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326 US ATOMIC ENERGY

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COMMISSION

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Collection

Division of biology Medicine

PROGRAM

Box

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// Friday Morning - Room O-475, Medical School

9:30 Greeting by Dr. Donald Anderson, Dean, School of Medicine and Dentistry

9:45 Brief descriptions of the research programs of the Project
Dr. Bale, Division of Radiology and Biophysics
Dr. Hodge, Division of Pharmacology and Toxicology
Dr. Howland, Medical Division
Dr. Pearse, Flash Burn Section

10:30 Break

10:45 Shortening of Life-Span by Radiation - H. A. Blair

11:05 Effect of X-rays on Spermatogenesis - J. B. Hursh

11:20 Radiation Induced Changes in Properdin in the Dog - S. Michaelson

11:35 Tissue Specific Antibodies - I. Spar

11:50 Radiation Dose to Lungs from Radon and Thoron - S. Black

12:00 Lunch at Faculty Club

Friday Afternoon - Room O-159, Medical School

2:00 Inhalation Studies - J. K. Scott, D. A. Morken, J. N. Stannard,
P. E. Morrow and H. C. Hodge

3:00 Lymphocytes with Bi-lobed Nuclei as Indicators of Radiation Exposure
M. Ingram

3:15 Protein Metabolism - L. L. Miller

3:35 Break

3:50 Visit to laboratory for study of breathing of alpha emitters

6:30 Dinner, Green Room, Sheraton Hotel

Saturday Morning - Room O-183, Medical School

Meeting to be arranged by Advisory Board and Division of Biology and Medicine

10:30 Break

12:15 Lunch, Hospital Cafeteria

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Attempts at Therapy Following Whole Body X-irradiation on Rabbits and Guinea Pigs	L. T. Steadman	A-214
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<u>Drosophila melanogaster</u> as a Tool in Radiobiologic and Toxicologic Investigation (Effects of Cobalt Gamma Radiation on Life Span of Irradiated Adults, Effects of Highly Irradiated Food on Life Span)	Robert Baxter B. J. Henderson Lawrence Tuttle	B-239
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FLASH BURN SECTION

The task of this project is the analysis of the characteristics of thermal burns from nuclear weapons.

This required the development of suitable laboratory sources of intense thermal radiation, the construction of shutters to control the time of exposure or to simulate the bomb pulse, the design of radiometric instruments to measure the thermal flux and the fabrication of reflectometers to measure and deduct this ineffective portion of the thermal pulse.

Then the dose-response, i. e., the effective thermal flux times exposure time was determined on bare skin in about 3000 burns and its modification by ambient temperature and wavelength was measured. These dose-response studies have been basic to all subsequent laboratory work and to casualty prediction both civil and military.

The validity of our laboratory data has been confirmed by observations in the field and correlation between pig burns and human burns has been established.

Next, the protective effect of skin creams, clothing and fabric shields has been studied both in the laboratory and the field. These and other studies are being continued. The work now in progress is as follows:

1. Histologic and histochemical studies of healing burns.
2. Relationship of pulse shape and exposure time to depth of damage.
3. Effect of fabric spacing in one and two layer clothing assemblies.
4. Pathology of sub-fabric burns.
5. Effect of thickness of a protective cream layer.
6. Tissue temperatures during burning.
7. Chemical changes in blood from a burned area.
8. Field calorimeter.

SHORTENING OF LIFE-SPAN BY RADIATION

H. A. Blair

It is becoming well established that whole-body exposure to penetrating ionizing radiation leads to shortening of life span. Partial body exposures to external sources have received little study but internally deposited radioactive materials which usually have a partial body distribution also shorten life. The simplest assumption to make to account for these phenomena is that radiation injury is only partially reversible and that the irreversible portion constitutes wholly or partly a form of premature ageing. In the rodent, shortening of life is about 1% per 100 r from divided doses and is an increasing function of dose with single doses in excess of 100 r which may attain levels as high as 40% to 50% for survivors of a single LD₅₀ dose (about 700 r).

Irreversible injury is measurable in at least one additional way as a decrease of LD₅₀. Animals which have been exposed to radiation and allowed to recover as fully as they will succumb to lower doses of radiation than do those not previously exposed.

