ARGONNE NATIONAL LABORATORY
LONG-RANGE PROGRAM

VOLUME II

APPENDICES

February, 1959

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Introduction

This second Volume of the Laboratory's Long Range Program contains appendices which give detailed information on the program of the Laboratory from the standpoint of its component organizations: the Scientific and Technical Divisions, the Supporting Technical Services and the other Supporting Services. The appendices were originally prepared by the division and departments concerned; they have been reviewed and modified somewhat from the over-all Laboratory standpoint and edited to give as much consistency as seemed essential to the over-all presentation. Since the Laboratory's program is basically that of its scientific and technical divisions and their staff, it seemed appropriate that these appendices be as spontaneous an expression of opinion as possible, complete consistency of form and compatability of content being of secondary importance.

The scientific and technical divisions were requested to prepare their long range programs in accord with their capabilities, their interests, and their understanding of the Commission's responsibilities and needs and of the Laboratory's place in its program. They were encouraged to be as specific as they could be in describing their programs for the next five to ten years, recognizing that many of the details of programs and even programs themselves will have changed or vanished when the next review is made. Despite this unavoidably tentative quality, it is believed that a presentation in this vein is the only possible way to present an over-all picture of the Laboratory's responsibilities, capabilities, and potentials. They must be read with full understanding of their provisional character. In almost every case these appendices were distilled from much more detailed suggestions supplied by members of the staff of the division involved. Many items of the current program and of the future one as seen today have been omitted or are presented in highly abbreviated form. It is believed, however, that what is presented here does give a reasonably representative view of the types of programs which the Laboratory will be engaged in for the next five to ten years and of the support which will be necessary if such programs are to be carried out.

APPENDIX

DIVISION OF BIOLOGICAL AND MEDICAL RESEARCH
LONG-RANGE PROGRAM

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DIVISION OF BIOLOGICAL AND MEDICAL RESEARCH
LONG-RANGE PROGRAM

I. SCIENTIFIC AND TECHNICAL OBJECTIVES

Biological work in the Laboratory was established originally because it was clear that the utilization of radiations and radioactivity would soon run far ahead of our knowledge of their hazards. This is as true today as it was then. There is a continuing need to learn as much as possible about the toxicity and hazards of radiations. The broad base of the program of the Laboratory and its unique facilities provide a climate which is particularly well suited for evaluation of the many vexing problems of radiation toxicity. It is necessary not only to consider the effects of a wide variety of radioactive agents on large populations of experimental animals, but also to relate such information to man, which in itself raises formidable question of interspecies relationships. Although the principal objectives of the Division are oriented to practical matters of radiation toxicity, the scope of the program is necessarily broad, since radiation has its effects on most biological systems, and since many of these effects lack interpretation owing to deficiencies in our knowledge of basic phenomena.

Earlier studies in the Division contributed in a major degree toward the formulation of standards of radiation safety. To cite examples in one area, many of the presently applied industrial permissible amounts of radioelements (Sr^{89}, Sr^{90}, Pu^{239}, C^{14}, and H^3) were determined on the basis of direct experimental work in the Division. At the present time, it appears likely that the more recent findings in regard to retention in the body of alkaline earths (such as strontium, barium, and calcium) and the relative toxicities of alpha and beta rays will result in significant modification of earlier predictions - fortunately in a direction indicating that present levels are probably conservative.

For the future it is certain that it will be necessary to determine on very large populations the effect, or lack of perceptible effect, of small amounts of radioactivity considered as safe for the industrial population. The immediacy of the need for this is obvious from the gradually mounting levels of widespread human radioactivity from weapon tests and from the rather large-scale geographical distribution of measurable radioactivity from the Windscale mishap in England.

