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Biology - 5-year Plan

PLANNED PROGRAM OF THE BIOLOGY DIVISION OAK RIDGE NATIONAL LABORATORY FY 1966-1970

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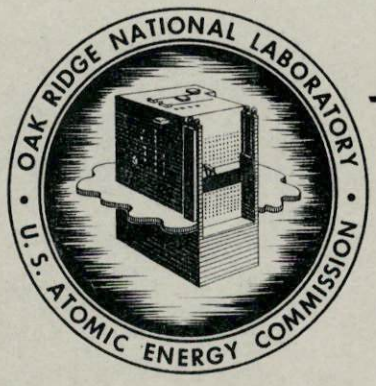
May 25, 1965



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SECTION I

PREFACE

PLANNED PROGRAM OF THE

BIOLOGY DIVISION

OAK RIDGE NATIONAL LABORATORY

FY 1966-1970

Preface

This report has been formulated to serve as a broad general outline for the development of the research programs of the Biology Division, ORNL, for the next five-eight years. The material herein was first developed by the individual senior investigators in the Division and then thoroughly evaluated by the management of the Division as to scientific content, its pertinence to the general broad long-term aims of the Division's research programs and, finally, as to the realism of achieving the goals in the five-eight year period.

A brief general overall statement of the research programs proposed for development and expansion and the estimated research and facilities cost may be found in Section II.

The detailed program material submitted by each group was summarized by individual programs and may be found in Section III.

Another discussion concerning the broad aims of programs to be supported by the NIH are given in Section IV. While not all of this work will be done in the Biology Division, it is submitted as a part of this proposal because of the close relationship of the programs to the needs of Biology. These programs will be coordinated by the Biology Division until such time as they are fully operational.

The facility needs outlined in Section V are the result of a thorough study conducted over several months and represent what we consider a realistic estimate of needs if the proposed program is to be achieved.

Sections VI and VII outline in very brief form the strengths of the Division upon which the proposed program can be built.

Special attention should be called to the programs proposed for support by the NIH. We feel, because of the unique research programs built up to obtain an understanding of the mechanisms of radiation damage and its repair, that the Biology Division is in an ideal position to attack a number of problems of major public health interest without distorting the aims of programs supported by the AEC. In fact, the programs we have proposed for AEC and NIH actually supplement and complement each other and are built upon the current strengths of the Division. Public health problems such as cancer, aging, developmental anomalies resulting from environmental contaminants (radiation, pesticides, pharmaceuticals, etc.) and many virus-caused diseases are all problems which are similar to those caused by radiation or may be deeply involved in the responses of animals and man to radiation. Certainly the techniques needed to study these public health problems are almost identical to those used in studies of radiation effects.

The programs proposed in the health resources research area deserve special mention because of the truly unique opportunity existing at Oak Ridge for the interaction of engineers, physicists, chemists, and other physical scientists with biomedical scientists. Here these physical

scientists are actually eager to work with biologists on the problem of the biologist--thus, the zonal liquid centrifuge has been developed from the gas centrifuge technology by the K-25 engineers in consort with the cell physiologists--very specific kinds of nucleic acids have been successfully separated by chemical technologists working in close association with biochemists--our animal physiologists and virologists are currently working in close cooperation with Y-12 and K-25 engineers to develop better facilities for containing virus-infected materials and animals. We feel these successes have come because the engineers and physical scientists have worked closely and eagerly at every stage of these developments with biologists--a situation required for the development of useful biological tools.

The strong postdoctoral program within the Division (50 per year), the presence of graduate students (6-10 per year), and our many interactions with biologists at Southern Universities give the Biology Division the close and much-needed association with the academic community. Further details in this regard are outlined in Section VI. These programs which provide about 30% of the scientific manpower in the Division will be strengthened along with the research program. Very recent discussions with the NIH, AEC and The University of Tennessee present the strong likelihood that a new Graduate College of Biomedical Sciences as a branch of The University of Tennessee will be created in Oak Ridge immediately adjacent to the Biology Division. This development could create in a relatively short period a major educational "center of excellence" in a region which relatively speaking has been scientifically underdeveloped.

Interactions with the Health Physics Division of ORNL, the Medical Division of the Oak Ridge Institute of Nuclear Studies, and The University of Tennessee-AEC Agricultural Research Laboratory are being strengthened and will grow with time. All of these interactions place the ORNL Biology Division in a very strong position to be the focus of biomedical research and education in the whole southeastern part of the nation.

In summary, we feel that the programs outlined in the following pages can make outstanding contributions to the further development of basic science in this country as well as to bring science to bear on many of the important problems facing man and, by so doing, to improve man's health and welfare.

Alexander Hollaender
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Stanley F. Carson
Associate Director

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May 25, 1965

Section II

Highlights of Research Plan

and Summary Budgets

INTRODUCTION

In the next few pages are outlined some of the major problems in radiation and environmental biology which we propose to attack during the next five-eight years with all of the techniques and approaches, as well as much of philosophy which has characterized our research programs over the past two decades.

It was visualized in 1946 when the Biology Division was formed that if we combined several large projects on "mission-oriented" research of vital importance to the atomic energy program with the wide backing of basic biological studies, an interesting and very useful program could be developed. This broad approach, combining an attempt to understand fundamental phenomena with an effort to obtain information of practical significance, has been very successful--an approach which has been rather unique to the Biology Division of the Oak Ridge National Laboratory.

Where do we visualize this laboratory will be in five years? Interest in biology is growing, and all over the world young people--biologists, physicists, and chemists--are turning more and more toward experimental biology. We would like to see this laboratory developed as a prominent center for biological research.

The central core of our program will be addressed to understanding some of the major biomedical problems facing society today: hazards of radiation, of certain infectious particles, of noxious chemicals, of drugs and of other materials which are constantly being added to man's environment. These materials are almost completely unevaluated insofar as they may, under chronic exposure conditions, cause cancer, result in physical deformities and mental deficiencies, affect man's hereditary apparatus or be detrimental in other ways. Researchers conducting this central core of mission-oriented work will be surrounded and supported by researchers in the fields of biochemistry, biophysics, genetics, physiology, morphology, immunology, etc., who will attempt to understand at the most fundamental level the biochemical or biophysical basis for the anomalies.

Major expansions are proposed in the area of somatic and genetic effects caused by radiation, viruses and chemicals acting singly and combined. These large mission-oriented programs can only be kept progressive, productive, and vigorous by a simultaneous expansion of the programs in biochemistry, biophysics, genetics, cytology, immunology and mathematics

which surround and support them. An attempt will be made in this section to indicate the pertinence of these latter areas to the highly mission-oriented areas. Additional programs in which there are strong interactions between biologists and physical scientists and engineers--the area of technology--are also proposed for considerable growth. No special attempt, however, will be made in this section to relate the specific work to a particular source of support--rather the attempt will be made to present a coherent picture of the direction which the Biology Division should take during the next 5-8 years.

It will become obvious during these presentations that many of the programs outlined are equally important to the National Institutes of Health and to the Atomic Energy Commission. Thus the principal rationale behind the initial interest of the NIH in establishing programs at Oak Ridge stems from the success of this laboratory in bringing into focus and strongly emphasizing cooperation between scientists in the large practical programs and those in the basic science groups. As a matter of fact, this very strong and experienced core of basic biology is the heart of this unique type of organization.

Genetic Studies

The first major large-scale study was the investigation of the effect of ionizing radiation on gene mutations in mice as being typical for studies of effects of radiation on man. The outstanding contributions to the National Academy of Sciences and to the United Nations Scientific Committee on Atomic Radiation made by this program depended in large measure on developing a sophisticated and highly accurate test system for assessing radiation damage to the genetic machinery. This test system in the mouse involves seven genes with widely varying sensitivities to X and gamma radiation. One of the most important results obtained with this test system was the unexpected discovery that dose rate, as well as total dose, is an important factor affecting the number of mutations induced. Further tests suggest that a repair mechanism is operative at the lower dose rates.

This mouse test method has also been used to show that the biological effectiveness of fission neutrons is from 5-20 times greater in mutagenesis than gamma or X rays. Their effect is independent of dose rate in the male. More extensive experiments are planned to check a preliminary finding that neutron dose rate does, however, have some effect in female mice. A most important recent finding is that the mutation rate in neutron-irradiated female mice drops to near zero a few weeks after exposure even to high-dose-rate radiation. It is obviously vitally important to find out whether the same effect occurs with X and gamma irradiation.

This same technique which has proven useful in determining the mutagenic effects of radiation also appears applicable to studying the mutagenic effects of chemicals such as triethylenemelamine, which at certain concentrations was found in our laboratories to be as mutagenic as 300 r of X-irradiation. Although scientists are still undecided about whether a

mutational event is involved in radiation-induced somatic anomalies, viral or chemically induced cancer, or other malformations, it is in any case extremely important to use this very accurate method to evaluate the mutagenic effects of various compounds including those which are carcinogenic in a mammal. While it seems meaningful to explore the effects of these matters in microorganisms and insects, the fact that a mammal must absorb the chemicals or viruses through the gut, skin, lungs or other entry portal suggests that their effectiveness as mutagens may not be the same in mammals as in microorganisms. We are in an extremely strong position, almost unique in the world, to attack the important questions facing the nation now of whether the air and water pollutants and various drugs are indeed mutagenic.

Additionally, out of this program have come a series of gene mutations, chromosome aberrations and physiological mutants which may prove to be as important to the furtherance of science as is the mutation-rate work itself. These mutants are now beginning to be used by physiologists, biochemists, and cell physiologists in this and other laboratories to better understand the mechanisms of viral infection and related matters.

Companion to this major program in mammalian genetics are programs in cytology, cytogenetics, cytochemistry, biochemical genetics, genetics of the fruit fly, bacteriophages and various microorganisms, etc. These programs are aimed at understanding the physical structure of the chromosome, the mechanisms of mutagenesis, the mechanisms of repair of radiation damage, the mechanisms of duplication of the genetic material and how the gene behaves during development and differentiation of the organism. Such studies are absolutely basic to understanding the nature of the mutagenic event whether caused by radiation, chemicals, or viruses and must expand alongside the more mission-oriented research if a vigorous modern program is to be maintained.

These programs have made a number of important contributions to fundamental genetic and cytological problems. Among others may be cited work on repair of chromosomal damage. For instance, the work showing that the reunion of chromosome breaks which were caused by radiation is a metabolic process was first discovered in this Division. Other work here has shown that X-ray damage which would otherwise lead to gene mutation can also undergo repair.

It is most important to recognize that these basic findings in nonmammalian systems have given definite clues to help explain the findings with mice that the same total dose given at low rates is much less damaging than when it is given at high dose rates, i.e., apparently the radiation damage incurred at low dose rates can be repaired.

Evidence for repair of radiation damage at the molecular level has been obtained by our biophysics program in studies on bacteria. It has been found that one mode of killing by ultraviolet irradiation is the result of the formation of thymine dimers in the nucleic acids of chromosomes. Recently, a specific enzyme has been found which seems to repair this lesion by

removing the dimer, thus permitting another enzyme to reinsert the correct information in the chromosome so that the DNA behaves normally again. It is very important to determine whether there is a similar enzyme for repairing mutational events caused by X or gamma radiation (i.e., ionizing radiation) either in bacteria or in mammals and, if so, how it behaves.

Somatic Effects Studies

A second major program which has evolved here in the past two decades is concerned with the somatic effects of radiation, i.e., answering the questions of what are the ill effects of acute or low-level exposure of the individual to ionizing radiation of various kinds, intensities, and energies. In many cases the end result is cancer of one kind or another or life shortening, as well as numerous other malfunctions. The acute effects of radiation are relatively well defined; however, the low-level long-term effects of radiation are just beginning to be known. These latter studies should develop during the next five years to the point where the nature of leukemia induction and its relation to radiation become well established. It appears already that a virus is involved in the pathogenesis of this disease and that, moreover, the neoplasm can be induced by irradiation as readily in the germ-free mouse as in conventionally reared animals. This suggests that the virus is transmitted across the placenta from mother to young and "activated" in some as yet unknown manner by exposure to radiation although such a concept remains to be established.

It has been necessary in connection with these experiments to develop extensive barrier-type animal facilities in order that these and other possible causes of leukemia can be investigated, i.e., to evaluate the relative roles of virus and of radiation in the induction of the disease. Since these facilities are tremendously expensive and inflexible when built of steel and masonry, we have turned to engineers in Y-12 to develop more flexible and less expensive facilities. The details of this operation will be brought out in the section on bioengineering.

The other pronounced somatic effect of radiation is life shortening, but we have not yet obtained any real clues as to what is responsible for this phenomenon except that the animals whose lives are shortened become more susceptible to disease early in life. A clue as to how this may happen has come from our recent experiments in immunology. These results in mice demonstrate that the ability of the immune system to respond to insult reaches a peak at about 1/4 the mean life-span (16-20 years in man) and decreases thereafter. The high death rate among older individuals may be a result of autoimmune phenomena, and infection coupled with the marked decrease of the immune potential. It may also be possible that the reason man develops cancer at about age 45 and beyond is that his immune system is no longer maximally responsive.

If loss of immune potential can be shown to be responsible for the high death rate among older individuals, it may be possible to extend the mean life-span of these people by infusing immunologically competent stem cells

from young individuals (immunologic rejuvenation). Because these stem cells can be frozen and stored indefinitely, the setting up of stem cell "banks" might be feasible. The opportunities afforded if these results can be confirmed are so important that they will receive one of the top priorities for study during the next few years.

The studies on the modification of radiation injury by the use of chemical protectants have essentially reached a plateau in regard to productivity, and this particular program will be maintained at a very low level unless promising leads become evident. It is now apparent that future studies on recovery and protection can only be successful if they take into account the stages in the mammal in which immunity is established, i.e., in the early neonatal stages when one can study the development of immunity in detail. This research will be aimed at developing practical methods for replacement of injured tissues through transplantation. In addition, the cellular repair of sublethal injury will be investigated further with a view toward development of means for promoting recovery from radiation damage.

The studies on the mechanism of loss of immunity during aging mentioned earlier, coupled with these neonatal studies, provide two approaches in one laboratory from the opposite ends of the animal's life span, which should prove to be of fundamental interest and of great practical significance.

Virology

There is an urgent need to enter the field of basic virology. We have several small groups working on bacteriophage and transforming principles as well as on the genetics of bacteria, fungi, and other microorganisms. These, together with the studies in biophysics and biochemistry discussed below, will lead to a firmer basic understanding of the action of viruses. The X-ray diffraction studies being initiated on proteins and other macromolecules will become quite important in this connection. The buildup of a broadly based mammalian virology program will be extremely important for the future development of this laboratory and for answering many practical as well as basic questions both for the radiation diseases, and for cancers which have virus interactions.

It has been found that a certain virus, injected into rabbits, can "transduce" certain of its own genetic information into the mammalian genome. If this finding turns out to be generally true, there is an important possibility of using this means to cure certain inborn metabolic diseases in man. We need to know much more about the mechanisms involved, and some very interesting clues may well come from studies already under way in this laboratory on virus-chromosome interactions. These studies involve infection of fly larvae with a virus-like material or with a protozoan which causes the chromosomes of the fly to be enlarged in volume twenty to thirty times their normal size. Along with these changes in size are also changes in banding patterns along the chromosome. This tool which permits an experimental control of increase in chromosome size may

be a means of getting at the nature of virus infection and, most importantly, of the way in which the virus genome gets incorporated into the host genome.