There is some evidence that irreversible injury has the same effect on life span independently of the age at which it is sustained. This indicates that it is a state which once laid down does not spontaneously decrease or develop. If it could be changed by some agent a method would be provided for altering this form of ageing and its variations could be studied in young animals as changes in LD₅₀. Any way of decreasing the irreversibility of injury when it is being laid down subsequently would, of course, have a direct bearing on permissible exposure.

The present experimental indications regarding irreversible injury and shortening of life-span will be reviewed and the major areas in which data are deficient pointed out.

ABSTRACT

EFFECTS OF CHRONIC LOW LEVEL WHOLE BODY DOSES OF X-RAYS ON SPERMATOGENESIS IN DOGS

This project investigates the effect of chronic x-ray at dosage levels near the maximum permissible limit on spermatogenesis, chosen as a sensitive biological criterion. As the experiment progresses into its later stages other effects associated with aging will be measured.

The principal experiment contains three groups of beagle dogs receiving 10 minute doses each dog (5 days per week) of 250 KVP x-rays at rates of 0.3 r per week (20 dogs), 0.6 r per week (10 dogs), and 3.0 r per week (10 dogs) compared with a fourth group of sham-irradiated controls (20 dogs).

Sperm is collected from the dogs at monthly intervals, the number and concentration of living and dead sperm measured, and a functional estimate made on the basis of the number and type of morphological abnormalities. Fertility is periodically checked by mating with proven bitches.

This experiment has been going on for more than 6 years. The dogs radiated at the two lower levels 0.3 r week (total dose = 61 to 94 r) and 0.6 r per week (total dose = 122 to 181 r) have shown no consistent differences from the control group in respect to the quantity and quality of the sperm production or the test-mating results. In the 3.0 r per week group (total dose = 606 to 864 r) eight out of ten dogs are infertile. In general samples from these dogs showed a decline in sperm count at total doses of 60 to 90 r and a marked reduction (10% pre-exposure) at 120 to 180 r. Two resistant dogs (total dose = 613 and 648) continue to provide semen samples with sperm counts which fluctuate about the critical reproductive level and irregularly continue to father litters when test-mated.

A supplemental program likewise using dogs and pursued at a rate permitted by our facilities has yielded some information concerning the effect of dose size and rate on impairment of spermatogenesis and on the recovery process. In general these data suggest that a latent period of about 10 weeks intervenes between the occurrence of the injury and its manifestation in the collected sperm. Total doses of 477 r and 634 r delivered at a rate of 15 r per week produced aspermia with no recovery in more than two years. A single dose of 300 r produced a sperm count depression which recovered completely. The details of these experiments considered in conjunction with the results from the main experiment suggest to us that the effects of x-ray on sperm production depend not only on total dose but perhaps more importantly on daily dose rate. It appears that the most efficient use of x-ray to produce sperm injury is made when the dose is delivered at a rate somewhere between 0.6 r per week (ineffective at total dose = about 150 r) and perhaps 15 r per week (producing zero sperm count at total dose = 375 r). These considerations have a demonstrated application only to a 10 minutes per day, 5 days per week irradiation schedule, but are believed to be of more general import. This question will be explored further in subsequent experiments with particular attention to the production of permanent sterility.

RADIATION INDUCED CHANGES IN THE PROPERDIN SYSTEM OF THE DOG

S. Michaelson

ABSTRACT

Considerable evidence has been accumulated to indicate that infection with gram negative organisms is of considerable importance in the morbidity and mortality of laboratory animals subsequent to whole body exposure to penetrating ionizing radiation.

In 1954, Pillemer and his associates described the Properdin system consisting of Properdin, complement or complement like antibodies and Mg^{++} . This system participates in certain bactericidal processes especially against gram negative organisms such as *Shigella* spp, *Salmonella* spp, *Pseudomonas* spp, *Proteus*, *Paracolon*, and has some virus neutralizing activity (Influenza, Newcastle).

Reports from Dr. Pillemer's laboratory indicate a marked fall in the serum Properdin level among whole body irradiated rats and mice. Preliminary experiments revealed some decrease in mortality of irradiated mice by Properdin administration.

