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MONSANTO CHEMICAL COMPANY, CLINTON LABORATORIES

OUTLINE OF RESEARCH OF BIOLOGY DIVISION

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Alexander Hollaender, Director

December 1, 1946

The outline given below is a tentative one because it may have to be modified to a considerable extent, depending on the men who we will be able to obtain and the problems which may come up in the course of this work.

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Responsibility of the Director

It will be the responsibility of the Director of the Biology Division to organize a program on the basic problems of the effect of radiation on living cells. The Director at the same time will be the representative of the National Institute of Health at the Clinton Laboratories of the Monsanto Chemical Company and coordinate the work between the National Institute of Health and Clinton. It also will be the responsibility of the Director to establish cooperative studies with different universities and research institutions.

The Director will select and direct a permanent staff of biologists and biochemists which will reside at Oak Ridge. He will outline research along broad lines and supervise the investigators in a general way. He will rearrange the limited space available to biology at Clinton and arrange the space, in the temporary structure to be made available, as well as help to design the permanent Biology Building which is planned to be completed by 1951.

REPOSITORY Oak Ridge Opr. [redacted]
COLLECTION Records Holding area Doc. 1944-94
BOX No. H-108-5 Bldg. 2714-H
FOLDER Research + Medicine

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By Authority of VAR
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By M. R. THIESEN, ANALYSAS CORP. 1/12/95
Date
R P Anderson
JAN 24 1994

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General Outline

The major part of the work at the Biology Division of the Clinton Laboratories will concern itself chiefly with the basic aspects of the effects of radiation on living cells. The radiations used will be the ones available at Clinton as a result of nuclear disintegration in the pile, radiation emitted by substances irradiated in the pile, as well as radiation emitted by new sources like betatrons, Van der Graff machines, etc. Other radiations like infra-red and ultraviolet will be used to help us in the study of the mechanisms of the effects of ionizing radiation. The presence at Clinton Laboratories of excellent Physics, Chemistry and Health Physics Divisions will be most helpful in connection with the physical and chemical aspects of our work, for instance in the availability of radiation sources, the purity of radiation and energy measurements. It is hoped that a considerable part of the work of the Biology Division will be done in close cooperation with the above three groups.

It is hoped to take advantage of the facilities of the Chemistry Division in regard to isolation and purification, as well as to the chemical studies which this division is conducting in connection with the production of radioisotopes.

Most of the biological work done in connection with the Manhattan District until now concerned itself with the question of the tolerance dosages. Animals were used mainly in the work. The limited time available for preparing the raw materials for the atomic bomb made this type of study most logical. It is hoped to continue this work on tolerance in a limited way in the new Biology Division. However, the main effort will be shifted to more basic aspects of radiation work.

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The immediate problems to be attacked are:

1. What is the lowest dosage of Alpha, Beta, Gamma radiations, as well as x-rays and neutrons which will interfere with the normal function of the cell?

2. Will this effect be the same if the minimum energy is given in a fraction of a second or spread over many hours?

3. Is the effect the same if radiation originates outside the cell or if the radiation is emitted by liquids or gases within the cell?

The need for answers to these questions is quite urgent because the accepted dosage of 0.1r per day for human exposure may not be as safe as we would expect from the usual statements. This is mainly true for certain types of penetrating radiation, which may produce secondary radiation in blood-forming organs (See Failla). One of the most important reasons why the use of nuclear energy in industry will have to be slow is the problem of the maximum safe exposure. It might also be possible to reduce some of the protective measures which at present have been recommended in connection with the applications of nuclear energy. If we could reduce safely the protective wall around a nuclear energy power source, the expense of constructing such a power source would be considerably reduced. The problem of maximum safe exposure is at present a major Public Health problem in connection with the practical use of nuclear energy.

A concerted attack of the different sections of the Biology Division at Clinton will be launched on this problem.

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Program of Sections

It is planned to organize the Biology Division in the following sections: Biochemistry, Cytogenetics, General Physiology (Physical Chemistry), Physiology, Experimental Radiology and a Cooperative section. The planned activities and personnel for a minimum and standard staff of the sections follows:

1. Biochemistry

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|---|---|
| Minimum Staff: | Principal Biochemist<br>Biochemist<br>2 Assistant Biochemists<br>4 Technicians |
| Standard Staff: | Principal Biochemist<br>2 Senior Biochemists<br>2 Biochemists<br>4 Assistant Biochemists<br>6 Technicians |

The work in this section concerns itself with the effects of radiation on cell constituents. It has been found that it is possible to change the physical structure of certain types of nucleic acids by either x-radiation or ultraviolet without resulting in a noticeable change of the chemical structure of these compounds. Similar effects have been noticed in regard to proteins. It is planned to extend this work. The investigation of those compounds is considered especially important because they are the main constituents of living cells. The nucleo-proteins are the most essential structures of chromosomes and the nucleic acid appears to control the production of protein in living cells. The distribution and function of nucleo-proteins seems to be governed by certain types of enzymes. It is planned to make a very careful study of the effects of radiation on those enzymes.