In addition to these studies on virus-chromosome interaction, research on radiation-virus interaction in leukemia, the virus transduction studies, and a basic program on the biochemistry of viruses and bacteriophages has been under way for some years in this Division. Our own broadly based biochemical and biophysical studies on viruses and bacteriophage will be further enlarged by a planned cooperative program with the NIH. All of these virus programs can take advantage of the recent developments in our Centrifuge Program in which ultracentrifuges have been developed that are capable of separating large quantities of virus particles in virtually pure state. For example, new techniques for the preparation of virus suspensions and virus subunits have been developed and evaluated in close collaboration with the National Institute of Allergy and Infectious Diseases program for vaccine development and with three pharmaceutical firms. Experimental vaccines for human use made possible by Oak Ridge centrifuges have now reached the clinical trial stage, demonstrating that new biophysical theories and concepts can here be taken the full distance toward the alleviation of human ills. The resolution of zonal centrifuges has now reached a point such that a method is now available for searching tumor tissues for viruses that far surpasses any other known method; it is certainly superior to the use of an electron microscope without first being able to concentrate and resolve the virus(es). The development of a new biophysical tool for the physical separation of the parts of cells contributes to the research capabilities of biophysicists generally.

The cooperation of these various and experienced basic science groups, together with the technological developments of the Centrifuge Program and of the Chemical Technology Division, particularly with the added support of the NIH, could make this one of the strongest all-round virology programs in the country, and a program which would strongly support the missions of both the AEC and the NIH.

Biophysics and Biochemistry

The present biophysics programs are directed toward understanding the details of the molecular changes that are produced by the action of radiations on cells and cellular components, and to explain, at the molecular level, radio-biological phenomena such as inactivation of cells, repair mechanisms of cells, chromosome breaks and free radical production, as well as gain new and important information about the structure and function of intracellular compounds such as DNA and RNA. We expect to initiate new studies of problems in biophysics concerning the central nervous system and coding problems, X-ray diffraction analysis of macromolecules, intramolecular forces, and protein-DNA interactions.

The intense developments in this laboratory on the biochemistry of nucleic acids and proteins which have evolved in the last sixteen years have come of age. The Division has an excellent group of established investigators studying the structure of the nucleic acids, how they are produced, how their structure relates to the structure and action of the gene, how they direct the synthesis of proteins, and related problems.

A number of widely recognized landmarks in modern biochemistry have come from the research conducted in these laboratories. The application of ion exchange chromatography for the separation and purification of nucleic acids was pioneered here in 1949. These new methods led directly to the discovery a few years later in this Division of the precise linkages involved in the primary structure of the RNA molecule. Finally in 1956, again in this laboratory, "messenger RNA" was discovered; this large molecule plays an indispensible role in conveying the "information" from the genetic material (the DNA) to the protein synthesizing machinery of the cell.

Such a clear understanding of detailed mechanisms underlies the solution of many practical problems in cancer and radiation biology. In the area of "molecular biology" an entirely new and very valuable technique was opened up here, namely, enzymatic means of synthesizing many types of polydeoxynucleotides; a large variety of these new compounds, which are important for understanding the mechanisms of enzymatic DNA synthesis, need to be made and characterized by chemical and physical methods, and the biological properties of these new polymers need to be tested in living systems.

The Enzymology Group expects to expand its already successful efforts in connection with the Chemical Technology Division of ORNL in the isolation, purification, and study of the properties of macromolecules of biological importance. We expect to split out of the "enzymology group" a new research group on "biochemical regulation"; this group of investigators has already been very successful in their studies of the mechanisms of hormonal control of protein synthesis, and they would like to expand their efforts into two new fields: (1) a program investigating the role of adrenal hormone in chemical induction of hepatoma, and (2) mechanisms controlling enzyme levels during development.

Developmental Biology

The fundamental biophysical and biochemical approaches used above lead us directly into the fundamental aspects of developmental biology. It has become obvious on the basis of work in this and other laboratories that the biochemical and biophysical understanding of some stages of embryonic development can now be tackled with our present tools.

The long-term aim of the research conducted in this program is to understand the mechanisms which control growth and differentiation, and how these mechanisms are modified by radiation, chemicals, viruses, hormones,

and other environmental factors to lead to congenital malformations, the cancerous state, and so on. An understanding of how radiation and chemicals cause these modifications should provide clues concerning possible recovery mechanisms and how these might be furthered by the proper therapy. The model system in the present program is lens development in the amphibian eye. Immunochemical, cytochemical, chromatographic and electron microscope techniques are being used to follow the time course of transformation of various constituents of cells of the pigmented iris into the lens, and especially how radiation modifies these processes.

This already established program in growth and differentiation is leading us into a broader attack within the field of "developmental biology" and has elicited the interest of several of the National Institutes of Health, in particular the new Institute of Child Health and Human Development. The enlarged program will not only explore the physiological, biochemical, genetic, and biophysical aspects of development, but also the mechanism of gene control of differentiation.

Carcinogenesis

Cooperative studies have been initiated with the National Cancer Institute in regard to carcinogenesis. These experiments concern the effects of radiation, chemicals, and virus infection, alone or in combination, in regard to induction of lung tumors and other forms of cancer. A much broader and basic attack on carcinogenesis will be developed as soon as the new laboratories in Bldg. 9211 are completed within the next year. It should be pointed out that the fundamental studies at this laboratory, the know-how which has been developed here and the staff which has been assembled, could serve very well as a basis for much broader cooperative studies with the National Institutes of Health in carcinogenesis, virology, basic pharmacology (i.e., somatic and genetic action of chemicals on cells and intact animals), and developmental biology. Such discussions have been initiated and the strengthening of the fundamental work as well as the mission-oriented work under AEC sponsorship would encourage such cooperation.

Bioinstrumentation and Biotechnology

In addition to the constant interplay of disciplines and groups within the Biology Division, we enjoy equally important and unique collaboration within the large atomic energy complex here in Oak Ridge. We have been able to draw upon the vast chemical, instrumentation, engineering, and design resources which have been built here at tremendous expense over the past twenty years. We have had several notable successes from this type of collaboration, for example, in the development of the highly successful centrifuge technology, the separation of transfer RNA by cooperation with the Chemical Technology Division, and the fabrication and design of the experimental device for the Gemini-3 shot which was done in the Y-12 Plant and which accomplished its scientific mission with honors.

Nevertheless, we find that we really have only begun to scratch the surface of the bioengineering and biotechnology problems in which the highly skilled technical divisions in Oak Ridge can give us support. A case in point is the problem which was mentioned earlier in connection with the special barrier-type animal facilities which need to be designed and constructed for the viral leukemia research. In the Y-12 Plant there exists over twenty years of unique design and fabrication experience in "containment problems," and we are just entering into a program with the Technical Division to develop special containment facilities for animal experiments which should be considerably cheaper and much more flexible than those heretofore available. If the approach we are taking proves feasible, and the many years of containment design and engineering at Y-12 indicate that it should be, it is expected that the whole art of animal facility construction as known at present will be drastically revised. It is pertinent to this point that the NIH has similar problems, but on a much larger scale, and beginning in FY 1966 will support part of this "animal containment technology" development program here.

With some further successes, and with the rising interest of the National Institutes of Health in the biotechnology and bioinstrumentation programs, it is of utmost importance that these highly skilled technical groups in Oak Ridge be kept intact. The engineering, design, instrument, electronic, technical and shop support in the Oak Ridge plants is unique and probably as extensive as in any very advanced research and development center in the world. Collaboration between the Biology Division and the several Technical Divisions in Oak Ridge has already led to the solution of some very difficult biotechnical problems. We expect that the combined efforts of these talents will become increasingly important for the solution of even more difficult physical, chemical, instrumentation, and technological problems now facing any modern experimental biomedical effort.

Education and Training

It should be pointed out that the Biology Division has been very active in training activities at the post- and predoctoral levels as well as in trying to get students from small colleges in the South interested in graduate research work. Seven hundred people have been trained in our laboratories since 1949; a substantial number of these have stayed here from one to two years. This laboratory should continue to broaden its educational interests, and, as a matter of fact, discussions have been held with officials of the NIH, AEC, ORNL, and the University of Tennessee in regard to setting up a Graduate School of Biomedical Sciences adjacent to the Biology Division in Oak Ridge as a branch of the University of Tennessee.

Conclusions

The results of the last eighteen years' experience since this laboratory was started have demonstrated that the several large-scale mission-oriented projects organized here in connection with radiation effects prospered

exceedingly well, and in large measure because of the closely interwoven and strong support from the many basic fields discussed above. As a matter of fact, this successful interplay of practical problems supported by a very broad program in basic science has elicited the strong interest of other government agencies, in particular the NIH, to add within our structure work on some additional major biomedical problems facing this country today. It appears now to be well established that the successful elucidation of the large-scale and long-term difficult biological problems, which have been discussed briefly in this section, depends upon the very strong and tightly interwoven basic programs; hence, these latter as well need to be continually strengthened and kept vital for the success of the overall program.

In Section V it is demonstrated that the laboratory facilities available even for the present programs are already significantly inadequate. The continued success of both the AEC and the Interagency Programs depends upon a sizable and rapid updating and expansion of the physical laboratory facilities of the Biology Division.

PLANNED BUDGET FOR AEC-NIH-ORNL BIOMEDICAL PROGRAMS

($ in Thousands)

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Total in Biology Division	12,145	14,370	18,105	22,825	28,430
AEC Support	7,560	9,200**	11,500	14,700	18,500
NIH Support	4,585*	5,170	6,605	8,125	9,930
Biomedical Research	3,815	4,270	5,480	6,850	8,505
Technological Support	770	900	1,125	1,275	1,425
Total in Other Programs	2,045*	3,045	3,885	4,275	4,780
NIH Support					
K-25	1,095	1,180	1,365	1,285	1,300
X-10	470	865	1,185	1,465	1,680
Y-12	480	1,000	1,335	1,525	1,800
Grand Total - Oak Ridge	14,190	17,415	22,035	27,100	33,210

* These items are from the "A" budget of NIH, shown along with "B" budget in Table on Page 2.13.
**The FY 1967 "189 budget submission" shows this total as 9,455, as it contains allowance for "B" budget items.

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TOTAL AEC BUDGET BY ACTIVITY

($ in thousands)

		FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
06 01	Somatic Effects of Radiation	1,880	2,380	3,135	4,030	5,190
06 02	Radiation Genetics	2,655	3,155	3,875	4,750	5,730
06 03	Combating Detrimental Effects of Radiation	975	1,115	1,400	1,955	2,510
06 04	Molecular and Cellular Level Studies	2,050	2,550	3,090	3,965	5,070
	Totals	7,560	9,200*	11,500	14,700	18,500

*The FY 1967 "189 budget submission" shows this total as 9,455, as it contains allowance for "B" budget items.

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SUMMARY BUDGET FOR NIH PROGRAMS

	FY 1966		FY 1967		FY 1968		FY 1969		FY 1970	
	A	B	A	B	A	B	A	B	A	B
Co-Carcinogenesis*	2,995	2,995	3,000	3,000	3,590	3,590	3,970	3,970	4,355	4,355
Virology*	200	200	300	500	500	900	730	1,400	1,400	2,000
Developmental Biology*	350	600	600	1,200	900	1,700	1,500	2,000	1,900	2,300
Mathematical Biology* and Physical-Chemical Biology	270	440	370	640	490	800	650	1,050	850	1,350
Sub Total	3,815	4,235	4,270	5,340	5,480	6,990	6,850	8,420	8,505	10,005
TECHNOLOGY										
Containment**	850	1,700	1,450	3,250	1,950	3,800	2,050	3,600	2,300	3,500
Centrifuge Development**	1,350	1,600	1,375	1,750	1,500	1,850	1,550	1,925	1,625	1,990
Biotechnology-** Bioengineering	615	980	1,120	1,570	1,550	2,260	1,950	2,490	2,280	2,900
Sub Total	2,815	4,280	3,945	6,570	5,000	7,910	5,550	8,015	6,205	8,390
In Biology	770	975	900	1,275	1,125	1,575	1,275	1,650	1,425	1,725
Elsewhere	2,045	3,305	3,045	5,295	3,875	6,335	4,275	6,365	4,780	6,665
Grand Total	6,630	8,515	8,215	11,910	10,480	14,900	12,400	16,435	14,710	18,395

A - This is considered a reasonable minimum level.
B - An optimal level of operation.
* Totally in the Biology Division.
**Biology Division will provide guidance and consultation and do the biological testing and experimentation required for development.

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TOTAL GPP PLUS LINE ITEM REQUIREMENTS

($ in thousands)

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	Grand Total
I. GPP						
A. Non-Laboratory Modifications (From Section V, Table 3, Part A)	348	448	535	650	425	2,406
B. Laboratory Construction (From Section V, Table 2, Part B)	930	1,170	665*	1,200*	1,500*	5,465
Subtotal	1,278	1,618	1,200	1,850	1,925	7,871
II. Line Item Construction (From Section V, Table 2, Part A)	**	7,600	9,400	8,500	6,000	31,500
Total	1,278	9,218	10,600	10,350	7,925	39,371

*These GPP laboratory construction items refer to rough engineering estimates to overhaul those laboratories in Bldg. 9207 that will be 20-25 years old, and to convert the remaining non-laboratory space in that building to laboratories. If the Commission prefers, for FY 1968, 1969, and 1970 conceptual design engineering can be accomplished to bind this into a line item request.

**The $1,860,000 authorized for FY 1966 is not included in this table.

June 8, 1965

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Section III

Details of AEC Programs and Budget

TOTAL AEC BUDGET BY ACTIVITY

($ in thousands)

		FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
06 01	Somatic Effects of Radiation	1,880	2,380	3,135	4,030	5,190
06 02	Radiation Genetics	2,655	3,155	3,875	4,750	5,730
06 03	Combating Detrimental Effects of Radiation	975	1,115	1,400	1,955	2,510
06 04	Molecular and Cellular Level Studies	2,050	2,550	3,090	3,965	5,070
	Totals	7,560	9,200*	11,500	14,700	18,500

*The FY 1967 "189 budget submission" shows this total as 9,455, as it contains allowance for "B" budget items.

May 17, 1965

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Somatic Effects of Radiation

Budget Category 06 01

06 01 SOMATIC EFFECTS OF RADIATION

Members of the Pathology and Physiology Section are concerned with somatic effects of radiation. Radiation-induced leukemia and other neoplasms, and the role of virus in these diseases are under intense investigation. Studies on life shortening caused by radiation and chemical insults are being carried out. A large-scale, long-term, and very difficult program is now under way on the effects of low levels of radiation. In addition, hemorrhagic aspects of radiation injury are being studied.

Effects of radiation and other environmental factors on plants are under investigation in the Plant Physiology and Morphogenesis Group. Plant ultrastructure and mechanisms of growth and differentiation are parameters of special interest.

The program on Growth and Differentiation is concerned with understanding specific mechanisms that control those processes in the developing animal. Of particular interest here are abnormal conditions produced by radiation and by chemicals. The Developmental Biology program, which now consists of small and diversified efforts within various groups in the Division, will be expanded to cover much broader aspects of "growth and differentiation." The NIH is quite interested in our efforts and plans in this field, and it is proposed that they support part of this work. We expect the two programs discussed here to eventually become one of the most significant parts of the Biology Division program.

The Biomathematics and Biostatistics Group will intensify its statistical analysis support of both the AEC and NIH portions of our programs. It is significant that this group plans to expand into new programs of mathematical biology that are becoming increasingly necessary for modern experimental biology, and are discussed in the following section.

06 01 SOMATIC EFFECTS OF RADIATION

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Pathology-Physiology, General	535	650	815	1,000	1,190
Physiology of Blood Platelets	100	115	165	200	250
Low-Level Experiment	600	800	1,000	1,200	1,260
Plant Physiology	160	190	230	260	300
Growth and Differentiation	345	435	535	650	900
Developmental Biology	--	--	150	430	800
Biomathematics and Biostatistics	140	190	240	290	490
Totals	1,880	2,380	3,135	4,030	5,190
% increase from previous year		27	32	29	29

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06 01 SOMATIC EFFECTS OF RADIATION

Pathology-Physiology, General

Present Programs -- The long-term aims of the programs conducted herein are to elucidate the late somatic effects of radiation in mammals and to relate this information to man where possible.