This need has indeed been recognized by the Division for many years. There are two ways in which this problem is approached experimentally: (a) on the level of large-scale statistical studies, which may be carried out on both human and animal populations; and (b) on the level of basic investigation of radiation effects on cells including the processes

occurring in irradiated tissue which tend toward cancer, the conditions of exposure which make cancer more or less likely to result from a given amount of radiation, and the nature of the aging process itself which in some way predisposes to cancer.

Work on these aspects of the problem has proceeded mainly within the rather broad scope of the basic research programs in the Division. Changes in the fine structure of cells are under constant investigation using the electron microscope and other modern tools of cytology. Processes of growth in relation to cancer formation and the spatial distribution of radiation in relation to cancer are being studied in both basic and applied programs. The effects of combining radiation with chemical agents that produce cancer have been studied, in one case by pathologists in the Division, and in another case by direct collaboration with a university group interested in carcinogenic co-factors. Such experiments as these contribute to an understanding of basic problems in biology and, in addition, they form a major part of the national effort to determine the toxicity of small amounts of radiation.

The significance of the aging process, and its relation to the formation of cancer is one in which the Division pioneered and has continually expanded. Our approach started as the mathematical one of verifying and trying to interpret data which were originally developed over the last century by a few biologists. The first definitive experimental studies were conducted at another laboratory with the substantial support of this Division and showed, unexpectedly, that the mean life span of animals irradiated at low levels actually exceeds that of unirradiated animals. While this has been verified here and elsewhere a number of times, it requires further study. In particular, it must be related to basic physiologic and pathologic processes in some manner not known at present but which may become evident in subsequent studies. Until a half dozen years ago this type of study was being pursued almost entirely within this Division. Now, however, many investigators both in this country and abroad are concerned with this subject and are cooperating in the study of this problem. The acquisition of two gamma-ray animal exposure rooms by this Laboratory has greatly increased the scope of this work.

The interest stimulated in this area by our earlier work has resulted in many fruitful collaborative studies. One of the large universities on the West Coast is at present collaborating with us in the study of the histochemical and physiological results of irradiating their stock of aged animals.

A number of investigations of large human populations has been undertaken under the direct programs of this Division, in close collaboration with the Radiological Physics Division. Long before some recent, largely speculative, publications pointed out the possibility that small

amounts of radiation might produce small but absolutely important increases in cancer, a program was initiated to investigate the incidence of bone tumors in relation to natural levels of radium in human beings. As a result of the original background radiation survey that was carried out at the time the new Laboratory site was chosen, it was found that the deep-well water supply in this vicinity had an unusually high radium content. Subsequently, it was discovered that local water supplies in several mid-western states also have a very high radium content. A survey of the human population served by these water supplies was initiated in an effort to determine the true incidence of bone tumors, using as controls persons living in adjacent areas. Thus far, no difference in bone tumor incidence attributable to the higher radium content of the water has been detected. A study of this sort encounters certain basic problems as for example the accuracy of diagnosis in different geographical areas, the possible history of medical injections of radium and occupational exposure, and the number of cases which might be attributed to elevated levels of fluorine in certain potable waters. These problems are obviously of critical importance and can be attacked only through an expansion of the present effort.

Studies of large populations of irradiated animals have not been carried out up to the present time although it now appears that they will be necessary if we are to attempt to answer certain questions concerning the possible effects on large human populations exposed to low levels of radiation. The anthropological milieu is not subject to controlled experimentation and so for obvious social reasons this question will have to be studied on the basis of risks already being incurred at various places. Although such work is being expanded, the use of experimental animals would permit closer control over the variables to be encountered. While a prohibitively large number of small animals would be required to detect the cancer response to amounts of radiation comparable to the natural background, it is still possible to design experiments which will at somewhat higher levels, determine whether the response is or is not truly proportional to dose. We are suggesting, tentatively, that with a colony of 200,000 mice it might be possible to determine the general rules relating dose to probability of cancer, and perhaps to infer from this what might occur at truly low doses. Such studies might at least establish some general ground rules which would give a better picture than is available from present speculations and from the few past experiments that are available for study and evaluation. Such a program, which would require a major expansion in personnel, is currently under discussion.