Experiments performed with whole body irradiated dogs reveal that the drop in Properdin level is related to the lethality of the radiation dosage. With increased radiation dosages the Properdin decrease is more precipitous reaching lowest measurable levels by the 10th to 14th days. Among the animals which survive, there is a return to the pre-exposure Properdin level by the third month. There was no correlation between Properdin, other circulating blood proteins, leukocyte level or bacteremia at any stage of the radiation syndrome in the dog. Zymosan, the purified cell wall residue of

fresh yeast which alters Properdin level in vivo, induced a twofold increase in leukocytes in dogs when injected seven days after exposure to LD-80/30 dose of x-rays at which time the leukocytes ordinarily are at a critically low level.

ABSTRACT

TISSUE SPECIFIC ANTIBODIES AS POSSIBLE THERAPEUTIC AGENTS FOR THE TREATMENT OF CANCER

Radioactive isotopes will be much more useful in the radiation therapy of cancer when means are developed for concentrating them in tumor tissues as specifically as inorganic radio-iodine will concentrate in the human thyroid following intravenous injection. A possible tool in accomplishing this specific radiation effect may be a radioactive isotope attached to an antibody that will be preferentially bound to some antigenic component associated with the tumor. This project is designed to investigate the possible use of anti-tumor antibodies coupled with a radioactive isotope, as a therapeutic agent of this type.

Antisera, labeled with I^{131} , have been prepared against normal rat tissues and several transplantable mouse and rat neoplasms and studied by in vivo and in vitro techniques. In general, the experimental work indicates that for most tumors a necessary step in obtaining an antibody with a high specificity for binding in tumor will be a preliminary separation of specific tumor-directed antibodies from those antibodies capable of reacting with both normal and tumor elements. If this separation is not carried out, antibodies to stromal elements localize strongly also in vascular normal organs, such as liver and adrenal.

Various diverse methods are under investigation for preventing the production of antibodies common to normal as well as malignant cells or for removing tissues. These techniques include (1) the use of induced immunological tolerance, (2) the growth of tumor in foreign species to separate the neoplastic elements from the stromal elements; i.e., growth of mouse and human tumors in rats, (3) the use of multiple specific absorptions of antisera with cross-reacting tissues, and (4) the purification of antisera by multiple absorption-elution procedures using the tissue against which specific antibody is desired as the absorbing agent. For this purification technique, two new reagents were discovered, urea and sodium salicylate, that act almost quantitatively in breaking bonds between an insoluble antigen and an antibody, thus putting into solution a major proportion of antibodies from such an antigen-antibody complex.

Since specific antibody localization in cancer presumably occurs largely in extravascular space, measurements were made of the rate at which intravenously injected gamma globulin reaches the extravascular spaces of various rat organs and tissues. To differentiate between vascular and extravascular space, red cells labeled with radioactive chromium and gamma globulin labeled with I^{131} were used. The measurements indicate that in one hour about 5% of the gamma globulin in the plasma entered the extravascular space of 1% of the body weight of liver, kidney, and adrenal. Values for other tissues ranged from 1.5% for lung and lymph node, 0.7% for Walker carcinosarcoma 256 to about 0.02% for muscle and fat.

RADON EXPERIMENTS WITH MICE

J.K. Scott and D. Morken

All of the experiments performed have been carried out in a chamber designed by Morken which has a radon concentration, relatively free of daughters, of 2.4×10^{-4} curies per liter. The dose is varied by varying the duration of exposure. CAF₁ and Strain A, Heston, (Bar Harbor) mice have been used. The following experiments have been completed: life-span shortening vs dose, pathologic and hematologic studies, and incidence of pulmonary adenomas.

The LD₅₀ - 30 days is 6-8 mc hr/L. Life span shortening has been studied in doses from 0 to 5.7 mc hr/L; these indicate a threshold less than 5.7. Histopathologic studies were essentially the same as whole body x- or gamma irradiation except for the development of a renal lesion about 5 months after exposure. Hemograms were essentially the same as whole body x- or gamma irradiation. The incidence of pulmonary adenomas in both Strain A and CAF₁ mice has been about one-half that of unexposed controls.

TISSUE DISTRIBUTION OF RADON DAUGHTER PRODUCTS

D.A. Morken and P.S. Miller

It has been observed that lifespan shortening produced by inhalation of radon (essentially free of daughter products) is considerably less than that produced by equivalent radiation doses from injected Po^{210} (RaF). In the former case, alpha doses are received not only from radon itself, but from Po^{218} (RaA) and Po^{214} (RaC').

