alpha and lithium particle radiation resulting from neutron capture by injected boron-10 are presented.