The current programs are centered around the pathogenesis of (a) radiation-induced leukemia and other neoplasms, (b) a definition of the role of viruses in such phenomena, and (c) life shortening by radiation and chemical insults, and (d) an experimental mammalian microbiology program.

Future programs will be aimed at correlating the clinicopathological effects of radiation with physiological, biochemical, genetic, and microfloral changes, as well as to study the role of somatic mutations, chromosome aberration, cell killing, virus activation and virus-host interactions, etc., in causing or modifying these clinicopathological effects. Experiments smaller in scope but otherwise quite similar to some of those in the low-level experiment will be conducted with germ- and virus-free animals.

A new but small effort on automating animal care procedures and in developing new approaches to animal facility construction is planned. The aim of such a program is to reduce costs of animal care and of facility construction and, at the same time, to make the facility subject to modification and updating as techniques are improved or modified. As the program diversifies, it may be divided into separate projects.

Physiology of Blood Platelets

The long-range aims of this program are to understand the physiology of blood platelets as they relate to the hemorrhagic syndrome caused by whole-body irradiation. In particular, studies will be carried out to determine the factors that regulate platelet production, maturation and longevity, and those properties of the platelet which permit it to maintain the integrity of the capillary endothelium.

Present studies are directed along two lines: (a) the determination of platelet size and the biological function and activity of platelets as related to their age, and (b) a study of the factors which regulate platelet production.

Future programs will continue along lines above with emphasis on studies of recovery from radiation damage as affected by platelets or agents which affect platelet production.

Low-Level - Long-Term Effects of Radiation

Long-term goals in this study are to define the nature of the effects of low levels of radiation on microbially defined animals. The principal endpoints will be life shortening, leukemia induction, induction of other forms of cancer, cataractogenesis, and reduction in fertility and vigor. Within limits, the results should allow a determination of whether there is a threshold effect in radiation damage below which no deleterious effects of radiation can be demonstrated.

The present and future programs are related to establishment of the necessary experimental animal breeding stock, training of monitoring personnel, and establishment of detailed protocols for the complete study based upon preliminary experiments now being conducted. This program should reach an optimum operating level by the end of FY 1968 and level out during FY 1969 except for cost-of-living increases which will be expected from time to time. Some results from the major experiment are expected to start becoming available during FY 1967 as a result of serial sacrifice, hematology, virology, and related examinations.

Plant Physiology and Morphogenesis

The long-range effort of this group is concentrated on determining the effects of radiation and other environmental factors on growth, differentiation and morphogenesis of seed plants.

The present program centers around comparing cell elongation and cell division in plants derived from heavily irradiated seeds with those from non-irradiated seeds in attempts to dilineate differences between these two processes.

Future programs will be directed at analyzing anatomically and physiologically the essential similarities and differences between a normal growing point and one induced by chemical means, and to continue to look for and at those plants offering unique systems for studying differentiation and plant ultrastructure. A new effort will be initiated using plant tissue culture techniques to study the mechanisms of cell division and elongation as well as to explore the mechanisms of virus infection in plants and possible effects of radiation on such mechanisms.

Growth and Differentiation

The long-term aim of the research conducted in this program is to understand the mechanisms which control growth and differentiation and how these mechanisms are modified by radiation and other environmental factors to lead to malformations, the cancerous state, etc. An understanding of how radiation and chemicals cause these modifications should provide clues concerning possible recovery mechanisms and how these might be furthered by the proper therapy.

The present program involves a multifaceted attack on the problem of lens development on the amphibian eye. Immunochemical, cytochemical, chromatographic and electron microscope techniques are being used to follow the time course of transformation of various constituents of cells of the pigmented iris into the lens and especially how radiation modifies these processes.

Future programs will expand into the following areas: (a) use of in vitro tissue cultures for studying those factors responsible for tissue transformation and embryonic induction, (b) development of immunological techniques for studying various tissue differentiation pathways, (c) studies of sensitivity of various developmental phases to teratogenic environmental factors such as radiation, (d) biochemical approaches to determine the cellular conditions regulating tissue--specific protein synthesis and the role of hormones, and (e) attempts to correlate ultrastructural changes in chromosomes, and other cellular particulates with cellular synthetic activities.

Developmental Biology

The long-term aims of these programs are to elucidate the various physiological and biochemical steps which occur from the time the egg is fertilized until the individual has fully matured. By knowing those processes which occur in the normal sequence of growth and differentiation and how these processes are altered by various factors such as radiation, viruses, and chemicals, it may be possible to actually devise measures to negate the cause of the anomaly observed in the mature individual.

Currently a small effort in this general area is funded under other programs but the Division has no really well-rounded many-faceted approach to studying the development of the individual. The programs envisaged would explore the physiological, biochemical, genetic, and biophysical aspects of development, particularly those many processes which are involved in differentiation and the mechanism of gene control of differentiation. One aspect of the work would involve an extension of current efforts on a unique class of nucleic acids found in the egg which appear to act as modifiers or controllers of gene function during differentiation. Additional programs on the modification of orderly control of development by various environmental factors such as radiation and viruses, and on the development of the immune system in various life forms will be followed. These studies on growth and differentiation in animals, insects, and plants will make use of those systems which offer unique properties for understanding the normal situation and which can also be manipulated so as to explore the effects of radiation, viruses, chemicals, etc.

A similar effort is being proposed for support by the National Institutes of Health in the area of the pharmacology of development and differentiation. This will be a companion program to that being proposed here.

Biomathematics and Biostatistics

In the past this group has consisted of two scientists who, with the help of computer programmers, provided mathematical and statistical consultation, instruction, and computational aid for the Biology Division.

In FY 1966 this group should be supplemented by adding two scientists, who are statisticians, as well as the necessary support personnel, so that it may have the opportunity to do independent research as well as to provide the necessary consulting services.

It is planned that either in connection with this unit, or as a completely separate group, the area of application of mathematical, physical and chemical theory will be built up so as to attack with the powerful techniques of these sciences the relationships between the chemical and physical structure of macromolecules, viruses, various subcellular particles such as chromosomes, mitochondria, membranes, etc., and their biological activity.

Investigation of the application of techniques such as spectral analysis, information theory, birth-death processes, Markov chains, etc., to problems in biology is necessary for effective analysis of data from experiments in cell physiology, biophysics, and phage genetics. Analysis of data dealing with specific-locus mutations, mammalian recovery, mammalian cytogenetics, pathology and physiology, and chemical carcinogenesis will require ever increasing use of data handling and data processing equipment. Additional research into computer techniques for handling biological data is contemplated.

Some examples of anticipated computer oriented problems in biology are the construction and testing of simulation models in genetics and epidemiology, and the construction of models for the analysis of physiologic and biochemical systems which often involve systems of differential equations. Moreover, such problems as data storage and retrieval, involving access to patient or animal records, analysis of these records, and assistance in diagnosis by automatic coordination of laboratory and clinical findings will be resolved by the use of large computers.

It appears particularly important and appropriate to enrich our group of extremely well-qualified experimentalists with a few individuals who will bring to bear their abilities to theorize on important biological and medical problems.

Radiation Genetics

Budget Category 06 02

06 02 RADIATION GENETICS

In the field of mammalian genetics there are three studies that should be considerably expanded: (1) The recent finding that the mutation rate in neutron-irradiated female mice drops to an extremely low level a few weeks after exposure must now be tested with X and gamma rays. Because this test must be done at low total doses, in order to preserve continued fertility of the females, it requires very large numbers of animals. (2) The even more recent results which indicate that low doses, like low dose rates, may produce fewer mutations than expected on the basis of the mutation frequency observed at high doses is of obvious importance in the estimation of human genetic hazards. Again, unusually large numbers of offspring will have to be scored to answer this question. (3) The clear demonstration in this laboratory in pilot studies with triethylenemelamine that this chemical is mutagenic in spermatogonia of mice suggests the development of a major program in chemical mutagenesis in mammals. We plan to start by adding one or two people. A program in mammalian genetics that we plan to initiate is the radiation induction and chemical induction of chromosome aberrations. This will focus on the possibility of obtaining inversions which might then be used in special stocks to provide an efficient technique for the detection of mutations.

A special area of "cell physiology" is becoming increasingly important and during the next five years should play a much larger role in the general program; information concerning the function of the nucleolus, the relation between the structure and function of the chromosomes of higher organisms and a number of other problems along these lines need to be pulled together and elucidated. Work on all of these problems is in progress in the Division, but it is scattered through various groups, and is secondary to the main interest of these groups. In bacterial genetics we expect to expand the work to include the lethal and mutagenic effects of agents other than the radiations now being studied. In mammalian genetic cytology we expect to expand the efforts into a new area of somatic cell genetics. We expect that this mammalian genetic cytology program will expand into the field of the chemical co-carcinogenesis project. In chromosome cytology we plan to exploit studies, already under way, of the combined effects of various mutagens, and we expect to go much further into studies which will help elucidate the structure of the genetic apparatus (genes and chromosomes). In fungal genetics we expect to expand into new areas involving enzymology: for example, to correlate genetic and biochemical information in regard to "feedback and repression" in the regulation of adenine biosynthesis. In addition we expect to initiate studies of the correlation of protein structure with mutagenic origin or complementation pattern of the mutants. In Drosophila genetics, new areas we expect to exploit are reverse mutations, biochemical studies, and Drosophila tissue culture. We plan to initiate this year new studies in the field of "virus-chromosome relationships," and will exploit the unique techniques which Professor Pavan and his group will bring to this laboratory; this group has demonstrated that they can produce a virus infection on a chromosome in an insect, and thus one has the first instance of a possibility to study directly virus-chromosome interrelationships. The work of the tissue culture group will continue with applied aspects of human radiation hazards, and will emphasize basic work in the areas of mammalian somatic cell genetics, chromosome structure, mammalian cell survival, and primate cytotaxonomy. In regard to the human hazards chromosome analysis study, a separate activity is being set up to cover "instrumentation," i.e., machine and computer techniques in karyotype analysis.

06 02 RADIATION GENETICS

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Biotechnology	--	--	110	300	400
Mammalian Biochemical Genetics	115	120	130	135	145
Mammalian Genetics	1,000	1,110	1,225	1,340	1,500
Bacterial Metabolism	55	65	85	85	100
Bacterial Genetics	115	145	170	200	240
Bacteriophage Genetics	45	60	85	120	150
Molecular Photobiology of DNA	70	75	80	110	125
Effects of Radiation on Paramecium	140	175	200	270	370
Fungal Genetics	145	200	300	365	450
Drosophila Cytology and Genetics	285	310	355	370	425
Chromosome Cytology	135	170	220	255	300
Cytochemistry and Cell Reproduction	145	200	240	315	400
Mammalian Genetic Cytology and Comparative Mutagenesis	50	100	175	250	350
Virus-Chromosome Interactions	155	180	200	250	300
Human Cytogenetics	200	245	300	385	475
Totals	2,655	3,155	3,875	4,750	5,730
% increase over previous year		19	23	23	21

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06 02 RADIATION GENETICS

Biotechnology and Bioengineering

Efforts to exploit the capabilities existing in Oak Ridge for developing new biophysical tools have been explored for some time and have led to the development of the zonal ultracentrifuge and automated analytical systems for mixtures of nucleotides and nucleotide derivatives, sugars and proteins. There is currently a small but quite successful effort in the Chemical Technology Division on the development of methods for separating macromolecules of biological importance. Discussions have been held and a few exploratory steps taken on devising a tool for automatically doing analyses of chromosome number, shape, breaks, etc. We would like to extend these efforts and arrange for their continued support.

There are individuals in X-10, K-25, and Y-12 with talents in almost any area of technology or engineering which could be applied to biology. The program proposed here would provide funds for encouraging the development of various instruments and techniques which are needed to attack biological problems. Once such instruments are to the prototype stage, they would be turned over to industry for exploitation. The program would involve development of new types of animal containment facilities and new methods for animal care, karyotype analyzers, improved electron microscopes, adaptation of gaseous diffusion processes, barrier technology, liquid-liquid extraction procedures, and electrophoresis, chromatography, and related techniques to separation of biologically important molecules and particles. These are only a few examples of things which can be done under such a program, and almost uniquely so at Oak Ridge because of the strong biology group interacting with people from one of the world's largest and most highly sophisticated physical scientist and engineering talent pools.

Mammalian Biochemical Genetics

The long-range aim of this program is to understand in biochemical and physiological terms the growth and differentiation of mammalian cells and the mode of gene action with particular emphasis on qualitative and quantitative changes in tissue proteins.

Current efforts are on (a) using amino acid sequence techniques to study inheritance and properties of mouse hemoglobins, (b) the inheritance and properties of serum esterases, and (c) the comparative growth of different bone marrow cells transplanted into different hosts and of the factors controlling the success of the transplant.

Future programs will be along the same line with studies of proteins of the capsomeres of adenoviruses to see why viruses are oncogenic in some mouse strains and not in others.

Mammalian Radiation Genetics

The first paragraph on page 3.8 summarizes important new aspects of this program.

The long-term objective of this program is to estimate the genetic hazard of radiation to man through work on the laboratory mouse, using the specific locus and other methods as well as cytological techniques. Man himself is used when possible.

The present efforts in this program are concentrated on determining (a) the effects of total dose, dose rate, and dose fractionation of gamma rays, X rays, and neutrons, on mutation rate and type of mutation produced; (b) the effect of gametogenic stage on type and frequency of genetic damage; (c) estimation of that part of the total genetic damage that is expressed in the skeleton; (d) utilization of mutations and chromosome aberrations recovered in the program to answer basic questions on organization of the genetic material and gene action; (e) analysis of radiation effects on the dynamic cell populations of the gonads of mouse, man, and other mammals.

Future programs will (a) continue all of the work in progress, with much effort having to be devoted to experiments that will probably yield low mutation rates (low doses; late litters of irradiated females, see page 3.8); (b) follow up our pilot studies on chemical mutagenesis and interaction effects, using our test systems and stocks; (c) develop systems for detecting radiation and chemically induced inversions; (d) follow up our discovery that only one mammalian X chromosome is fully active, by attempting to elucidate the mechanisms of chromosome differentiation and inactivation; (e) expand cytological work particularly by the use of electron microscopy; (f) continue earlier developmental studies, particularly in connection with induced and spontaneous mosaics.

Mutagen Mechanisms - Bacterial Metabolism

The long-term aim of this program is to explore the biochemical and physiological basis for radioresistance in microorganisms and to determine the mechanisms by which radioprotectors and radiosensitizers operate. The future programs will add one junior investigator to aid in the exploration of the radioprotectors and sensitizers as well as in the studies on postirradiation phenomena.

Mutagen Mechanisms - Bacterial Genetics

Present programs are aimed at understanding the genetic basis for radioresistance in microorganisms, in particular, the location of the gene or genes which may be involved and the nature of the processes which the gene controls.

Programs in the next five years look toward the addition of a senior biochemist to aid in a concerted attack on the more biochemical aspects of radioresistance and repair of radiation damage in microorganisms of various kinds. The addition of junior people at the postdoctoral level will permit an orderly study of the comparative effects of various physical and chemical agents on mutation production. The principal aim of the expanded program is to determine if there are similar mechanisms involved in mutation production by radiations of various kinds and by various chemicals.

Bacteriophage Genetics

Present programs are concerned with theoretical and experimental studies related to the physical and genetic aspects of recombination in bacteriophage.

Future programs are to be directed toward (a) the analysis of the molecular basis for mutation induction, (b) a program in physiological genetics aimed at understanding the relations between genes and morphogenesis of proteins in phage coats, and (c) the relation between the structure of the genome and time of gene action.

Molecular Photobiology of DNA

Present work is concentrated on the enzyme which repairs UV damage to DNA.

Future work will explore the nature of a second lesion produced by UV, the nature of the enzyme which repairs this damage, and the biochemical nature of the repair.