A possible cause of this difference might be due to differences in the kinetics of dose distribution in the two cases. Experiments are in progress in which the tissue distribution of radon daughter products is determined as a function of exposure time and post-exposure time. Preliminary data show that kidney, liver and lung evidence a large ratio of decay products to radon. The accumulation of these daughter products in a tissue appears to be related directly to the blood minute volume of the tissue.

Distribution alone does not appear to offer a clear-cut explanation for the difference in effectiveness since Po^{210} also accumulates in the kidney.

Experiments will continue until all tissues have been studied. These data will then be compared with similar data from Po^{210} experiments.

Radon	$\mu = 0.0013$	
	3	Ratio
	5	17
	1	2

Lat 7

POLONIUM STUDIES

J. N. Stannard

Over the past several years the Project has amplified and extended the war time work of R.M. Fink et al on this interesting alpha emitter. The influence of routes of administration, state of aggregation, etc. on distribution and excretion, its combination with various tissue constituents and its long term effects in terms of histopathology and life span shortening have been studied in rodents. Particular emphasis has been placed on the effects of a maintained body burden.

More recently, inhalation and intubation studies with this element have been completed. These show that the metabolism on inhalation is not identical with that seen after any other route of administration and thus actual inhalation exposure is needed for determination of its behavior. Most recently, the inhalation studies have been extended to the dog and determinations of pulmonary retention and clearance made possible. The inhalation studies have been carried out by Drs. Harry L. Berke (rodents) and P.E. Morrow (dogs).

THORIUM-IONIUM

J. N. Stannard

Earlier work demonstrated the essential inertness of thorium and its compounds as chemical hazards. Also, the extreme insolubility and lack of mobility of thorium in body fluids and tissues has been demonstrated. Despite these facts, the possibility of a radiation hazard from thorium has been the subject of much speculation and many recent discussions. During the summer of 1956, R.G. Thomas et al checked the metabolism of ionium (Th^{230}) after intra-tracheal injection. This isotope was chosen because while chemically thorium, it is free of the daughter product chain which complicates metabolic studies with many other members of the thorium series. The results confirm previous ideas and are essentially as follows:

1. There is little or no urinary excretion of this isotope and, therefore, attempts to measure thorium body burdens by urine contents appear almost impossible.
2. Fecal excretion is essentially complete in one week. Thus examination of feces very soon after exposure might permit some estimate of body burden but only if accomplished quite early.
3. Absorption from the lung is very slow. Most of the lung clearance can be attributed to removal to the gastrointestinal tract by ciliary and/or phagocytic action.
4. Appreciable amounts of ionium are deposited in the skeleton by what appears to be a serum-concentration-limited process.
5. Both absorption from the lung and deposition in the skeleton are considerably smaller than after administration of equivalent amounts of plutonium.

BIOMEDICAL FIELD TEST OF PLUTONIUM INHALATION

J.N. Stannard

The inhalation hazard from a plutonium contaminated field is being investigated at NTS by direct exposure of animals. The acute phase involved exposure of 26 dogs and 43 rats preplaced at 500, 1000, and 2000 feet from ground zero along lines parallel to it. In addition, a few rats were flown from balloon cables in the cloud. The rats and 10 dogs were removed at 1/2 to 2 hours post-detonation for determination of the plutonium content of tissues and its localization therein. Most of the remaining animals for the acute phase will be sacrificed serially, but some retained for study of long-term effects.

A chronic exposure array was prepared by placing 24 dogs and 3 burros on each of three "isodose" lines, nominally $1000 \mu\text{g}/\text{m}^2$, $100 \mu\text{g}/\text{m}^2$, and $10 \mu\text{g}/\text{m}^2$. They were placed in groups of 8 dogs at west, center, and east of the line of prevailing southwest winds. A portion will be sacrificed serially at times extending to 165 days post-detonation. The balance will be returned to the laboratory for long-term observation (tumor incidence, fertility, life span). Sheep will be placed in the field as the dog pens become available.

The total experiment includes 109 dogs, 9 burros, 43 rats, and an indeterminate number of sheep and should provide a check of the inhalation hazard under very severe conditions of dust and resuspension. No quantitative results have been obtained to date since they await radiochemical plutonium analyses. The animals out to 1000 feet from ground zero carried quite high pelt counts as measured by monitoring instruments.