Two other illustrations of the close and intimate relations between basic research and practical application will be given. It has been of interest to consider the possibility that some of the acutely toxic effects of radiation might be reversible by some sort of treatment. Light was shed on this question as a result of experiments in the Division which

showed that animals treated with Sr^{89} could endure a much larger dose of radiation than those given an equivalent dose of bone marrow irradiation by X-ray. Careful study of these animals revealed that some of the blood-forming functions of the bone marrow had been taken over by the spleen which, being remote from bone, had received only nominal amounts of irradiation. This resulted in an investigation of the possibility that the spleen might contain protective principles. Further work carried out under a collaborative project, showed that bone marrow itself, as might have been suspected, was protective. This discovery, made under a programmatic study designed for other purposes, has resulted in the most favorable approach to treatment of acute radiation sickness now known. This is now being studied actively in many laboratories and clinics.

As a result of our basic biochemical studies of the effect of radiation on enzymes it was suggested that certain normally occurring reducing substances might be important in determining the intensity of the radiation response. It was indeed found that the injection of certain natural reducing substances just before exposure greatly mitigated the effect of the radiation. The implications of this were firmly established in a series of studies in the Division and stimulated intensive investigation elsewhere.

Certain areas likely to become more active deserve special mention here. A separate appendix to this report will deal with potentialities in the plant sciences emerging from the biosynthesis program. A special biology reactor, now under construction, will within the next two years begin to provide information about the effects of high and low dose rates of fission neutrons, which so far represent a serious gap in our practical knowledge. Epidemiological studies will be expanded, including radium effects on bone tumors and leukemia as well as further explorations in human genetics. Acquisition of new dog quarters will make it possible to study the effects of about ten fission products, hitherto studied only in mice and rats, which are potentially of importance in the event of reactor accidents. This facility is under preliminary design. For the immediate future it is proposed that a substantial increase in small animal quarters will enable us to explore the unknown questions, soluble only with the use of large numbers of individuals, relating to the probable effectiveness of small radiation doses in producing perceptible human damage.

It is not proposed that all of the basic biological programs be expanded to the same extent. On the other hand, it would seem that in some of these areas we have not been as active as current problems would require. It is proposed to place more emphasis on cancer and human genetics and to strengthen such fields as basic embryology, which should be brought in more intimate contact with radiation research.

The philosophy of operation of the Division has been to combine programmatic studies of certain practical problems in toxicity of radiation with the maintenance of a broadly based group of biological specialists in all fields of life science, whose common interest in radiation is reinforced by the close collaboration of physical scientists and of the various service groups within the Laboratory. Thus, the practical scientist studying a specific problem may seek advice from persons with a clear understanding of the implications of the various areas of basic biology in relation to his particular problem, while the man studying a particular basic problem is kept aware of its possible practical implications in the general area of radiation toxicity.

The Division possesses a rather large collection of special equipment and facilities for biological research which are more or less peculiar to the radiation field. As will be discussed in the context of the special problems in biology, major physical equipment is so far of less importance here than in the physical and engineering sciences. On the other hand, the Division's equipment for producing fission neutrons has been of great importance to university scientists in the area and, for that matter, from coast to coast. Our unique facilities for biosynthesis have been duplicated both in this country and abroad and have been utilized by many investigators from university and government laboratories for the solution of problems which could not otherwise have been investigated.

An important function of the Division is the training of other scientists in radiobiological methods and theory. This has been carried out at all levels. Graduate students in biology from several universities have made use of the special equipment and, more importantly, staff talents of the Division. Individuals in key positions in foreign atomic energy projects have benefited by periods of research in our environment. A summer course in the methodology of radiobiological research has attracted a number of investigators, new in the field, who, hopefully, have saved valuable time in the development of techniques through such experience. It is felt that the staff, program, and facilities of the Division make it particularly appropriate that it become increasingly active as a training center in the theory and practice of radiobiology in its basic and practical aspects, and especially in the interplay between the two.