Effects of Radiation on Paramecium

Present programs are concerned with (a) repair and/or recovery in mutation induction processes, (b) the comparative mutagenesis of chemicals and radiation, and (c) the cell cycle, how it is modified by various agents and how stage in the cell cycle is related to sensitivity to radiation.

Future programs will involve extension of work on how the cell cycle can be modified and on the basis for recovery from such modifications. The program is to be expanded by addition of new young investigators as new facilities become available, with their efforts being concentrated on the basis for recovery from alteration of the cell cycle and reasons for persistence of the alteration for several generations.

Fungal Genetics

Present programs include (a) comparative genetic effects of different kinds of radiation, (b) comparative genetic effects of different chemicals, and (c) gene and chromosome structure.

Future programs, in addition to the above, will be directed toward (a) nature and extent of repair from radiation damage, (b) biochemical genetics of the adenine locus, and (c) characterization of the proteins made by purine mutants and correlation of their structure with mutagenic origin or complementation pattern of the mutants. The area receiving the greatest emphasis in the expanding program will be that on comparing the mutational mechanisms of different kinds of radiation and the nature and extent of repair mechanisms.

Drosophila Cytology and Genetics

Present programs cover (a) genetic control of spermatogenesis as observed in sterile males, (b) nature of meiosis in females, (c) chromosomal nature of mutagenesis, (d) gene fine structure, (e) cytological studies of mitosis, spermatogenic cycle and ring chromosomes, (f) computer techniques for handling genetic crosses, and (g) revision of the handbook on mutants of Drosophila melanogaster.

Future programs will continue along some of the same areas, but will expand to include (a) cytochemical and electron microscope studies of spermatogenesis in sterile males, (b) genetic comparison of autosomal recessives affecting meiosis recovered from mutagen-treated flies and from natural populations, (c) cytological studies of oogenesis, (d) comparative ability of different mutagens to produce lethal and sterile mutations, (e) reverse mutations, (f) biochemical genetics of Drosophila, and (g) Drosophila tissue culture.

Chromosome Cytology

The ultimate aim of this group of studies is to elucidate the physical structure of the genetic apparatus and to understand the damaging effects of radiation and chemicals in a physical and biochemical way.

The present programs are directed toward understanding the gross structural aspects of the chromosome and of chromosomal aberrations induced in plant and mammalian cells by radiation and chemicals and the chemical nature of such aberrations.

Future programs will explore in more detail the chemical nature of chromosome aberrations caused by various agents and the time-sequence of their fixation into the chromosome structure. Other studies will examine the structure of the chromosome using biochemical and biophysical techniques aimed at understanding the radiation-induced mutation process in higher organisms, particularly plants.

Cytochemistry and Cell Reproduction

The ultimate aims of this program are to understand the mechanics and biochemistry of gene replication, the controlled release of information by the gene and the influence of the cellular environment on these processes.

Present programs concern (a) mutagenesis in yeast and Habrobracon, (b) biochemical genetics of the metabolism of tryptophan, (c) transmutational events in bacteriophage using thermal neutrons, and (d) studies of biosynthetic regulation through synchronous culture.

Future programs, in addition to a continuation of the above, will expand into comparative biochemical genetics of the adenine and tryptophan pathways in various kinds of organisms and new studies on chromosome structure and function and a very small effort on the use of genetic techniques to control various types of plant, animal, and human pests.

Mammalian Genetic Cytology

Present programs concern studies on the cytogenetic effects of radiation and other mutagens on mammalian cells grown in culture.

Future programs will be expanded to include a broadened program in (a) mammalian cytogenetics, (b) the molecular basis of chromosomal and cellular damage caused by radiation chemicals, (c) determining if there is a correlation between chromosome morphology and tumorogenesis, both chemically and radiation-induced, and (d) somatic cell genetics.

Virus Chromosome Interactions

This is a new program being instituted to exploit the recent observation that chromosomes of the fly, Rhynchosciara angelae, are caused to be enlarged in volume 20 to 30 times their normal size (i.e., up to 0.5 mm in length) by infection of the larvae with a virus-like material and by a protozoan. Along with these changes in size are also changes in bonding patterns along the chromosome. This tool which permits an experimental control of increase in chromosome size may be a means of getting at the nature of virus infection and of the way in which the virus genome gets incorporated into the host genome. Additionally, if the chemical nature of the substance or process causing the enlargement of cells and chromosomes can be determined, a new approach to studying problems in basic biology will result.

Human Cytogenetics

Present programs are directed toward (a) determining the correlation between chromosome aberrations in leukocyte cultures and radiation dosage in humans, including standardization of the technique using in vitro systems, (b) changes in structure and function of mammalian chromosomes during the cell cycle, and (c) relation between chromosome aberrations and cell death.

Future programs will continue (a) on the relation between background radiation in natural areas and the occurrence of chromosome aberrations in man and animals, (b) on the relation between degree of chromosome aberrations and cell death, (c) the time course of cell death following irradiation, (d) structure and function in mammalian chromosomes, and (e) metric studies of human chromosomes as a background for application to automating scoring of chromosomal alteration.

Combating Detrimental Effects of Radiation

Budget Category 06 03

06 03 COMBATING DETRIMENTAL EFFECTS OF RADIATION

The excellent program in basic immunology will expand considerably to capitalize on recent findings which indicate that an important factor in radiation-induced aging is related to a decreased capability of the immune system. If viruses play any important role as initiators of such diseases as leukemia or various forms of cancer, means of rejuvenating the immune system could lead to a reduction in the detrimental effects of radiation. New programs in virology, particularly as they relate to the above, will also be budgeted in this category until such time as they become better defined in terms of program content. The current programs in chemical protection, muco-protein structure and enzyme catalysis will be further reduced and these efforts shifted into studies affecting viral attenuation, viral penetration, and host susceptibility as these studies expand. The programs on mammalian recovery will be maintained at a fairly constant level with consideration being given to shifting the emphasis to studies of neonatal biology as related to development of the hematopoietic system. If these new studies prove important, then further increases will be needed in future years.

06 03 COMBATING DETRIMENTAL EFFECTS OF RADIATION

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Chemical Protection and Enzyme Catalysis	75	80	85	90	100
Mammalian Recovery, General	400	420	440	465	510
Radiation Immunology	430	515	600	800	1,000
Recovery from Somatic Effects of Radiation	70	100	130	200	275
Virology	--	--	145	400	625
Totals	975	1,115	1,400	1,955	2,510
% increase from previous year		14	26	40	28

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06 03 COMBATING DETRIMENTAL EFFECTS OF RADIATION

Chemical Protection and Enzyme Catalysis

Present programs involve research on mixtures of two or more radiation protection compounds to determine if there is an enhanced protection with smaller total doses of chemicals so that the toxic side effects of these chemicals could be reduced. Other studies are directed toward understanding the role of the "active site" on the enzyme in determining radiation sensitivity.

Future studies will continue along the same general lines with only very slight increase in effort.

Mammalian Recovery, General

The aim of this program is to do the basic research required to make the bone marrow therapy approach to radiation protection a practicable art.

Present programs are concerned with secondary disease in radiation chimeras, distribution and properties of hemopoietic and lymphatic tissue stem cells, bone marrow tissue culture, cell separation and preservation, and in vitro recovery from radiation damage. The major current activity is the study of secondary disease in radiation chimeras; this is an immunologic disorder, frequently leading to death, and is the major complication of bone marrow transplantation from one individual to another.

Future programs will concentrate (a) on ways of separating tissue stem cells from other hemopoietic and lymphatic cells, (b) on "transplantation genetics," (c) on the immune system, and (d) on the basis of cellular repair of radiation injury. Internal budgetary shifts will largely be into this program. Since the newborn for a short time after birth has not established its "immune system," this provides an excellent opportunity to study the establishment of immunity. This period in the mouse lasts only a few days, and in man a couple of weeks. This study will mesh quite well with that in radiation immunology on ontogeny and senescence of the immune mechanism.

Radiation Immunology

The aim of this program is to understand the basic nature of the immune response, the responsible cells, and their time course of development as related to age of the individual and the impact of radiation on these parameters so as to provide the information needed for successful organ or tissue transplantation.

The present programs involve studies on growth and senescence of antibody-forming cells of conventional and germ-free mice, the role of phagocytosis in the antibody response, quantitative evaluation of graft reactions, effects of various antimetabolites,

irradiation and physical treatments on properties of immunologically competent cells, and the role of nucleic acids and proteins in the differentiation and proliferation of immunologically competent cells.

The above programs will continue into the future, but a major new effort will be devoted to confirming and determining the importance of the recent observation that the ability of the immune system to respond to insult reaches a peak at about one-fourth the mean lifespan and decreases thereafter. These results suggest that the high death rate among older individuals due to infective and autoantigenic agents may be due to a marked decrease of the immune potential. If such can indeed be proven to be the case, then it may be possible to extend the mean lifespan of an old individual by infusing genetically compatible stem cells from young individuals (immunologic rejuvenation). These results also indicate why the lifespan of an individual receiving 400 r total body exposure is not significantly lengthened even after marrow therapy.

Recovery from Somatic Effects of Radiation

The long-term aim of this program is to determine the relation between the genetic constitution of the cells of the hemopoietic system and their susceptibility to radiation, chemical or viral insults.

Present programs are (a) attempting to answer the question of whether different types of blood cells have a common precursor, (b) to study the heterogeneity or homogeneity of marrow lymphocytes in respect to their hemopoietic competence (are all marrow lymphocytes stem cells or not?), and (c) to study the specific genetic control of marrow transplantation.

Future programs will include parts of the present programs, as well as experiments in somatic cell genetics: (a) genetic effects of viruses on mammalian cells, and (b) somatic crossing-over and mutation. These studies will make use of five linked genetic markers in the H-2 region which control the synthesis of five distinct strong histocompatibility isoantigens. With these markers, attempts will be made to detect variant cell lines, irrespective of whether the mechanism was crossing-over, mutation, chromosomal deletion, etc.

Virology

The long-term aim of this program is to determine the degree to which viruses are involved in radiation-induced phenomena such as leukemia, cancer, and related scientific anomalies; and, if they are causally involved, to develop the necessary information on which to base the therapeutic measures necessary to prevent the radiation damage.

The present programs in the Division in this area are conducted in the 06 01 category and may be described as the biology of leukemia. The programs which will be supported herein are those aimed at determining the lesions which viruses cause, the role of passenger and/or carrier viruses in infection, the possible mutagenic effects of viruses, and the manner in which portions of the virus genome (chromosome) may be incorporated into the genome of the experimental object. This latter point could be particularly important if it turns out that

leukemia and related radiation-induced diseases are caused by viruses. The question then arises as to how the viruses got into the animals in the first place, whether the virus existed as a "provirus" prior to the irradiation insult and whether or not a "provirus" is anything more than a piece of virus genome which has been incorporated into the normal genome of the animal. The high susceptibility of some animals to radiation-induced leukemia would suggest such a possibility.

This is an area in which the National Institutes of Health also has a considerable interest and it may be explored as a companion program to this with the specific emphasis in the case being upon the role of chemicals and viruses in causing cancer. The combined rate-zonal and isopycnic-zonal centrifuge systems for trace virus isolation are being applied to the problem of searching human tumors for virus particles.

Molecular and Cellular Level Studies

Budget Category 06 04

06 04 Molecular and Cellular Level Studies

We plan to continue the studies on DNA genetics and DNA electron microscopy; we expect this group to lead a bacteriophage program which will consist of this small group plus the several, at present scattered, excellent people that we now have in this field. We expect to initiate new studies of problems in biophysics concerning the central nervous system and coding problems, X-ray diffraction analysis of macromolecules, intramolecular forces, and protein DNA interactions. In the area of "molecular biology" an entirely new and very valuable technique was opened up here, namely, enzymatic means of synthesizing many types of polydeoxynucleotides; a large variety of these new compounds, which are important for understanding the mechanisms of enzymatic DNA synthesis, need to be made and characterized by chemical and physical methods, and the biological properties of these new polymers need to be tested in living systems in conjunction with RNA, protein, and DNA. The enzymology group expects to expand its already successful efforts in connection with the Chemical Technology Division of ORNL in the isolation, purification, and study of the properties of specific transfer RNA's. We expect to develop from within the Division a new research group on "biochemical regulation"; this group of investigators has already been very successful in their studies of the mechanisms of hormonal control of protein synthesis, and they would like to expand their efforts into two new fields: (1) a program investigating the role of adrenal hormone in chemical induction of hepatoma, and (2) mechanisms controlling enzyme levels during development. The cell physiology group plans to go into two important new areas, namely, a study of the conformation of macromolecules and the role of water, and also into studies of permeability of membranes.

Our strongest biochemical virology program centers in the nucleic acid enzymology group; we expect their well-known and successful work on the biochemistry of bacterial viruses to expand considerably, and to include research on mammalian and cancer viruses.

The program in subcellular and viral physiology has led to the development of methods for isolating subcellular constituents and viruses in a high state of purity and for preparing antigenic viral subunits. These techniques are now being used to prepare a new class of high purity vaccines for human use.

06 04 MOLECULAR AND CELLULAR LEVEL STUDIES

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Microbiology	50	55	60	65	75
Nucleic Acid Chemistry	110	125	145	170	200
Enzymology	380	485	585	740	875
Biochemical Regulation	160	200	270	320	400
Nucleic Acid Enzymology	290	335	400	505	650
Molecular Biology	175	230	295	395	550
Biophysics	325	440	540	790	1,135
Molecular Biophysics	100	135	160	215	275
Photosynthesis	110	120	130	145	165
Cell Physiology	125	160	200	270	320
Subcellular and Viral Physiology	225	265	305	350	425
Totals	2,050	2,550	3,090	3,965	5,070
% increase from previous year		24	21	28	28
Division Totals	7,560	9,200	11,500	14,700	18,500
$ increase from previous year		1,640	2,300	3,200	3,800
% increase from previous year		22	25	28	26

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Microbiology

Present programs are investigating the detailed molecular mechanisms of basic biochemical processes, in particular electron transport reactions. Spectral, optical rotatory, and fluorometric properties of enzyme-bound nicotinamide adenine dinucleotide indicate that oxidized NAD-acetone may be a good model for investigating the relation between conformation and chemical structure in pyridine nucleotide reactions.

Future programs will attempt to elucidate the conformational features of adenine dinucleotide molecules which determine their optical rotatory properties; these studies are pointed toward a clearer understanding of the catalytic properties of pyridine nucleotides.

Nucleic Acid Chemistry

The present programs involve a chemical approach to structural problems in the nucleic acid field. In particular the chemical parameters of ion-exchange chromatography of polynucleotide materials will be examined with the purpose of separating various oligonucleotide species.

Future programs will take purified RNA species and apply techniques of ion-exchange chromatography and of organic chemistry to the isolation, chemical characterization, and modification of RNA species of interest in work on protein synthesis and information transfer.

Enzymology

The long-range goal of this program is to determine the base sequence of a specific isolated gene, the base sequence of its specific messenger RNA product and the amino acid sequence of the protein whose structure is determined by these molecules. With such systems available, it will be possible to understand the mechanism by which hormones stimulate the synthesis of specific proteins, how substrate induction occurs, how an antigen can give rise to a specific antibody, how chemical carcinogens, mutagens, radiations and viral infections alter the information content of a cell, thereby changing its enzymatic profile, and how such a change can either be beneficial or detrimental to the cell and/or host.

Present programs are aimed at the following questions, (a) what is the minimum molecular weight of a specific gene? (b) in chemical terms, how is the information that determines the structure of a specific protein coded in DNA? (c) what is the nature of the molecules that carry this information from the gene to the protein-forming system? (d) what is the mechanism used in translating this information into specific amino acid sequences? (e) how do mutant genes act to produce altered proteins? (f) what are the mechanisms used by cells to control expression of genetic information? (g) what is the nature of the damage to DNA caused by UV and x-irradiation, and how can this damage be prevented or repaired?