ABSTRACT

MEASUREMENT OF RADIATION DOSE TO LUNGS FROM RADON AND THORON DEGRADATION PRODUCTS

One of the important exposures of human subjects to ionizing radiation in the Atomic Energy Commission program occurs in the mining of radioactive ores. Today this hazard is associated primarily with radon and its airborne degradation products. A similar type of exposure to the degradation products of thoron may be important in the future.

This program is directed toward obtaining measurements of radiation dosage to the principal parts of the respiratory system of experimental animals breathing various atmospheres containing radon and thoron, to measure human retention of radioactivity in such atmospheres, and from such data to arrive at valid estimates of the dose to the various parts of the respiratory tract of human beings breathing such atmospheres. This program also aims at the development of methods for measuring integrated human exposure to radon, both as a monitoring procedure and for possible correlation with lung cancer incidence among a population of miners exposed to radon contrasted with a normal control population.

An eventual product of the radioactive decay of radon is radiolead with a 20 year half-life. Previous work in this program has shown that storage of radiolead occurs in the bodies of individuals exposed to radon up to 100 times as much as in similar tissue samples from persons with no history of radon exposure; and that polonium, produced in turn from radiolead, appears in the urine since urine from active miners contains up to 100 times as much polonium as urine from laboratory personnel. Potentially therefore polonium in urine can be used to measure integrated previous radon exposure in living individuals and the radiolead content of autopsy specimens can also be used to measure the individual's previous exposure to radon. Additional information on the sites of deposition and rate of excretion from the human body burden of lead derived from radon are needed. Radiolead in autopsy specimens is determined by measuring the polonium produced by its radioactive decay.

In cooperation with the U.S. P.H.S. (Mr. Duncan Holaday), the Grand Junction Veterans Administration Hospital (Dr. Stanley Crosbie) and the Union Carbide Nuclear Co. (Mr. Arthur Schaeffer) four adult beagle dogs were placed in the CFC mine near Uravan, Colorado last November. After several months' exposure in an area of relatively high radon and radon daughter concentrations, they will be returned to Rochester for measurement of polonium excretion and the biological half-life of radiolead as a function of time after exposure.

Two adult beagle dogs were given high radon exposures in a new radon exposure chamber here at Rochester in a joint experiment with the Radioactive Inhalation Section. Polonium and radiolead excretion is being followed in these animals exposed to a known amount of radon. In terms of activity, these two dogs excreted 16-38 times as much radiolead as polonium the first two days after exposure. This activity ratio had dropped to 5-10 within two weeks and has remained about the same for the following four weeks.

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Mice exposed to radon at various dosages up to two years prior to death or sacrifice were analyzed for polonium and radiolead content. The data indicate that the effective half-life of radiolead is long (approximately 700 days) even in this species.

Polonium analyses were made, and radiolead determinations are being done on human autopsy material forwarded by Dr. Geno Saccomanno, Grand Junction, Colorado and on human autopsy specimens obtained at Rochester from cases with no recorded history of exposure to naturally occurring radioactive materials. Sternum and rib specimens of one case from Grand Junction show polonium contents ranging from 2,850 to 4,350 micromicrocuries per kilogram fresh tissue contrasting with values of 4 to 75 from similar material obtained at Rochester.

AEROSOL STUDIES IN MAN AND DOG

P.E. Morrow and F. Gibb

Comparative studies on the deposition of various "carrier" aerosols in human and canine subjects are continuing. Seventeen studies on seven human subjects with a NaCl aerosol (CMD 540 Å σ_g 2.25) resulted in 63.4% mass deposition (95% confidence limit for mean, 57-69%). In five studies on two dogs, the mass deposition values and the role of various physiologic factors appear to be quite similar. Two experiments wherein the sodium chloride was aerosolized as a carrier for polonium²¹⁰ have been completed. Plans are being completed for the exposure of dogs to plutonium aerosols.

Handwritten notes:
7 males
5 females
2 dogs
30 mg

Handwritten notes:
7 males 6000
(1.1) 100-100
2 dogs 3 > 6000
(5) 15-70

AEROSOL AGGLUTINATION STUDY

L. Dautrebande, K.E. Lauterbach, A.D. Hayes, P.E. Morrow

The study of agglutination is of considerable interest because it is one phenomenon which can greatly affect the stability of a submicronic aerosol. Not only is the agglutination of importance in aerosol research but it appears to be a "de-dusting" method of practical use. Some of the materials and methods being used will be discussed and representative electron micrographs will be shown.