II. DETAILS OF LONG RANGE PROGRAMS

A. Staff Requirements.

Table 1

STAFF REQUIREMENTS

Research Area	Present				Estimated, Total		
	Continuing	Temporary	Student	Total	1962	1965	1969
Toxicity of External Radiations	9	-	-	9	11*	12	12
Toxicity of Radioelements	9	-	-	9	12*	14	14
Radiation Epidemiology	-	-	-	-	4*	6	6
Biosynthesis	4	1	-	5	Refer to Appendix on Plant Sciences		
Techniques and Instrumentation	6	-	-	6	7	8	8
Theoretical Biology	3	-	-	3	5	5	5
Biochemical Systems	9	4	-	13	14	14	14
Fine Structure	4	4	1	9	9	9	9
Cell Systems - Function and Regulation	10	3	-	13	16	16	16
Genetics	4	1	-	5	7	7	7
Cancer	4	-	-	4	6	7	7
Administration	4	-	-	4	6	6	6
Totals	66	13	1	80	97	104	104

*This combined figure should be expanded to include 16 more staff members between 1962 and 1965 if a facility to handle large numbers of mice is constructed for large-scale study of radiation epidemiology in animals.

Table 2

HOURLY EMPLOYEES

Totals			
Present	1962	1965	1969
92	120	130	130

B. Research Programs

1. Toxicity of External Radiations

Sources for studies of the biological effects of gammas and x-rays on the one hand and fission neutrons on the other are important facilities in the investigation of the toxicity of external radiations. Considerable attention is given to physical and biological factors in radiation sensitivity and to the physiological bases of radiation responses. Emphasis in the study of gamma ray effects has shifted somewhat during the past several years from the acute to the more delayed effects of irradiation and from high to low intensities and levels of exposure, approaching currently accepted permissible values. This trend continues, and will apply also to fast neutron toxicity when the Biology Reactor becomes available in FY 1960. This reactor will provide dose rates from about 0.001 to 10,000 rads/hour of fission neutrons. Specifically, the reactor will enable us to carry out, simultaneously, experiments at much higher and lower dose rates than have previously been possible. Provision has also been made for activation analysis and for a continuation of present exploratory studies in neutron capture therapy. Thermal and resonance neutron capture of special compounds containing certain nuclides offers a possibly fruitful approach to therapy of neoplasms.

The gamma ray program is providing extensive data in the low dose and low dose rate range. A similar actuarial statistical approach for fission neutrons will parallel that utilized in the studies of life shortening, carcinogenicity and degenerative diseases with gamma irradiation. Investigations in the acutely lethal dosage range indicate certain basic differences between neutron and gamma ray action. These findings will be amplified and the pathologic manifestations of chronic exposures to the different radiation qualities will be compared. Knowledge gained from application of various prophylactic and therapeutic agents will be helpful in elucidation of modes of action and may also point the way to more effective methods of treatment. Determination of the parameters of acute and chronic radiation toxicity for different causes of death and for different species may have important practical and theoretical consequences.

The physical basis of radiation effects is of considerable theoretical as well as practical importance. On the theoretical side the utilization of different types of radiation and different conditions of exposure enable us to explore many of the basic parameters of biological action. On the practical side, the formulation of permissible levels of exposure must take into account differences in efficiency of the various radiations. It is well known that the biological effectiveness of a given amount of energy varies with the spatial distribution of ionization and excitation and, in particular, with linear energy transfer along the path of an ionizing particle or photon. These relationships are complex and depend on many

physical and biological factors. Where single particles cause a considerabl
release of ionizing energy in a small space, as for example in the case of

Investigations in this area have included the effects of the more important radioelements on longevity and on the incidence of neoplastic and degenerative diseases. Studies are carried out on several species from mice, which can be used in large numbers for statistical analysis, to dogs, where effects are observed after a delay of many years. Related studies of radium toxicity in animals and man represent an important aspect of the program. Strontium-90 is another isotope of great interest. Present experiments cover a wide range of doses and have taken into account the probable differences in the effects of single and continued parenteral and dietary administration to young and adult animals and their progeny. These investigations, which are facilitated by development of techniques for in vivo dosimetry, should furnish answers to important questions about the influence of age and of the uniformity of strontium deposition on various parameters of toxicity.