A variety of organisms, green plants, bacteria, and mammalian systems, both cell-free and in vivo, are being used in efforts to answer these questions. Future programs are expected to continue to develop in the direction of obtaining specific DNA or RNA effects on protein synthesis in all of the systems currently under investigation. Increasing emphasis will be directed toward understanding the level (i.e., DNA, RNA, amino acid assembly into protein) where control is exerted and the nature of the control mechanism. Attempts will be made to develop cell-free systems that will synthesize specific proteins under the direction of DNA or RNA. These systems will thus become bioassays for a particular gene or an RNA gene product. The large-scale facilities currently available should permit the isolation of milligram or gram quantities of these purified macromolecular components. During FY 1966 the Chemical Technology Division will be deeply involved in these programs and will have developed methods suitable for the isolation and characterization of these macromolecules.

Biochemical Regulation

The goal of studies in this program is to elucidate the degree to which genetically controlled processes can be modified by hormonal action.

The present programs are centered about the effects of steroid hormones on the regulation of RNA and enzyme synthesis.

Future programs will include (a) studies on the mechanism of hormonal control of protein synthesis, in particular to determine the biochemical basis for differences in turnover time between various enzymes, as this control appears to be of major importance in "regulation," (b) a program to investigate the role of adrenal hormone in chemical induction of hepatoma, and (c) a study of mechanisms controlling enzyme levels during "development."

Nucleic Acid Enzymology

The major present programs use microbial systems, especially bacteriophage, to study the primary mechanisms involved in DNA replication and recombination. Studies of the biochemical events which determine the genetic phenomena are under way utilizing RNA-containing bacterial viruses, whereby it is possible to study the biochemistry and genetics of a biological system exclusive of the direction of DNA. In particular, the mode of transcription of genetic information for specific protein synthesis is being investigated by isolation and a study of the properties of specific DNA and RNA molecular species. A smaller program is concerned with a unique class of RNA molecules which may affect the course of cellular differentiation in fertilized amphibian eggs.

Future programs will involve (a) attempts to determine the primary nucleotide composition and possibly sequence of specific DNA cistrons, (b) investigations of enzymatic mechanisms responsible for recombination

and heterozygosis in phage and bacteria, and (c) an examination of the enzymatic mechanisms responsible for genetic recombination in Neurospora and Drosophila. Also, attempts will be made to define precisely the coding units of the various transfer RNA's for the twenty amino acids; and studies will proceed on the biochemical means by which RNA alone can carry out the processes of inheritance. The smaller program will emphasize studies on the physical association of oligonucleotides to the larger molecular weight nucleic acids and the possible relationship to "repression," and release from repression. The possibility that oligonucleotides perform an important function during development by either being converted directly to polynucleotides or by acting as regulators of RNA synthesis will be explored by attempting to isolate an enzyme from developing embryos that will polymerize oligonucleotides, and by determining the effect of oligonucleotides on an RNA polymerase system from developing embryos. Studies of the oligonucleotide changes in lethal hybrids, and the structure of amphibian egg ribonucleic acids will be conducted.

Molecular Biology

Present programs consist of studies on the mechanism of DNA biosynthesis using purified enzymes, pure precursors, and isolated DNA templates--and by comparison of the products formed in this in vitro system with natural DNA. This group is actively pursuing its discovery of methods of preparing polydeoxynucleotides biosynthetically.

Future programs will capitalize on the ability to prepare fairly large quantities of polydeoxynucleotides biosynthetically for use as model compounds to study the mechanisms of DNA synthesis and the action of radiation on DNA-like materials. These compounds will be characterized by chemical and physical methods, studies of new routes to synthesize other types of polymers will be explored, the biological properties of these polymers will be examined in enzyme systems (with RNA, protein, and DNA), and in living systems.

Biophysics

Present programs are directed toward understanding the details of the molecular changes that are produced by the action of radiations on cells and cellular components, and to explain, at the molecular level, radiobiological phenomena such as inactivation of cells, repair mechanisms of cells, chromosome breaks and free radical production, as well as gain new and important information about the structure and function of intracellular compounds such as DNA and RNA. Experimental approaches to these problems center around (a) the correlation of the biological action of ultraviolet and ionizing radiations with molecular changes produced by these radiations using isotopic tracers, ultracentrifugation and electron microscopy; (b) investigations by the effects of various combinations of ionizing, ultraviolet, visible radiations and chemical agents on cells and their constituents; (c) electron spin resonance studies of naturally occurring

free radicals, as well as radiation-induced free radicals in simple and in complex systems; and (d) nuclear magnetic resonance studies of chemical structures and reactions.

Future programs will include (a) high-resolution electron microscope techniques to observe directly some of the changes produced in DNA by radiation action; (b) studies on basic mechanisms of action of radiation on biological materials will be extended using ESR techniques; (c) UV work will involve assessing the role of repair mechanisms in mutagenesis in bacteria and viruses using as a basis the known structure and effects of UV-induced lesions; (d) research in the field of high resolution electron microscopy and radioautography working on the structure of DNA and the modes of replication and recombination of DNA and how radiation and repair mechanisms affect structure and function; (e) structural studies on proteins and nucleic acids using X-ray diffraction techniques; this endeavor is a necessary one if we are to correlate structure with the function of biological systems; (f) protein-DNA interactions; (g) central nervous system and coding problems, and (h) theoretical studies on intramolecular forces.

Molecular Biophysics

Present programs concern studies of (a) mechanisms of transfer of DNA in bacterial mating; (b) origin of normal replication of DNA in the bacterial chromosome; (c) methods in high-resolution autoradiography; and (d) characterization by electron microscopy of the DNA of lambda bacteriophage.

Future programs will (a) study by high-resolution autoradiography (electron and light microscopic autoradiography) of the behavior of lambda DNA in the bacterial cell following injection, in virulent infection and in lysogenization; (b) study the mode of attachment of the DNA of lambda bacteriophage to the bacterial chromosome in lysogeny; and (c) explore the relation of virus infection to the integrity of the cell, especially its genetic mechanism, the chromosomes and their nucleic acids.

Photosynthesis

The present programs involve physical measurements of energy transfer and other closely related phenomena in photosynthetic systems.

The future programs will concentrate on the preceding, as well as on biochemical studies of chloroplasts so that direct comparisons can be made with the more biophysical studies presently being carried out.

Cell Physiology

Present programs are composed of studies on (a) freezing in cells, mechanisms of injury, preservation of cells and tissues; and (b) the state of water in cells and biological materials.

Future programs will concentrate on studies on (a) the role of water in the conformation of macromolecules and on macromolecular structural interactions; and (b) permeability and membranes.

There is increasing indication that water plays a vital role in protein conformation and perhaps in membrane structure, both of which are important in biological systems. The matter of water-solute interaction, macromolecular conformation, and membrane structure and function probably bear importantly on enzyme and gene function and appear involved in radiation damage. The studies on freezing provide a powerful tool for investigating the role of water, as well as provide information of value to members of the Division who need to preserve cells, viruses, or enzymes, or who need to study phenomena in the absence of water.

Subcellular and Viral Physiology

The ultimate aims of this program are to devise, perfect, and explore new methods for isolating and visualizing cell substructures down to the molecular level and applying these methods to the study of cell division, cellular organizational aspects of protein synthesis, the mechanism of muscular contraction and intracellular events preceding, during, and following virus infection.

The present program is largely concerned with the development of centrifugal separation methods in collaboration with the Oak Ridge Gaseous Diffusion Plant, The National Cancer Institute, and the National Institute for Allergy and Infectious Diseases. Zonal centrifuges capable of spanning the range of particle sizes from whole cells to protein molecules have been taken from concept to application to specific biological problems.

In the future the presently envisioned series of centrifuges will be finished, new vaccines prepared with centrifugal systems developed at Oak Ridge will be in clinical trials, and definitive programs to search human tumors for virus particles will be under way at Oak Ridge and several other laboratories. The groundwork for attacking the difficult problems of isolating transplantation or specific tumor antigens and for attempting to isolate tumor specific nucleic acids will have been laid and an attack on these problems will begin.

Section IV

Summary of NIH Programs and Budgets

The materials included in this section were provided to the U. S. Atomic Energy Commission and to Dr. James A. Shannon, Director, National Institutes of Health, in February, 1965, and were revised in May, 1965. They represent our current thinking in broad terms of the areas of interaction between the National Institutes of Health and the Atomic Energy Commission's Oak Ridge programs.

SUMMARY BUDGET FOR NIH PROGRAMS

	FY 1966		FY 1967		FY 1968		FY 1969		FY 1970	
	A	B	A	B	A	B	A	B	A	B
Co-Carcinogenesis*	2,995	2,995	3,000	3,000	3,590	3,590	3,970	3,970	4,355	4,355
Virology*	200	200	300	500	500	900	730	1,400	1,400	2,000
Developmental Biology*	350	600	600	1,200	900	1,700	1,500	2,000	1,900	2,300
Mathematical Biology* and Physical-Chemical Biology	270	440	370	640	490	800	650	1,050	850	1,350
Sub Total	3,815	4,235	4,270	5,340	5,480	6,990	6,850	8,420	8,505	10,005
TECHNOLOGY										
Containment**	850	1,700	1,450	3,250	1,950	3,800	2,050	3,600	2,300	3,500
Centrifuge Development**	1,350	1,600	1,375	1,750	1,500	1,850	1,550	1,925	1,625	1,990
Biotechnology-** Bioengineering	615	980	1,120	1,570	1,550	2,260	1,950	2,490	2,280	2,900
Sub Total	2,815	4,280	3,945	6,570	5,000	7,910	5,550	8,015	6,205	8,390
In Biology	770	975	900	1,275	1,125	1,575	1,275	1,650	1,425	1,725
Elsewhere	2,045	3,305	3,045	5,295	3,875	6,335	4,275	6,365	4,780	6,665
Grand Total	6,630	8,515	8,215	11,910	10,480	14,900	12,400	16,435	14,710	18,395

A - This is considered a reasonable minimum level.
B - An optimal level of operation.
* Totally in the Biology Division.
**Biology Division will provide guidance and consultation and do the biological testing and experimentation required for development.

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CO-CARCINOGENESIS RESEARCH PROGRAM

This program is directed toward a study of the independent actions of viruses, chemicals, and radiation in causing various kinds of metabolic disorders which may lead to cancer of various kinds. In addition, the program will study the interaction of these various environmental factors in causing cancer or making an individual more susceptible to cancer.

That part of the program currently active involves carcinogenic effects of inhaled chemicals, biochemical aspects of cancer, particularly as they relate to virus interaction, enzymology of the carcinogenic state, and research in the basic medical sciences directly and indirectly related to cancer. The program was initiated in 1962 between the National Cancer Institute and the Oak Ridge National Laboratory of the AEC. The Atomic Energy Commission has secured Congressional approval for a $2.1 million building to be completed in March, 1966 for occupancy by the NIH-supported part of the joint program.

In addition, the AEC has provided space on an interim basis to initiate the basic program, has already provided other construction amounting to $600,000 from its General Plant Project funds, and has two major construction items in the FY 1966 budget now before Congress which will be heavily utilized by the co-carcinogenesis program. The NCI-used part will amount to an additional $620,000. Thus, the AEC-provided construction for the NIH part of the joint program by June, 1967 will amount to over $3.3 million.

The National Institutes of Health support for this program for research during FY 1965 amounted to $1.1 million, in addition to allocations for the purchase of equipment to be installed in the building as it is constructed. The projected program for FY 1966 is estimated at $2.9 million, although Endicott and Kotin only have programmed a maximum of $2 million for that period. This program, when fully developed, in our opinion should have approximately the proportion of mission oriented to basic research as is presently in existence in the Biology program supported by the Atomic Energy Commission, i.e., about $4 dollars in mission oriented to $1 dollar in the basic program. In the basic program there would be microbial genetics, microbiology, molecular biology, biochemistry, biophysics and such other programs which are related in an indirect manner to carcinogenesis. The proposed budget for this program is outlined on the attached page.

SUMMARY BUDGET - NIH-AEC CO-CARCINOGENESIS PROGRAM

$ in Thousands

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Inhalation Co-Carcinogenesis	850	950	1,050	1,125	1,200
Biochemistry of Co-Carcinogenesis	250	300	330	390	425
Enzymology of the Carcinogenic State	240	280	300	330	360
Mammalian Chemical Co-Carcinogenesis	105	135	160	190	220
Biophysics	200	200	240	290	325
Chromosomal Effects of Chemicals & Radiation	60	100	145	190	225
Physical-Chemical Properties of RNA	80	85	95	100	150
Molecular Biology of the Nucleic Acids	40	45	70	125	150
Mammalian Chemical Mutagenesis	150	200	250	350	450
Basic Medical Sciences and New Programs	540	365	550	420	330
Equipment	250	300	350	400	450
Occupancy of New Facilities	200	-	-	-	-
Minor Renovations	30	40	50	60	70
Totals	2,995	3,000	3,590	3,970	4,355

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VIROLOGY RESEARCH

This area can be considered as an integral part of the co-carcinogenesis program or, because of its great importance, it can be set up as a separate program as is being proposed here. The Atomic Energy Commission is committed to a program in this area because of strong evidence linking radiation induced leukemia in mice with a virus-like agent. The principal question needing exploration is whether, in fact, leukemia is caused by a virus and, if so, what the nature of the radiation triggered virulence really is. Additionally, the relation between other types of radiation induced anomalies and viruses needs exploration. The Atomic Energy Commission will provide support for this mission oriented area, as well as for some of the basic backup research needed.

The recent development of an ultracentrifuge capable of separating large quantities of particles in nearly pure state opens up an avenue for exploration of whether viruses are involved in tumor formation and in the development of other kinds of anomalies. This technique makes it easily possible to obtain large quantities of materials to study the properties of viruses per se, and when coupled with the abilities extant in the Oak Ridge National Laboratory for separating large quantities of macromolecules like specific messenger RNA's, etc., the Oak Ridge complex has an almost unique ability to move rapidly in this important area.

The lesions which viruses cause, the role of passenger viruses or carrier viruses in infection, the exploration of possible mutagenic effects of viruses and the manner in which portions of the virus genome get incorporated into the genome of the experimental objects are problems needing immediate attention. This latter approach, in particular, when fully explored could have tremendous potential for therapy since if an individual were lacking a particular enzyme to carry out a specific metabolic step, and a particular passenger virus was known to carry the information for the synthesis of such an enzyme (whether as an integral part of the virus or transductively), then the virus could be used to supply the lacking genetic information in these individuals.

It is known at this time that chemicals and their carcinogenic action are sometimes related to a joint action with viruses. A strong program to explore such parameters of interaction is needed. It is clear that a program in virology is going to be developed at Oak Ridge, and the added support of the NIH would help to make this one of the strongest programs in the country--a program which would contribute to the needs of both the Atomic Energy Commission and the National Institutes of Health.

A specific area that must be explored in addition to those outlined above relates to comparing the metabolic activities of normal cells (mammalian, microbial, plant, insect, etc.) with its virus-infected or diseased counterpart, so as to determine the specific lesion or lesions present in the diseased cell. Once these are known it will be possible to specifically treat the diseased state in many instances. Indeed

in the foreseeable future, this may be the only hope of providing specific therapy for neoplasia regardless of cause and of therapy for virus diseases in general.

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VIROLOGY RESEARCH

	FY 1966	FY 1967		FY 1968		FY 1969		FY 1970	
Biochemical Virology	50	90	150	150	250	200	300	400	450
Mutagenic Effects of Viruses	50	70	100	150	200	160	300	250	400
Comparative Biochemistry of Normal and Virus-Infected Cells	50	90	150	110	250	250	500	500	750
Genetic Manipulation of Virus Genome	50	50	100	90	200	120	300	250	400
Minimum	200	300		500		730		1400	
Optimum			500		900		1400		2000

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DEVELOPMENTAL BIOLOGY AND TERATOGENESIS

The Biology Division of the Oak Ridge National Laboratory has become deeply involved during the last four years in studying the normal biochemical and physiological processes which occur from the time of fertilization of the egg until the individual reaches full maturity. The studies conducted thus far range from those along the more classical lines of the physiology of embryological development to ones involving the specific enzymes which appear during development and how the synthesis and activity of these proteins are regulated by specific genes in the chromosome and the role of hormones in further modulating the processes involved in differentiation. Studies involving the effect of radiation and chemicals in inducing a teratological state have also been conducted. In addition, the way and rate at which the immune system is formed and how its effectiveness changes as a function of the degree of differentiation of the tissue and of the age of the individual have been explored.