The illustrations will give examples from tests with UO_2 and NaCl of the results from studies of these aerosols and also of carbon black, polystyrene and aluminum. Heterogeneous aerosols, e.g., UO_2 (CMD = 0.2 with range 1 - 0.01 μ) mixed with NaCl aerosols of very small and relatively uniform particle size (CMD = 0.04) would agglutinate to give very much larger particles, too large to be inhaled or to remain suspended. Relative agglutination by visual examination of hundreds of particles affected 80 - 100% of all particles in a suspension.

CHRONIC EXPOSURE TO URANIUM DIOXIDE DUST

by

Harold C. Hodge

For over a year monkeys, dogs and rats have been inhaling UO_2 dust at a concentration of 5 mg of uranium per cubic meter. The dust has a mass medium particle diameter of about 1 micron. A serial sacrifice program on rats with analyses of lung tissues has shown the gradual building up of uranium in the lungs during the year and the gradual removal in a post-exposure period of three months. Analyses of dog lungs are available from dogs that have inhaled this atmosphere for 6 months and for 1 year. Pulmonary lymph node analyses also are available. In general, the pulmonary lymph nodes contain much less uranium in the early months of exposure than was found in the lungs. However, by the end of the year the pulmonary lymph nodes contained considerably more than the lung tissue.

At the end of exposure, the mean uranium content in rat tissues, calculated as $\mu\text{g.U/g.}$ fresh tissue, was as follows: lungs, 910; pulmonary lymph nodes, 1740; kidneys, 0.80; femur, 0.45; liver, 0.065. During a three-month post-exposure period increased amounts of uranium were found in the lymph nodes, kidneys and liver, maximal values being 3500, 1.1, and 0.115 $\mu\text{g.U/g.}$ fresh tissue, respectively. In the case of the lungs a 35 per cent decrease was noted during this period. The post-exposure lung data indicates that the biological half-life of uranium dioxide in the lungs of rats is about 160 days. The build-up follows a hyperbolic function.

Re: ... using a/g tissue ...

LYMPHOCYTES WITH BILOBED NUCLEI AS INDICATORS OF
RADIATION EXPOSURES IN THE TOLERANCE RANGE

M. Ingram

ABSTRACT

The relationship between an increased incidence of lymphocytes with bilobed nuclei and exposure to small doses of ionizing radiation was discovered and confirmed experimentally in this laboratory several years ago and has since been confirmed by other investigators. Data obtained from studies of cyclotron workers and dogs are reviewed briefly.

Methods for preparing concentrations of intact viable leukocytes in order to facilitate the examination of blood for binucleate lymphocytes have been under study in this laboratory for some time and a great deal of progress has been made since the first studies were done on the blood of cyclotron workers. Methods in use at present were tested under field conditions in a preliminary study of uranium miners in the Colorado plateau. The methods are described and demonstrated. It is hoped that such procedures, requiring only standard equipment, will make it practicable for other investigators to employ the determination of the incidence of lymphocytes with bilobed nuclei as a monitoring procedure in selected groups of radiation workers under a variety of standard operating or field conditions.

Additional information about the precise nature of the cytological abnormality in the abnormal lymphocyte is needed. We have long been aware of the possibility that the cells may be polyploid, a characteristic

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which, occurring in company with multinuclearity, directs attention to the possibly malignant implications of an increased incidence of lymphocytes with bilobed nuclei. The importance of evaluating this possibility particularly in regard to the problem of leukemogenesis following repeated small radiation exposures, and the formidable problems involved in arriving at such an evaluation are considered.

ABSTRACT

THE MAJOR RESEARCH ACTIVITIES IN THE TRACER CHEMISTRY SECTION OF THE DIVISION OF RADIOLOGY AND BIOPHYSICS

The effects of chronic irradiation, and of sublethal acute irradiation seem to be largely in the direction of accelerating those involutional and degenerative processes, such as increased tendency to develop malignant disease, characteristic of aging in the mammal. On the biochemical level such natural and pathological changes are associated with major alterations in protein metabolism. Therefore, data provided by studies in this field are significant both in providing criteria for the magnitude of such processes and, it is hoped, in providing through new basic information clues that will make possible retarding, stopping, or reversing of such normal or abnormal involution, whether due to radiation, other toxic substances, or more natural causes.