Since many radioelements have an affinity for bone, chemical, radioautographic and electron microscopic studies of skeletal physiology and structure form an integral part of the program. Attention is given to the variables affecting skeletal development and to the relationship between retention patterns and areas of radiation damage in bone. Similar considerations apply to nonosseous tissues, and several lines of investigation are concerned with the way in which cancers and other pathologic changes are induced by radioelements.

The modification of poisoning by radioactive and nonradioactive metals is also an important objective. The approach, which is based on physicochemical principles involving chelation and ion exchange, has led to the development of agents which expedite removal of metals from the body and so are potentially useful in treatment of radioelement and metal poisoning. While such agents as have so far been developed are useful only in special circumstances, we are proceeding on the belief that the further development of physicochemical data may lead to more generally useful techniques and agents.

Many phases of the radioelement toxicity program, like that of the external radiation program, will require a sustained effort for a number of years and for the same reasons. Moreover, an expanded effort seems necessary in certain areas. The demographic study of environmental and population radium levels and bone tumor incidence in man is providing valuable information and early extension of this survey is contemplated to include larger geographical areas and other neoplasms.

An enlarged program on the toxicity of radioactive fission and activation products will be initiated in the near future with the construction of additional dog kennels which will enable us to add about 500 dogs to their experiments. Data on effects of isotopes in large animals are now limited to a very few radioelements. It is proposed

that acutely toxic levels for dogs will be established, and that on this basis a pattern of low-level exposures will be established. First emphasis will be placed on the more frequently encountered fission products (e.g. isotopes of Sr, Cs, Zr, Ce, Ru, etc.). Retention and tissue distribution will also be established using the most efficient means available. Since a main objective of the study is to estimate the hazards of exposure to fission mixtures, the study will include: (1) estimation of the effects of certain mixtures; (2) determination of differences between metabolically similar elements of long and short half-lives; (3) exploration of the physiological mechanisms underlying toxicity. Probable effects of exposure to the gamma ray spectra of typical fission mixtures will also be considered. Some dogs will be set aside for evaluation of therapeutic agents indicated to be promising by experiments with smaller animals.

It is proposed also to expand the program on smaller animals. Problems of future interest include the relationship of strontium-90 sensitivity to normal disease incidence of different mouse strains, the somatic and genetic effects of dietary administration of strontium-90 and cesium-137 for a number of generations, the comparative toxicity of discrete and mixed fission products, and the mechanism of action of drugs for removal of radioelements. Relationships between radiation dosage patterns and carcinogenicity and between tumor latency and age and species will also be examined more closely.

Prediction of the probability of damage from very small amounts of radioelements or external radiations requires quantitative understanding of dose-response relationships. Vexing questions of threshold and linearity are often difficult to resolve owing to "background noise." Estimates based on the spontaneous bone tumor incidence in a specific mouse strain (CF_1) indicate that hundreds of thousands of animals might be required for precise statistical evaluation of the probability of bone tumor production with ultra low levels of strontium-90, or of skin tumor production by external beta irradiation. A two- to three-fold increase in the present animal facilities and a large increase in staff would be absolutely minimal for a study which would increase sensitivity of present data by a dose factor of ten. The Division is entertaining the possibility of initiating a mass study to answer these questions if it is thought to be desirable by the Commission.