While the Atomic Energy Commission will support a sizable effort in this area over the next several years, this area seems one particularly favorable for interaction with the National Institutes of Health. The programs envisioned would explore the physiological, biochemical, genetic and biophysical aspects of development, particularly those many processes which are involved in differentiation, and the mechanism of gene control. One aspect of this work would involve an extension of the present study on a unique class of nucleic acids found in the egg, with respect to the role of these compounds as modifiers or controllers of gene function during differentiation. In addition, there are already ongoing programs in hormonal control of gene action, factors controlling eye differentiation, and a new program on the biochemistry of differentiation starting July 1, 1965. This group offers great potential for rapid expansion. An additional program would be concerned with the modification of orderly control by various environmental factors such as radiation, chemicals, or viruses to lead to a teratogenic state. Out of such studies should come an understanding of the various processes leading to development of a completely normal individual and how these are altered by various factors to lead to the abnormal. From this understanding it should be possible to actually devise measures to negate the cause of the anomaly.

A particular area sorely needing further exploration is one we have chosen to call developmental pharmacology or the pharmacology of development, i.e., studies of the teratogenic effects of chemical agents and drugs used routinely in medicine on the development and differentiation of mammals. Such a program would include a determination of the relation between structure and activity of the teratogenic agent, of the location of the cellular binding site, of the chemical or physical nature of the binding, of the relationship of these parameters to the teratogenic effect, etc. Such studies can make use of the physical scientists, engineers, and technologists in Oak Ridge who have been cooperating with our biologists in the separation of various cellular components — a cooperation not existing to any large degree elsewhere.

DEVELOPMENTAL BIOLOGY AND TERATOGENESIS

	FY 1966		FY 1967		FY 1968		FY 1969		FY 1970	
Basic Developmental Biology	150	300	300	600	450	900	700	1000	900	1100
Pharmacology of Development and Differentiation	200	300	300	600	450	800	800	1000	1000	1200
Minimum	350		600		900		1500		1900	
Optimum budget		600		1200		1700		2000		2300

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MATHEMATICAL AND CHEMICAL-PHYSICAL BIOLOGY

The well-established biophysics program will be broadened to include additional physical and physical-chemical techniques together with both theoretical and practical mathematical treatments of data. This program will be directed toward an understanding of how the structure and conformation of macromolecules and particles are related to their biochemical and purely biological properties. For example, we have recently turned up the first evidence available concerning mechanisms of enzymatic repair at a molecular level, and now a wide variety of chemical and physical methods have to be exploited in these studies to gain a reasonable understanding of the detailed mechanisms involved. It is crucial to have a detailed analysis at the molecular level so that the therapeutic measures which have to be designed to take care of various kinds of insults to the biological systems can have their basis at the same level in the molecular mechanisms involved.

We are just beginning work in the very difficult field of X-ray diffraction analysis of macromolecules. Additionally, recent experiments at Oak Ridge by Levy and associates elegantly demonstrate the ability of neutron diffraction techniques to determine the complete structure of small biological molecules and there is a good possibility that sophisticated data collection techniques will permit neutron diffraction analyses of macromolecules. Coupling this technique with that of X-ray and electron diffraction and computer programming offer unique possibilities for biology. These new techniques, coupled with our research in the field of high resolution electron microscopy and radioautography, yield important information on the structure of DNA, the modes of replication and recombination of DNA, and begin to show us how radiation, chemicals, and virus infections on the one hand, and repair mechanisms on the other, affect structure and function.

Theoretical, physical, and mathematical studies will be needed to gain a reasonable insight into the intramolecular forces involved in these mechanisms; theoretical and practical treatments of diffusion problems are basic to many of these studies.

	FY 1966		FY 1967		FY 1968		FY 1969		FY 1970	
Mathematical Biology	70	140	120	195	180	250	250	400	400	600
Chemical-Physical Biology	200	300	250	450	310	550	400	650	450	750
Minimum	270		370		490		650		850	
Optimum		440		640		800		1050		1350

HEALTH RESOURCES RESEARCH - CONTAINMENT

Rapid progress in the fields of virology and viral cancer research requires a concerted attack and the solution of many complex problems of "containment." The hazardous manipulations involved in concentrating large quantities of infectious viruses and of working with oncogenic viruses merit serious consideration. On the other hand, long-term animal experiments in virus cancer work involve an additional consideration, and that is the protection of these animals during their life span against outside infection, particularly viruses.

The technical and development division in Oak Ridge have had a long experience which bears on both of these principal problems. There has been at Oak Ridge an active program for the past two years in developing contained virus processing systems under the joint NIH-AEC zonal centrifuge program. The development of proper containment facilities for handling animals during life-span viral cancer work can use the resources of a large group of individuals in Oak Ridge who pioneered the development of special containment methods to handle radioactive gases and other highly toxic materials in controlled atmospheres. Equally important is the fact that the animals and methodology are already available here for virological containment research as a result of our studies with "germ-free" mice over the past three years. The technical and development divisions in the three Oak Ridge installations that contribute to the solution of these kinds of problems have a combined force of scientists and engineers totaling 766 people with an additional staff of 522 experienced technicians.

We need not only to estimate the particular hazards and ways of protecting research personnel and the experiment, but also to develop "unit" types of containment equipment which will yield a maximum amount of flexibility - for operation as well as for updating of design and construction. Within our present AEC program, we are already involved in the design of "unit containment cells" for a long-term life-span studies involving virus and radiation interaction. We make use of our experienced biological staff in the design and testing of new containment units. We fully expect that the enormous cost of large-scale facilities for handling the life-span studies can be drastically cut by devising "flexible unit type containment cells."

It should be noted that the "biohazards evaluation" is automatically built into the entire operation here in Oak Ridge in connection with any virus work, all the way from design of instruments and facilities through operation. The Biohazards Committee has the continuous advice of outside consultants such as Dr. Joseph Melnick of Baylor University and Dr. Alexander Langmuir, Chief of the Epidemiology Branch, USPHS, in Atlanta.

These combined skills and long experience can be brought together in an accelerated program to (A) further develop the completely contained virus laboratory operations, and (B) develop fully contained long-term animal and virus culture facilities.

HEALTH RESOURCES RESEARCH - CONTAINMENT

	FY 1966		FY 1967		FY 1968		FY 1969		FY 1970	
Centrifuge Containment	200	400	250	450	350	500	250	300	200	200
Small Facility for Gnotobiotic and Non-Gnotobiotic Animals	500	1000	800	2000	1000	2000	1000	1500	1000	1000
New Approaches to Animal Care, Virus Handling, etc.	150	300	200	300	250	300	300	300	300	300
Larger Facilities for Environmental Studies, i.e., population studies using ecosystems, etc.		0	200	500	350	1500	500	1500	800	2000
Minimum	850		1450		1950		2050		2300	
Optimum		1700		3250		3800		3600		3500

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HEALTH RESOURCES RESEARCH -

CENTRIFUGE DEVELOPMENT PROGRAM

A joint program for conversion of gas centrifuge technology to liquid phase centrifuge technology was initiated in 1962 between the Atomic Energy Commission and the National Cancer Institute with the work being conducted at Oak Ridge in the Biology Division of the Oak Ridge National Laboratory and in the Development Division of the Oak Ridge Gaseous Diffusion Plant (ORGDP). This joint program has led to the development of a number of low and intermediate speed zonal centrifuge rotors capable of separating various kinds of cellular and subcellular materials from other substances in the cell. The most promising development has been the demonstration that large quantities of virus-like particles can be separated in an essentially pure state from the other cellular debris.

Every attempt is being made to transfer the technology as it is developed to biological researchers and to private industry. One formal training course and information meeting has been held to acquaint researchers with the potential of the instruments; a number of centrifuges have been made available to research laboratories both in universities and in private and governmental research laboratories. In addition, blueprints are being made available to industry as rapidly as the usefulness of the new rotor systems are determined, in order that industry can supply them for purchase to whomever needs or desires them. The program has now reached a stage of maturity such that a broadened and better defined overall program is recommended.

Such a program would be constituted of a number of functional but still quite integrated parts divided somewhat as follows:

A. Rotor and Centrifuge System Development. The activities hereunder would continue to be directed toward producing workable prototype rotors which could be used routinely by biological and medical researchers. Such systems would range from those separating large quantities of materials at intermediate speeds (50,000 x g) either on a continuous flow or batch basis, to those centrifuges which could be used for very precise molecular weight determinations at ultrahigh speeds (1,200,000 x g). Such activities will involve the development of new and/or modified bearing systems, high strength materials, etc., as well as the development of the auxiliary systems and techniques for recording and interpreting results.

B. Biological Need and Evaluation. This program would tie in intimately with Program A outlined above. It would provide the initial biological criteria for developing the rotors and centrifuge systems and would provide the means for initial testing of the usefulness of the developed systems. Once the separations performed herein had become rather routine they would be shifted to Program C. Some biological research would be done in those interim periods when rotors were not being actually evaluated.

C. Separations Process Evaluation Laboratory. Use of the developed centrifuge systems to perform separations of many types of materials in order to determine the full potential of the systems would be carried out. Such an activity would involve the active participation of various kinds of scientists interested in knowing whether the centrifuge would be useful for their particular separations problems. In addition, once small scale separations had become routine in Program B, they would be shifted to this program for scale-up in size of separation, for improvement of techniques, for adapting to routine separation of large quantities of materials, etc. In those cases where it is either not feasible or is not desirable to undertake separations in Oak Ridge facilities, it may be necessary to loan rotors, centrifuges, centrifuge systems, etc., to others.

D. Interim Fabrications. In cases where industry is not yet capable of manufacturing such equipment, it may be necessary on an interim basis to actually manufacture and sell centrifuge equipment while a capability is being developed by private industry to take over the production. Presumably, this type of activity would be carried out on a full cost recovery basis.

E. Training and Research Assistance Program. To bring about an effective transfer of the developed technology, it will be essential to have several types of training programs: (1) "Visiting scientist" program, wherein individuals come and spend from two months to a year or more working on a particular problem utilizing the equipment on hand at Oak Ridge. (2) The "short course" approach would involve actual instruction in the theory and laboratory experience with the various kinds of rotor systems. Such courses would last approximately two weeks. (3) Information meetings. These would be two-three day meetings held two or three times per year for those individuals and industries interested in keeping abreast of the present state of the technology.

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HEALTH RESOURCES RESEARCH -

CENTRIFUGE TECHNOLOGY PROGRAM

	FY 1966		FY 1967		FY 1968		FY 1969		FY 1970	
Rotor and Centrifuge System Development	600	800	600	850	650	875	650	900	700	925
Biological Need and Evaluation	300	350	300	375	325	400	350	425	350	450
Separations Process Evaluation Laboratory	200	200	200	250	225	275	250	300	275	325
Interim Fabrication	100	100	100	100	100	100	100	100	100	100
Training and Research Assistance	150	150	175	175	200	200	200	200	200	200
Minimum	1,350		1,375		1,500		1,550		1,625	
Optimum		1,600		1,750		1,850		1,925		1,990

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HEALTH RESOURCES RESEARCH -
BIOTECHNOLOGY AND BIOMEDICAL ENGINEERING

In recent years an active program has been instituted in Oak Ridge to adapt AEC developed technologies and capabilities to tools useful in biological research. These capabilities exist in the Chemical Technology, Analytical Chemistry, and Instrument Development Divisions of the Oak Ridge National Laboratory, in the Technical Division of the Oak Ridge Gaseous Diffusion Plant, and in various divisions of the Y-12 Plant. Several general classes of problems are being actively attacked: (a) development of physical and chemical methods for separation of subcellular organelles, viruses, macromolecules, and low molecular weight, organic constituents of cells, (b) development of new detection or assay systems to monitor the separations achieved, (c) development of automated methods for routine assay of enzyme activities, etc. For instance, recent successful developments include an automated nucleotide-nucleoside analyzer, a system for automated analysis of sugar mixtures, a system for the high resolution fractionation of soluble tissue proteins, a device for determining total carbon in solid samples in the 10^{-9} gram range, etc. These techniques are in addition to the successful centrifuge development program outlined elsewhere and the development of centrifugal techniques applicable to separation of low molecular weight substances on the basis of crystal density, a new approach which appears to offer outstanding possibilities.

In addition to the above, the Chemical Technology Division has developed a new method for the purification and separation of transfer RNA and has set up a special laboratory in which it will soon be possible to isolate some of the transfer RNA's in large quantity and in a reasonably pure state; the starting material for such a difficult project consists of many kilogram quantities of bacteria produced in our own pilot plant. For the next few years this group will attempt separations of various other important biological molecules such as enzymes, proteins, nucleic acids, etc., which will permit sequence analysis and physical studies aimed at elucidating and relating structure and function. Also, the technologies available in chemical processing, including liquid-liquid separations, chromatography, dialysis, electrophoresis, and radiological and sterile containment, would be applied to the processing of biological materials.

A broadening of these efforts to other biological problems and extension to medical applications will be of considerable benefit. There are many areas in which the biological and medical scientists are unaware of the large benefits which result from combining biological skills with adequately engineered biomedical research equipment and procedures. This kind of effort is fruitful only when the needs of the biologist are made known to the engineer and physical scientist and the necessary follow-up improvement takes place. This project would allow for expansion of the biomedical engineering work, and would assure that benefits similar to those now being realized by limited groups in the NIH and elsewhere would be available to many others in the health field. In addition, a cooperative effort between the Oak Ridge groups and universities training students in biomedical engineering will aid to offset the shortage of trained personnel in this field.

HEALTH RESOURCES RESEARCH -

BIOTECHNOLOGY AND BIOINSTRUMENTATION

	FY 1966		FY 1967		FY 1968		FY 1969		FY 1970	
Separations Methods for Macromolecules	200	375	500	725	750	1,100	900	1,200	1,100	1,300
Automated Analytical Methods	90	105	120	145	150	210	200	240	225	275
Bioinstrumentation	150	250	250	350	350	450	450	550	550	750
Pilot Plant Operations	175	250	250	350	300	500	400	500	425	575
Minimum	615		1,120		1,550		1,950		2,280	
Optimum		980		1,570		2,260		2,490		2,900

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Section V

Capital Construction Needs

Present and Future

OUTLINE

Introduction

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(b) Interim partial solution
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3. Total GPP Requirements (including non-construction)

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Introduction

The present laboratory and animal quarter facilities for our AEC programs are already overcrowded. A space survey conducted by the Engineering Departments of both the Oak Ridge National Laboratory and the Y-12 Plant has demonstrated that our research laboratory space is already overcrowded to the point where there is a deficit of about 27,000 net sq. ft. at the present time (as we enter FY 1966). It appears obvious that the Biology Division of the Oak Ridge National Laboratory needs substantial new research laboratory space in order to continue its successful programs and to branch out into some of the new and important fields that are discussed below. As a matter of fact, the advent of the new joint AEC-NIH cooperative program has crowded us even further. The new laboratory facilities which are being constructed now in Bldg. 9211 with AEC funds and equipped by the NIH will not nearly take care of the laboratory requirements for the NIH portion of the program over the next three to five years.

The first new laboratory research building, if approved in FY 1967, could be made available to us as finished construction only by calendar year 1969. This means that we have an enormously difficult and very expensive interim period of several years, during which we have to move small sections of office space, certain administrative activities, chemical stores and other similar things to temporary structures in the vicinity of the Biology complex in order to gain some 20,000 net sq. ft. of space for laboratories within Bldg. 9207. This, unfortunately, is still only a fraction of the space needed by calendar year 1969. For the interim period of at least four years before the first new laboratory research building could be made available to us, further cramping will result because the Information and Control Building could not be funded in FY 1966.