The technique of surgically removing the liver and maintaining it alive by continuously pumping oxygenated blood through it has been used in studies bearing on the synthesis of the plasma and liver proteins in normal and abnormal rats including experimental cirrhotics, experimental diabetics, and carcinogen fed animals.

The isolated perfused liver continues to be used in extending our knowledge of the dominant role of the liver in the synthesis and metabolism of the plasma mucoproteins and the plasma lipoproteins with the aid of carbon-14-labeled acetate, C¹⁴-labeled lysine, and S³⁵-labeled sulfate. A number of interesting observations have been made:

1. A close physical and chemical association of the plasma lipids (? lipoproteins) and the plasma mucoprotein fraction (particularly the alpha-one and alpha-two mucoproteins) has been found.
2. Labeled lysine is incorporated into the alpha globulin fraction including the mucoproteins at a rate two to five times greater than into the other protein fractions.
3. The catabolism of plasma and liver proteins has been shown to give rise in the isolated perfused liver to enough urea nitrogen to account for almost all of the endogenous urea nitrogen produced by the intact rat (which corresponds in size to the rat supplying the liver for the perfusion). A study of the nitrogen-sparing action of the carbohydrates glucose and fructose and their related metabolites in the catabolism of liver and plasma proteins is under way.
4. The remarkable increase in the plasma mucoproteins after whole body radiation injury remains to be characterized with respect to the particular mucoproteins which increase after radiation injury and the relation, if any, to the hemorrhagic diathesis.

5. The effects of glutamine, glutamic acid and ammonia (as ammonium carbonate) have been studied and compared with respect to their effects on urea synthesis, plasma and liver protein synthesis. Glutamine supplementation has a remarkable depressant effect on the production of $C^{14}O_2$ from L-lysine-6- C^{14} and greatly enhances the incorporation of lysine-6- C^{14} into plasma and liver proteins.

6. Unequivocal evidence has been obtained for a direct action of insulin on the isolated perfused liver. In contrast to the failure of other investigators to demonstrate an effect of insulin on liver slice systems, we have been able to clearly demonstrate that the perfused alloxan diabetic liver responds to insulin with a correction of metabolic defects in lipid synthesis and carbohydrate metabolism. At the same time these studies have yielded valuable information concerning the effects of carbohydrate supplements, fasting, and insulin on plasma and liver cholesterol synthesis and ketone body formation.

A detailed study of the respective oxidative abilities of the liver with respect to amino acids and of the non-hepatic tissues, in particular the kidney, is well under way. Preliminary data obtained with regard to oxidative disposal of 8 C^{14} -labeled amino acids reveal that the non-hepatic tissues oxidized very little lysine, histidine, phenylalanine or tryptophane. Further, that the non-hepatic tissues are capable of oxidizing glutamic acid as well as the liver and also oxidize leucine, isoleucine, and glycine to a comparatively significant extent (5 to 12% of the dose).

The in vitro achievement of positive nitrogen balance in the isolated perfused liver has been effected in normal rat livers only by the simultaneous use of a complete amino acid mixture with a large supplement of glucose or fructose along with insulin and growth hormones (Miller, Burke, Haft, 1956). The use of this combination in the study of nitrogen balance and net protein synthesis remains to be studied in the isolated livers from tumor-bearing rats, diabetic rats, and rats fed carcinogen (3-Methyl butter yellow and acetylaminofluorene).

The nature of an hepatic factor favoring the abnormal synthesis of protein by the Walker tumor is being investigated. Attempts to devise an in vitro system for testing stimulation of tumor protein synthesis by a liver factor have led us to develop a method for growing the Walker tumor in tissue culture. By first inducing growth of the Walker tumor as an "ascites tumor," we have eliminated the troublesome complication of fibroblasts which overgrew the tumor cells in tissue culture. Now, with a "pure" growth of Walker tumor cells, we are in a position to explore the effects of various liver fractions on tumor growth. We plan also to study overall protein and amino acid metabolism in the isolated growing Walker tumor cells; in particular it will be possible to determine to what extent, if at all, the Walker tumors can directly utilize homologous plasma proteins for tumor protein synthesis.