3. Radiation Epidemiology

These studies are included variously under Toxicity of Radioelements (radium and bone tumor survey) and Genetics (human population studies). Since this field requires considerable expansion in the future in order to relate human radiation problems to the various experimental areas, it is included in the separate areas of research. The present studies are being carried out by the equivalent of two staff members assigned to the Toxicity and Genetics Programs.

4. Biosynthesis

The biosynthesis program was initiated some years ago to provide uniformly labeled tracer forms of plant products that could not be readily synthesized. Growth chambers developed for this purpose have been available for collaborative studies and have also served as prototypes for similar applications elsewhere. Early work, confined largely to carbon-14, had the additional objective of determining toxic levels of the incorporated radioisotope. This program has since been expanded to include deuterium, tritium, and nitrogen-15 with some consideration of isotope and radiation effects on plant growth. Development of analytical procedures for separation of labeled products represents an essential part of the program. Selection of plant species and the constituents to be labeled is determined mainly by the requirements for tracer problems. Applications of the labeled products and other studies in plant physiology are not oriented to a single program and for the present may be discussed more appropriately in terms of the Division's general interests in basic biological and radiobiological phenomena.

It has been recognized for several years that the potentialities of the equipment evolved for the biosynthesis program have not been fully realized, particularly from the point of view of applications to the plant sciences. A proposal for furthering developments in this field is the subject of a separate detailed appendix on Plant Sciences.

5. Theoretical Biology

Research in the general field of theoretical biology has been concerned mainly with the formulation of mathematical theories of radiation injury and recovery, utilizing data derived from the various toxicity and basic programs. From our standpoint, interspecies predictions are particularly important. Statistical relationships between mortality and physiological injury states are considered in terms of model systems with the aid of analog electronic computers. Studies in this area will continue at about the present level, although it is visualized that as these methods gain usefulness, more computer time will be used.

6. Biochemical Systems

These investigations encompass a number of problems in general metabolism and in the intracellular localization of biochemical events. Questions of amino acid and protein turnover, lipid and cholesterol metabolism and relationships of sulfonium compounds to nucleic acid formation are investigated in several biological systems with tracer and other radiation techniques. Other efforts are concerned with the localization of cell organelles in normal and abnormal states and evaluation of their biochemical properties. Many of the results of these studies can be applied

eventually to studies of radiation effects and related problems of growth and repair. Radiation effects on naturally occurring enzyme inhibitors may represent an important in vivo mechanism in both plant and animal systems and considerable attention is being given to this possibility and to the role of enzymes generally. Basic studies of chelation and ion-exchange are directed toward determining the significance of trace metals in enzyme activity and toward practical problems of radioelement poisoning and drug action.

There have been no essentially new directions in radiation protection in the past ten years, although many of the possibilities of existing principles are being exploited. We feel that extension of basic studies in biochemistry (e.g. enzyme inhibition) and in radiochemical techniques applied to biological material (e.g. paramagnetic resonance for detection of free radicals) is indicated and may reveal new modes of approach. It is anticipated that both theoretical and experimental work on energy transfer will broaden within a few years.

The elucidation of various problems of radiotoxicity and protection may require the handling of large quantities of material by modern methods of separation. It is anticipated that in the foreseeable future several groups may have occasion to utilize large-scale vapor phase chromatographic and counter-current extraction equipment.

7. Fine Structure and Related Cell Function

This category of investigations is concerned with general problems of relating ultrastructure to function. Studies in this area may also help to bridge the gap between early physical and chemical radiation events and their biological expression. Electron microscopic analyses are being performed on a variety of cells and tissues with consideration of replicating and differentiating mechanisms, the role of nuclear and extranuclear systems in cell functions and the radiation sensitivity of various organelles. The study of bone structure provides background data for interpretation of the effects of bone-seeking radioelements. Considerable emphasis is placed on the fine structure and formation of connective tissue, which is intimately related to many problems of growth, repair, and aging. Future efforts in this area will depend upon developments here and elsewhere in the methods for electron microscopic observation.