New facilities are urgently needed in order to recruit and to retain outstanding scientists for research in some of our own fields that are already becoming increasingly important and exciting, such as developmental biology (basic biological studies in genetic and other causes of developmental physical and mental defects), viral-cancer-radiation interrelationships, biochemical genetics, control mechanisms in living cells connected with normal and cancerous growth, bioengineering, and so on.

Normal progress in our unique large-scale mission-oriented experiments such as the mammalian genetics program, studies on the somatic effects of low levels of radiation and radiation-induced leukemia, intensified efforts in the new interagency co-carcinogenesis study, and the vital supporting basic investigations in genetics and biochemistry will be severely hampered if new space cannot be made available in the immediate future. Furthermore, we are at present unable to follow exciting experimental leads, many of them having potentially great practical significance. Lack of space has caused our important postdoctoral training program to reach its limit. We have at present some fifty individuals at the postdoctoral level in training, both from this country and from abroad.

Space requirements for both laboratory research and animal facilities, interim emergency steps, and requirements for research supported by other agencies are discussed in the following sections. It will be seen that the "research laboratory" requirements (in addition to special animal facilities) for both the AEC and NIH supported activities in the Biology Area will require by FY 1970 four of the $6,000,000 research laboratory increments.

* * * * * *

A. Facilities for AEC Programs

1. Laboratory Research Space

(a) Present and increasing deficit

Table 1 shows that there is already a deficit in research laboratory space. Recent surveys by the Engineering Departments of both the X-10 and Y-12 Plants show that we are short right now about 27,000 net sq. ft. of laboratory research space. As discussed in Section C below; the estimates of space deficits in Table 1 take into account only the space requirements for the AEC programs which do not involve extensive animal quarters intermixed with research laboratory space; hence, space for the programs of Dr. Upton and Dr. Russell are not considered here. By FY 1970 (calendar year 1969), the deficit will have risen to ~~108,000~~ 117,000 net sq. ft., which is equivalent to over two and a half buildings the size of the research laboratory building we have requested in the FY 1967 budget. That single building, if approved, could not be constructed and ready for occupancy before calendar year 1969.

The interim solution discussed below can at best take care of less than twenty per cent of the ~~108,000~~ 117,000 net sq. ft. deficit.

(b) Interim partial solution

The engineering surveys show that we can recover 20,000 net sq. ft. of space within Bldg. 9207 by moving out of the building every single function which does not require laboratory services, such as the Editorial Office, the Biostatistics Group, the stock room, and so on. It is quite significant that the space to be released in Bldg. 9207 is "prime laboratory space" because this building already contains all of the service lines and special drainage systems needed for laboratories, and is therefore already worth a substantial number of dollars to us before we begin to convert that space to laboratories.

Consequently, a detailed survey of possible moves and relocations has been accomplished by the Y-12 Engineering Department. The Y-12 Plant is building from their own funds an inexpensive block building to house the stock room and other functions; X-10 has approved GPP funds to construct an addition to the small office annex which was built last year, which will then be able to house the Editorial and Budget offices; the Biostatistics Group will move to a temporary wooden building near the Biology complex.

From 1965 GPP funds, X-10 has approved $340,000 with which we can begin construction of laboratories in some of the space which is being vacated. All of the laboratory moves are being planned with close attention to the long-term utilization of space by groups within Bldg. 9207; that is, we are attempting to clear space in certain sections of the building so that those groups that we feel will eventually require rather large amounts of laboratory space confluent with their present operation will eventually have it.

To convert the available 20,000 net sq. ft. will require over $1,000,000 of ORNL GPP funds over the next two to three years.

It is not only very expensive to accomplish a reorganization of laboratory space bit by bit as we have planned here, it consumes a very substantial amount of time of the Associate Division Directors, uses significant amounts of our operating funds for engineering planning studies, and is enormously difficult on the research personnel involved. Nevertheless, we have no choice but to try to gain as quickly as possible as much of the 27,000 net sq. ft. deficit as we have already incurred.

It is also important to understand that the Information and Control Building, which was not approved in FY 1966, would release an additional 5000 feet of "prime laboratory space" within Bldg. 9207 by use of that space which is now occupied by the presently deficient lecture room and library.

In Table 2, Part B, the second and third items refer to GPP funds required to convert the vacated space in Bldg. 9207. It is obvious that this type of "make do" is using and will continue to use enormous amounts of GPP funds.

(c) Long-range needs

Table 1 shows that the needs for the AEC programs (non-animal) through FY 1970 will require the equivalent of two and a half of the $6,000,000 research laboratory increments. The deficit in space becomes even more acute when one considers the research supported by other agencies discussed below.

From the long-range point of view, it is painfully obvious right now that we are several years behind in the laboratory construction program, and at a very crucial time in the history of this Division. Our research is not only recognized by the outside world for its excellence, but there has been a large upsurge of interest of agencies in addition to the AEC to capitalize upon the particular organization of interrelated basic and mission-oriented projects in progress here. In addition, recent events have demonstrated that outside institutions are interested in hiring some of our best people. With the advent of even more crowded conditions and no new laboratory research space to look forward to, it will become increasingly easy for other laboratories to lure our top people away.

Finally, it can be mentioned that the Biology Division of the Oak Ridge National Laboratory has never had a new general research laboratory building at its disposal. Over the past nineteen years, this Division has solved its physical space problems by remodeling piece by piece the inside of an old abandoned chemical processing building in the Y-12 area that was originally built in 1943.

2. Animal Facility Requirements

It appears that a large sum of money can be saved in the construction of certain types of animal buildings. A case in point is the "Animal Production Building" which is listed as the sixth item in Table 2, Part A, at $2,500,000 in FY 1968.

Long experience in the design, construction, and operation of animal facilities has amply demonstrated that drastic innovations in design and construction methods are needed. Not only have the past animal facilities been very expensive, but by the time they are built and in full operation they are approximately three to four years behind the state of the art; consequently, many changes are needed which are relatively impossible to accomplish because the facilities are built out of concrete and steel. A serious study of this situation has revealed an excellent possibility which may allow us to build such facilities at a much smaller total cost, while keeping the design and construction in such a state of flexibility that changes can relatively easily and inexpensively be made at any time.

It is pertinent to this point that the NIH has similar problems and interests, and beginning in FY 1966 will support an "animal containment technology" development program in the Y-12 Technical Division. The Biology Division will cooperate closely, and provide guidance and consultation, and, in addition, do the biological testing and experimentation required for the developmental work.

It is proposed that a warehouse-type building be built from ORNL GPP funds in FY 1966. In that year, and in each of the two succeeding years, we would plan to put approximately $100,000 into design and construction of modular units to go inside the building, and to contain the animals. If the design criteria are subsequently changed as the building is being completed inside, it will be a simple matter to remove any of the modules and replace them with ones of better design. This type of building will probably be used to produce pathogen-free animals, and if it were to turn out that one cell or module became badly contaminated, it would not be a very drastic procedure to simply remove the entire cell in question.

If such an approach proves feasible, it is expected that the whole art of animal facility construction as known at present will be drastically revised.

A similar type of construction could be used for the Mammalian Genetics Building, listed in Table 2, Part A at $2,500,000 in FY 1969. A substantial portion of this space is planned for research in mammalian chemical mutagenesis.

B. Additional Facility Requirements for Work Supported by Other Agencies

For the research projected in joint research programs with the NIH through FY 1970, it will be necessary to have available approximately 85,000 net sq. ft. of laboratory space. This space is not included within the requirements shown in Table 1 (AEC research). These programs are projected at $8,500,000 on the "A" budget (minimum) in FY 1970, and include co-carcinogenesis (which will need more space by FY 1970 than is now being constructed within Bldg. 9211), virology research, developmental biology and teratogenesis, and mathematical and physical-chemical biology. All of these programs will be directly involved with current research going on in the Biology area, which is the principal rationale for the NIH support of this research.

After the construction of the first three floors of Bldg. 9211 is completed, we hope to gain an additional 9000 feet gross (6000 net sq. ft.) of space by extending upward three floors from the cancer-chromosome extension at the rear of Bldg. 9211. The total net laboratory space to be gained in Bldg. 9211 plus the extension will therefore be approximately 25,000 net sq. ft. (the third floor will be an animal farm). This will still leave a deficit of 60,000 net sq. ft. of laboratory research space required for the programs to be funded as discussed above. This is equivalent to one and one-half of the $6,000,000 research increments.

There are several other programs involved in the joint research operation, but it does not appear now that these will need special facilities in the Biology area. Under the heading of Health Resources Research, the containment program will best be carried out within a large open building that the Y-12 Plant could make available, and is some distance from the general Biology area. The centrifuge development work is being carried out at the K-25 location, and there is sufficient area for expansion there; the biotechnology and biomedical engineering will be carried out largely within the laboratories and facilities of the cooperating Oak Ridge divisions.

C. Notes on Basis for Space Requirement Estimates

1. The assumption was made that the areas occupied by the Mammalian Genetics and the Pathology and Physiology Groups contain sufficient "research laboratory" space for the next three to five years.* The net areas of these research laboratories plus animal facilities, as well as the sixth floor animal farm (total, 85,000 net sq. ft.), was subtracted from the total net laboratory research area of Bldgs. 9207 and 9210, leaving 63,000 net sq. ft. for all other research laboratory operations in Bldg. 9207.

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*Future "animal facility" requirements for these groups are discussed in Section A,2.

2. The operating funds and scientific man-year increments to FY 1970 for those two groups were subtracted from the Biology Division totals for that period; this made possible the calculations for the research laboratory space requirements ("cumulative new sq. ft. needed" in Table 1). The dollars and man years shown in Table 1, however, include the entire AEC operation.

3. An optimum space per scientist was found to be about 600 net sq. ft. from the engineering surveys in our laboratories of "good," "fair," and "poor" space conditions. This figure includes a scientist's share of his space in the laboratory, plus all of the special facilities attached to the group such as instrument rooms, dark rooms, chromatography rooms, and office space.

4. In calculating the present deficit, shown as 27,000 net sq. ft. in FY 1966, the 600 sq. ft. per scientist was used. However, the scientist has in fact only about 450 sq. ft., as the calculations do not take into account the fifty postdoctoral and other scientists who are not counted within our scientific man years.

5. The term "net sq. ft." as used in this analysis is that space of a research nature used directly by the scientists for purely research work such as the scientist's share of his laboratory, plus all of the special research facilities attached to the group, for example, instrument rooms, dark rooms, chromatography room, his office space, and certain animal quarters. The "net sq. ft." does not in this case contain such support space as conference rooms, lecture rooms, library, office space for administrative, editorial, or non-scientific operating staff, change rooms used solely by scientific staff, vaults, storage rooms, shipping and receiving areas.

TABLE 1

Operating Budget, Scientific Man Years, and Square Feet of Research Laboratory[1] Space Required
(AEC Programs only; $ and Sq. Ft. in Thousands)

Fiscal Year	$ and Man Years Include Entire AEC Operation[4]		Cumulative NEW Sq. Ft. Needed[2] Net[3]	Gross
1966	$	7,560		
	man years	197		
	net sq. ft.	63	27	41
1967	$	9,200*		
	man years	212		
	net sq. ft.	75	39	60
1968	$	11,500		
	man years	268		
	net sq. ft.	93	57	88
1969	$	14,700		
	man years	330		
	net sq. ft.	120	84	130
1970	$	18,500		
	man years	395		
	net sq. ft.	153	117	180

1. Present animal space not included; also, future specialized animal requirements treated separately.
2. Including also special facilities: cold rooms, dark rooms, etc.
3. --Important definition of "net sq. ft." is on preceding page (par. no. 5).
   --Includes the present deficit of laboratory research space (see text).
4. --The net sq. ft. in this column includes presently occupied laboratory space.
   --It does not include, however, 85,000 net sq. ft. occupied by Dr. Russell's and Dr. Upton's entire operations, nor the sixth floor animal farm.
   --The man years and dollars do include the entire AEC operation.
   --Important definition of "net sq. ft." is on preceding page (par. no. 5).

*The FY 1967 "189 budget submission" shows this total as 9,455, as it contains allowance for "B" budget items.

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TABLE 2

Proposed Construction: Line Items and GPP

($ in Thousands)

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Part A -- Line Items*					
Virus Control Building	1,360				
Co-Carcinogenesis Mammalian Isolation and Control Building	500				
Biology Research Laboratory and Information and Control Building		7,600			
Biology Research Laboratory			6,000	6,000	6,000
Virus Research Laboratory (convert inside of Bldg. 9208)			900		
Animal Production Building			2,500**		
Mammalian Genetics				2,500	
Totals	1,860	7,600	9,400	8,500	6,000

*GPP construction items and grand totals on next page.

**This line item can be replaced by warehouse-type building (GPP; FY 1966, 1967, and 1968); funds considerably less than 2,500 can develop flexible and cheaper facilities, as discussed in text.

TABLE 2 (continued)

Proposed Construction: Line Items and GPP

($ in Thousands)

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Part B -- GPP					
Specialized facilities for animals and plants (utility-type bldgs.***) --Note: figures for FY 1969-70 estimated from current experience	530	300	465	500	500
Conversion of non-laboratory space in Bldg. 9207 to laboratories	400	670			
Conversion of library and lecture room to laboratories					300
Construct 2nd, 3rd, and 4th floors above Cancer-Chromosome Lab., Bldg. 9211 annex (hopefully, NIH will furnish lab benches and equipment)		100	100	100	
Rework oldest laboratories in Bldg. 9207		100	100	600	700
Totals	930	1,170	665	1,200	1,500

***This type of construction, with all technical requirements reduced to an absolute minimum, will permit large savings in line item construction funds. GPP funds of a larger quantity than previously utilized will, however, be required.

TOTALS	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	GRAND TOTALS
Line Items	1,860	7,600	9,400	8,500	6,000	33,360
GPP Laboratory Construction	930	1,170	665	1,200	1,500	5,465
FISCAL YEAR TOTALS	2,790	8,770	10,065	9,700	7,500	38,825

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TABLE 3

Total GPP Requirements

($ in Thousands)

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	GRAND TOTALS
A. Non-Laboratory Modifications (GPP)						
General modifications (animal farm disposal system; elevator modification; ventilation and air conditioning rework; etc.) --Note: figures for FY 1967-70 estimated on current experience	348	448	535	400	425	2,156
Replace cooling towers				250		250
Totals	348	448	535	650	425	2,406
B. Laboratory Construction (GPP) (from Table 2, Part B)	930	1,170	665	1,200	1,500	5,465
A + B: TOTAL GPP	1,278	1,618	1,200	1,850	1,925	7,871

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TABLE 4

Total GPP Plus Line Item Requirements

($ in Thousands)

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	GRAND TOTALS
I. GPP						
A. Non-laboratory Modifications (from Table 3, Part A)	348	448	535	650	425	2,406
B. Laboratory Construction (from Table 2, Part B)	930	1,170	665*	1,200*	1,500*	5,465
Subtotal	1,278	1,618	1,200	1,850	1,925	7,871
II. Line Item Construction (from Table 2, Part A)	**	7,600	9,400	8,500	6,000	31,500
TOTALS	1,278	9,218	10,600	10,350	7,925	39,371

*These GPP laboratory construction items refer to rough engineering estimates to overhaul those laboratories in Bldg. 9207 that will be 20-25 years old, and to convert the remaining non-laboratory space in that building to laboratories. If the Commission prefers, for FY 1968, 1969, and 1970 conceptual design engineering can be accomplished to bind this into a line item request.