8. Cell Systems - Function and Regulation

This category embraces all investigations with primary orientation to physiology. It includes studies on a variety of problems and biological systems. A principal objective is to provide background information for interpretation of radiation effects, which is a reflection of the transition

from the more nearly descriptive to the analytic phase of radiation physiology. Thus, attention is given to fundamental questions of cell division and differentiation, blood cell and sperm formation, immunity mechanisms, growth regulation and maintenance of the physiological steady state. Endogenous rhythms in plants and animals and problems of photoperiodism, photoreactiviation and photosensitization are also investigated. The early physicochemical events of irradiation are studied in simple biological systems. Other investigations are concerned more generally with evaluation of physical and biological factors in radiation sensitivity and with the development of protective agents. Although emphasis may shift from time to time, this sort of interaction of radiation and non-radiation problems will continue for a number of years.

There has been a tendency to think of late effects of irradiation as an acceleration of senescence. This inference is based mainly on mortality statistics, which point to a systematic displacement by irradiation of the function relating probability of mortality to age. Although there are qualitative similarities in certain pathologic processes in irradiated and aged animals, there are also differences, and the relationship between the two remains a moot point. The time dependency of basic biochemical and physiological events in irradiated and aging animals has received only cursory attention and it may be confidently predicted that this will represent a lively area of investigation in the future. Long-term studies of radiation and age effects on growth potential and regenerative capacity of several physiologic systems have already been initiated and systematic investigation of other parameters will eventually be included.

It is becoming increasingly apparent that more attention must be given to problems in embryology, and to phenomena of cell and tissue differentiation generally. The decision to differentiate is a crucial event in the life of a cell, but is poorly understood. This is an exquisitely radiosensitive stage and one which is intimately related to induction of cancer. Application of immuno- and cytochemical techniques in conjunction with electron and x-ray microscopy may represent a fruitful approach to this problem. Another area deserving of sophisticated attention revolves around the possible neurophysiologic components of radiation actions particularly in the low dose range. Expansion of efforts in these fields will require some additions to the scientific staff.

Studies of radiation effects on innate and acquired immunologic mechanisms will be carried on as at present with, however, increased emphasis on cellular and biochemical localization. Phenomena of acquired tolerance will be utilized to develop in vivo procedures for production of tumor specific antibodies, and immunologic techniques will also be applied to the related areas mentioned above.

9. Genetics

These studies encompass problems in physiological and population genetics. The genetic bases for latent radiation effects at the cellular level are investigated mainly in bacteria and protozoa. Other experiments are concerned more generally with analysis of mutations induced in plants and animals by radiation and other agents. There is some interplay in this area with the various toxicity programs. There are two important studies in human genetics. An extensive study of consanguinity is oriented to determining the number of mutant genes present in a normal population, which is a necessary datum to predict radiation effects on population; also, the history of descendants of irradiated women is being compiled and analyzed.

It is proposed that other basic studies will be initiated where possible: these would include extension of population studies, a search for biochemical mutants in special human populations, and an examination of methods of measurement of somatic variation in cells, which might be applied to studies of various modes of irradiation.

10. Cancer Research

Research in this area is intimately related to many problems in radiobiology. Important observations on cancer production are made in the various toxicity programs. These are complemented by several lines of investigation, which are directed more specifically to the fundamental differences between normal and neoplastic states. Studies are made of carcinogenesis by radiation and other agents, growth characteristics of tumors, and the physiologic and immunologic relationships between tumor and host. Applications of radiations and other agents to the modification of tumor growth represent an important part of the research. It is anticipated that increasing attention will be given to predisposing factors in carcinogenesis. The direction of future research will be determined, in large part, by developments in the several programs of the Division.