**The $1,860,000 authorized for FY 1966 is not included in this table.

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TABLE 5

Unusual Operating Expenses

($ in Thousands)

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970
Conceptual design reports, new line item facilities	28	114	141	127	90
Preliminary design and estimating, for proposals on GPP items	10	13	8	8	10
General engineering planning (space and area studies, etc.)	25	35	40	45	50
Sub-total, engineering and design	63	162	189	180	150
Minor building alterations and repairs, not applicable to GPP (spent $230,000 in FY 1965)	265	300	340	375	400
Totals	328	462	529	555	550

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Section VI

Brief History of

Biology Division

Oak Ridge National Laboratory

History

The Biology Division of the Oak Ridge National Laboratory was started in the fall of 1946 as a division of the Clinton Laboratories, which shortly afterward became the Oak Ridge National Laboratory. At that time the Biology Division consisted of the director and two senior scientists who worked in several small rooms in the rear part of the dispensary. In 1947 this Division was given a modest amount of laboratory space within an abandoned chemical processing building at the Y-12 site. Over the intervening years, with generous help and support from the Atomic Energy Commission every square foot of this large old building has become occupied by Biology Division activities. At the present time this Division consists of approximately 400 people, including the support personnel, and over 50 pre- and postdoctoral trainees. In regard to the AEC research programs, we are already very overcrowded and with no indication from the Commission of when positive action to alleviate this shortage will be taken.

In 1946 the Director wrote a report in which he envisaged basic work in biochemistry, cytogenetics, biophysics, physiology and radiobiology to support one or more larger mission-oriented programs in radiobiology. In anticipation of the importance of these general areas for an understanding and treatment of radiation damage, programs in radiation cytogenetics and the biochemistry of nucleic acids were among the first fields of basic research to begin. It turned out that this type of organization worked exceedingly well and continues to be the model around which the Biology research program has evolved during the last 18 years. And thus, during the past years in which the field of experimental biology has literally exploded with important basic findings on the genetics and biochemistry of inheritance, this Division has made some major contributions to these basic discoveries, and has made some very practical contributions as well.

Basic discoveries which have been made in areas of molecular biology, genetics, radiation pathology, biochemistry and biophysics are continuing to attract increasing numbers of topnotch investigators to these laboratories. Some of the major scientific contributions in other areas have resulted in practical applications. For instance, the very large-scale mammalian genetics program has given the National Academy of Sciences and the United Nations Scientific Committee some of the basic data for their reports on the genetic effects of atomic radiation (this work achieved here is internationally recognized as the authoritative work in the field). These large-scale experiments on the genetic effects of radiation in mammals were begun here in 1947. The initial experiments demonstrated that the maximum permissible dose level would have to be some 15 times lower than that which had been estimated from previous non-mammalian radiation data. Another significant and unexpected finding concerned the extreme sensitivity of the developing embryo during the very earliest stages of pregnancy; the damage to the embryos in the experiments carried out with pregnant mice were so severe even with very low doses of radiation that eventually the medical and dental professions recognized the danger of radiation and set limits for therapeutic and diagnostic x-raying with due regard for the critical times during the period of pregnancy, at a dose level and time consistent with our findings. It has been demonstrated in these laboratories that the radiation-induced leukemia depends upon the presence

of a virus which apparently can be transmitted through the placenta to the fetus. The well-known "oxygen effect" in relation to radiosensitivity was pioneered in the early days of this Laboratory; the presence of oxygen in the tissues was shown to enhance the effect of radiation, and in a practical way this phenomenon has been used to raise the effectiveness of x-irradiation in the treatment of certain tumors. The zonal centrifuge which has been so successful in banding virus and other types of particles was initially developed within the Cell Physiology Group in this Division, and subsequently large advances were made possible by collaboration with the Engineering Group at K-25, which had been responsible for development of the gas centrifuge for separating uranium isotopes. This program is now being supported generously by the National Cancer Institute as well as by the AEC. Substantial work in many other fields accomplished in these laboratories is also widely recognized, for example, methods of protecting animals against the effects of radiation, and much basic research at the cellular and molecular levels in the fields of genetics, biophysics and biochemistry. In the latter field, pioneering discoveries made in this laboratory paved the way for the more recent and exciting studies in this and many other laboratories on the genetic code.

In 1962 a major turning point came in the history of this Division. In that year the Director of this Division, the Director, National Cancer Institute, and the Director, Division of Biology and Medicine of the AEC discussed informally the possibility that the NCI would support a major program in this Laboratory in the field of co-carcinogenesis, i.e., the actions and interactions of radiation, viruses, and chemicals in the genesis of cancer. Additionally the possibility of a joint effort on the full development of a new type of ultracentrifuge was explored.

Such a joint effort in co-carcinogenesis was feasible, sensible and possible of attainment because the many types of basic and mission-oriented biological research carried out in the Biology Division apply directly not only to radiation damage, but also to the effects of pesticides, carcinogens, chemical mutagens, and other environmental factors or insults. The breadth and depth of our basic work would allow us to mobilize quickly around important pragmatic problems whether they be in radiation, cancer, or any other types of physical insults (such as carcinogenic agents and environmental factors)---phenomena concerning living cells and health. This is precisely why we are able to undertake the joint AEC-NIH studies on co-carcinogenesis with no change in overall objectives.

In 1962 further discussions were held with officials of the National Cancer Institute, which led to a formal agreement between the AEC and the NIH for funding and carrying out research, which is now well under way. For the initial interagency work planned two years ago, we have converted 10,000 sq ft of an empty building into functional laboratories. The remaining 40,000 sq ft of the same building are now under construction with completion estimated for March, 1966. The building remodeling and all equipment is funded jointly by AEC and NIH. The actions and interactions of radiation, viruses, and chemical agents in regard to cancer are the prime interests of the joint interagency program. These objectives are intimately tied in with those of some of the major AEC mission-oriented programs which have been under way

here in this Division for some time; for example, as pointed out above, our program on the somatic effects of radiation demonstrated that certain types of radiation-induced leukemia are caused by the presence of a virus, and these matters are under intense investigation here at present as this is exceedingly important to the business of the Atomic Energy Commission.

Because of our strengths in all areas of biology a number of the other institutes of the NIH have sought our collaboration. For example, the National Institute of Allergy and Infectious Diseases has entered into a contract with the AEC for our laboratory to isolate in quantity certain virus preparations.

This Laboratory is in a unique position, having a very strong program in fundamental biology tied in with a number of very important difficult, long-term mission-oriented projects. At the same time it is located at an installation where there exists some of the most important chemical, metallurgical, physical, and instrumental capacities that grew out of the work on reactors, chemical technology, isotope production, and weapons development. Only recently has the Biology Division been able to take even limited advantage of these resources; for example, in the last three years successful development of the density gradient centrifuge, and the cooperative projects with the Chemical Technology Division on the large-scale isolation of specific large and important macromolecules have come about. This cooperation is really only in its earliest stages, and a much broader cooperation between the Biology Division and the other Oak Ridge plants is visualized in the immediate future in the fields of biotechnology, virus containment facilities, virology research, and probably many others.

All of these things taken together mean that we can mobilize quickly to tackle and complete difficult, urgent, and practical biological missions of the AEC, NIH and other government agencies.

Section VII

Staff Accomplishments in Summary

1946 - 1965

ACCOMPLISHMENTS AND ACTIVITIES OF THE SCIENTIFIC STAFF

Many scientists on the Biology Division staff serve on editorial boards of scientific journals and study sections of granting agencies, and as officers of national and international scientific societies. A number of awards have come to members of this Division for outstanding scientific achievements, and, as a matter of fact, two staff members have been elected to the National Academy of Sciences on the basis of their scientific contributions accomplished in this Laboratory.

PUBLICATIONS

Attached is a bar graph (Table 1) showing the steady increase in Division publications since 1947. During the past five years 849 articles have been published in scientific journals, and Division members have presented 1,827 papers at scientific meetings. Members of the Division have, altogether, contributed dozens of chapters to various books on biological sciences during the past five years, and several advanced text books have been written by members of the Division.

In the past year the Division has taken over publication of the semiannually issued Microbial Genetics Bulletin. The proceedings of the quarterly bone marrow conferences have been published in the past in the journal Blood; however, the Mammalian Recovery Group of the Division has now started to publish the proceedings in a separate bulletin called Experimental Hematology. The second issue has just been published.

EDUCATIONAL ACTIVITIES

Attached is Table 2 showing the numbers of people who have received training at various levels in the Division since it began. Specific figures are given for the past five years. In addition to the training that has been received by investigators who work in the Division, scientists from the Division have taken leaves of absence from time to time to teach at the University of North Carolina, Duke University, Vanderbilt University, The University of Tennessee, Stanford University, the University of Georgia, and other universities. Under an ORNL-University of Tennessee cooperative program (sponsored in part by The Ford Foundation), staff members of the Division are now teaching at The University of Tennessee on a one-fourth time basis.

Various grants and other forms of financial support have made it possible for twelve investigators to spend approximately one year in laboratories in foreign countries where they have initiated new research programs and guided graduate students. Among countries visited by ORNL biologists have been Italy, France, Brazil, Israel, The Netherlands, Argentina, Japan, Chile, and Canada.

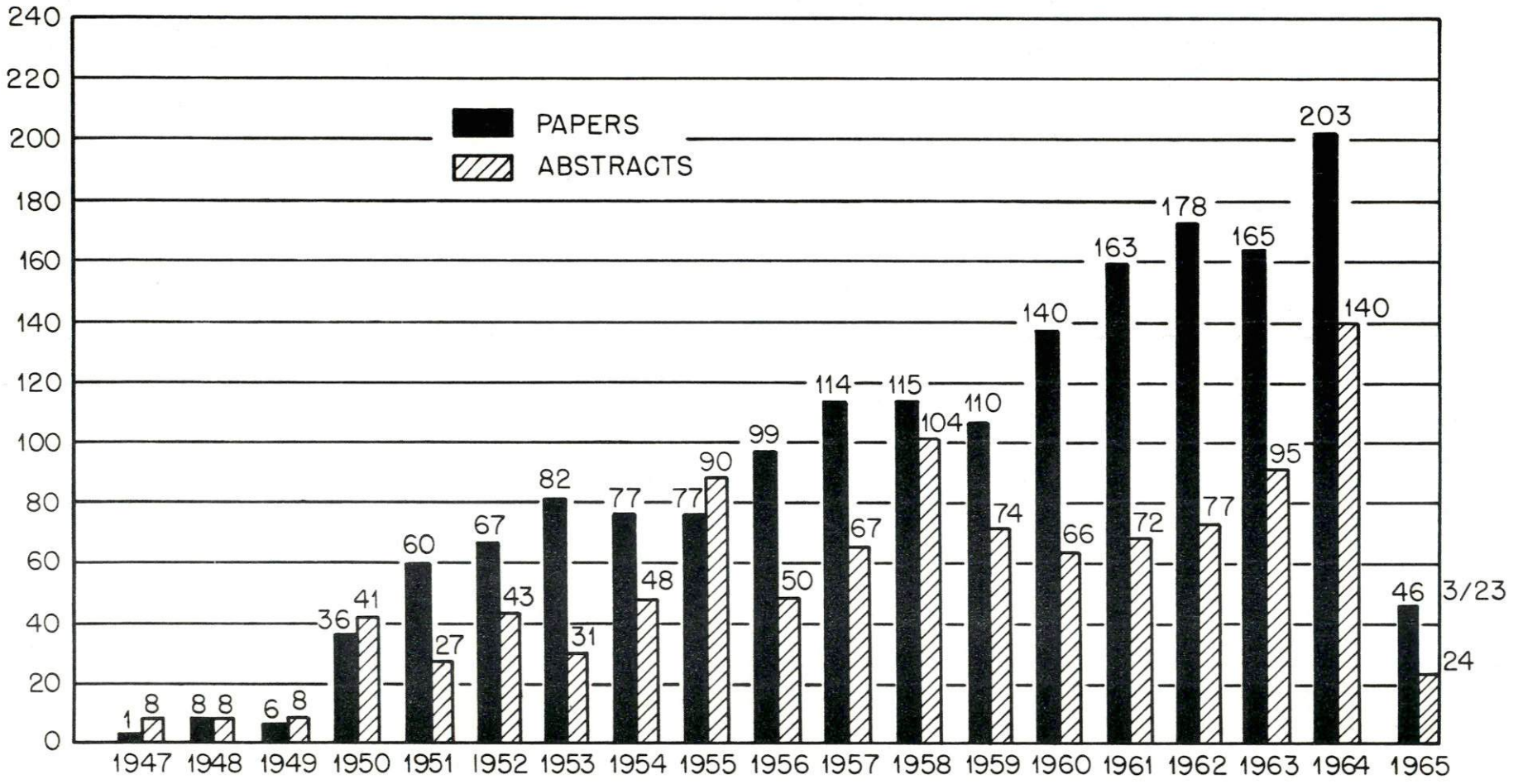
Division members also visit Southeastern colleges and universities under the Traveling Lecture Program, and approximately 242 lectures were given under this program in the last five years. Also, under the Small College Lecture program, staff members in the past three years have given 62 lectures.

Communication between individual scientists in groups is facilitated by informal luncheon seminars held daily. The groups holding regular seminars, some of them twice a week, are biochemistry, genetics, mammalian recovery, immunology, and others. A general seminar is held each Thursday afternoon, and a guest speaker is usually a visitor from another laboratory in the U.S. or abroad.

CONFERENCES

Aside from the manuscripts describing scientific research, several investigators have served as editors for proceedings of symposia which were jointly sponsored and organized by the Biology Division. Some of these are the conference on Comparative Effects of Radiation, Puerto Rico, 1960; Neurospora conference held in La Jolla, California, 1961; conference on Radiation Induced Chromosome Aberrations, San Juan, Puerto Rico, 1961; conference on Control of Cell Division and Induction of Cancer, Lima, Peru, and Cali, Colombia, 1963; and Genes and Chromosomes, Structure and Function, Buenos Aires, 1964. These conferences have been encouraged and supported in part by the Atomic Energy Commission and the Biology Division in an effort to strengthen our ties with Latin America. These conferences have in fact been extremely successful in furthering cooperative research between biologists of the North American continent and Latin America, and future conferences are being planned, the next to be held in Montevideo in 1965, and another is being planned for Mexico City in 1966.

The Division holds an annual research conference on a topic of current biological interest. The topic for 1964 was "The Molecular Action of Mutagenic and Carcinogenic Agents," the 1965 topic was "Hormonal Control of Protein Biosynthesis," and the 1966 topic will be "Differentiation and Growth of Hemoglobin and Immunoglobulin-synthesized Cells." Other small specialized conferences are held in the Division on such subjects as lens differentiation, blood platelets, bone marrow, photosynthesis, and others. We publish some of these, as mentioned above.



BIOLOGY DIVISION
PUBLISHED PAPERS AND ABSTRACTS

Table 2

Biology Division, Oak Ridge National Laboratory

Training Programs

	Total since Program Began	1960	1961	1962	1963	1964	Average per year 1960-1964
Postdoctoral							
Domestic	203	17	23	27	21	13	20
Foreign*	116	24	28	34	48	44	35
Predoctoral							
Thesis Research	43	3	5	5	6	5	5
B.S. Level and under	111	13	18	27	25	20	21
Visiting Scientists							
Research Participants	152	15	14	11	14	3	11
Sabbatical Leaves, etc.	75	4	4	7	4	3	4
	699	76	92	111	118	88	

*Countries from which they have come are:

Argentina - 6
Belgium - 5
Brazil - 4
Canada - 7
Chile - 3
China - 2
Denmark - 2
Egypt - 1
Finland - 1
France - 2
Germany - 9
Great Britain - 8
India - 3
Iraq - 1
Israel - 4
Italy - 19
Japan - 22
Korea - 1
Mexico - 1
The Netherlands - 3
Norway - 1
Pakistan - 1
Portugal - 1
Singapore - 1
South Africa - 2
Spain - 1
Sweden - 1
Turkey - 1
Uruguay - 1
Viet Nam - 2

June 10, 1965

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