11. Techniques and Instrumentation

The development of radiological and biological techniques is essential to the purpose of both the programmatic and non-programmatic research. There is a broad interest which extends from radiation detection and measuring instruments to problems of animal care. The biological spectrograph is providing useful information and further modifications will increase its utility for precise action spectrum determinations. Other problems of current interest include measurements of neutron-induced radioactivity in vivo, tritiation of organic compounds by self-irradiation, instrumentation for counting and sizing of cells and particles, and improvement of techniques for electron microscopy. Many of these efforts

will continue into the foreseeable future. Moreover, the needs for other developments and techniques, such as quantitative radioautography and the paramagnetic resonance method, are apparent in several of the research programs.

Certain other developments in biological and biophysical instrumentation are also under serious consideration for the future, in view of the fact that the Laboratory is unusually well suited to attempt them. They would include: a micromanipulator using modern remote control methods and allowing feedback to the operator; a microtome for electron microscopy capable of cutting successive sections at 90° to each other; improvements on optical centrifugal methods; and, (in collaboration with the Chemical Engineering Division) methods of mass culture of organisms in isotopic media. All of these are designed to resolve current problems in the radiobiological research program, and will also be utilized in the general biological programs of other institutions.

Special attention is given to the diseases and care of laboratory animals. Pathogen-free mice and rats are being maintained and bred, and it may be possible to supply large numbers of mice for experimental use within six months to a year. The increasing emphasis on long-term effects of irradiation and problems of aging is straining the capacity of the small-animal facility with consequent difficulties in animal care. Enlargement of the animal quarters is urgently needed in order to implement the investigations in this critical area. The limited study of parameters of animal health under different environmental conditions should be extended in the future as space and time permit. There is some question about optimal conditions and it is even possible that such research will establish that facilities less expensive than those currently considered necessary may be highly satisfactory.

III. FACILITIES

A. General Laboratory and Office Space

In order to carry out the contemplated program a 70 ft. long, three story addition to the west end of the west front wing of the existing building will be required. This will provide sufficient laboratory and office space for the proposed expansion.

B. Technical Facilities

Adequate facilities for animal maintenance are essential to a large fraction of the Division's program and, in fact, form its major basic expense. The additional dog kennels now being designed will permit the expansion of the radiation toxicity program as described. This facility will consist of four kennel buildings with outside runs, each building having a capacity of 66 dogs or a total capacity of 264 animals.

Enlargement of the small animal quarters has been requested in order to implement studies now underway. The existing animal quarters consisting of 31 animal rooms of 6360 sq. ft. of usable space were designed to accommodate 68,000 mice, or proportionate numbers of other kinds of laboratory animals. At the time of design they were thought adequate for the then existing scientific program. The expansions are mainly reflections of the need for statistical study of large populations in order to detect minimal effects of toxic agents. Also, certain additional experiments in neutron toxicity will have to be served from these facilities. Furthermore, it has become obvious that a breeding program must be instituted in order to stabilize the quality of animals being introduced into long term problems, as well as to prevent the importation of serious infections that can endanger these long term experiments. The proposed addition to the animal quarters will consist of 14 additional animal rooms beneath the present animal quarters at the service floor level. This will provide a compact geographic organization. The environments of the rooms will be controlled according to present standards. Some of the rooms will be designed to allow easier control of infectious diseases, and several will be provided with the special exhaust required for rooms containing radioactivity. Additional space will be needed if the Division undertakes a mass study of radiation epidemiology in small animals as described earlier.

Within two to three years the experimental programs will require an additional gamma room. The present gamma rooms will be utilized to capacity during the next several years to complete experiments now in progress and will be required in the future to answer questions resulting from these investigations. No other laboratory is conducting long term studies at extremely low levels of irradiation and it is imperative that such studies should be undertaken. This will be possible with the additional gamma room facility. Low radiation background rooms for animal maintenance may be included among the proposed items of future construc tion in order to evaluate the contribution of natural background to physiologic processes.