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The ready availability of radio-active isotopes has made their use in the study of certain metabolic steps a very promising problem. It is planned to cooperate with the Chemistry Division in the preparation of compounds containing the radio-isotopes in a specific location in their structure, and to follow the metabolism of these compounds with the help of microorganisms.

It has been found in the studies which we have been conducting during the last few years, that during the process of irradiation of human serum certain changes take place which can only be detected by immunological technique It is planned to follow this lead especially, since it may give us a clue in the regard to radiation sickness as well as other early changes in the blood which cannot be detected by any other method.

2. Cytogenetics

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|---|---|
| Minimum Staff: | Chief Geneticist<br>Senior Cytogeneticist<br>Geneticist<br>4 Technicians |
| Permanent Staff: | Chief Geneticist<br>Principal Cytologist<br>2 Senior Cytogeneticists<br>2 Geneticists<br>2 Assistant Geneticists<br>5 Technicians |

One of the most profound changes which radiation produces in living cells if they survive exposure is in the chromosomes including the genetical make-up of the cell. As a matter of fact the genetical changes may appear a long time before any chemical indication of change will be noticeable.

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The genetical studies would be directed toward a study of the effects of different radiations on Drosophila, fungi, etc. The cytological approach would concern itself with changes radiation produces in the chromosomes, mitochondria and other constituents of the cell. One of the ideal materials to be used in this connection are Tradescantia chromosomes. Considerable information is available on this subject, but very much more work will have to be done to understand the radiation effect especially since it has been found lately that effects similar to the ones produced by X-rays can be caused by mustard gas.

It has been found that the function of the cell which is most easily interfered with by radiation is the rate of mitosis, i.e., the speed with which the chromosomes move. It is planned to use this first for the study of the effect of alpha radiation later to be followed by studies with more penetrating radiation.

The preliminary work we have done in connection with the above type of investigations at Bethesda would indicate the need for making those very important sections of the Biology Division which promise to give results in a relatively short time.

3. General Physiology (Physical Chemistry)

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|---|---|
| Minimum Staff: | Principal General Physiologist (Dr. Arnold)<br>Physiologist (already engaged)<br>2 Assistant Physiologists<br>4 Technicians |
| Permanent Staff: | Principal General Physiologist<br>Senior General Physiologist<br>2 Physiologists<br>2 Assistant Physiologists<br>6 Technicians |

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The general functions of cell growth, diffusion, osmotic relation, metabolism, energy relations as effected by radiation will be the subject of study in this field. Certain types of radiation have shown to effect the different functions of the dell differentially. Certain types of radiation affects the normal respiration of the cell; others, the function of cell division without having any immediate influence on respiration. Preliminary tests have shown that these effects are definite and clean-cut and definite for the different types of radiation. This problem is ready for immediate attack and should give interesting results.

There appears to be a close relationship between the calcium metabolism and radiation effects. This lead will be followed up.

There are certain energy relationships from which it appears that the living cell may be able to use some of the absorbed radiation as energy source similar as the green plant uses the sunlight in photo synthesis. The evidence is fragmentary and not too definite. It would seem worthwhile to follow it up.

4. Physiology

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|---|---|
| Minimum Staff: | Principal Physiologist<br>Physiologist<br>Assistant Physiologist<br>3 Technicians |
| Permanent Staff: | Principal Physiologist<br>Senior Physiologist<br>2 Physiologists<br>2 Assistant Physiologists<br>5 Technicians |

One of the obvious effects of overexposure to penetrating radiation is the change in the blood picture of normal men. It appears that the blood forming organs are also changed by overexposure. The immediate task

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of the physiology group will be the study of the effect of radiation on different constituents of the blood. Special methods for the study of bone marrow will have to be developed.

Basic aspects of the physiological function of the cell could be studied more easily with lower cells: bacteria and fungi. Also viruses may give more detailed information of radiation effects. The Director's previous experience with this subject will make possible the immediate study of this field. It is planned to obtain the service of an experienced mycologist with some physiological background.

A line of work which is of considerable promise is the use of radioactive isotopes in certain metabolic processes which will give us information in regard to the function of radiation.

The work with microorganisms is the most promising one as far as quantitative aspects of radiation work are concerned. It is here where cooperation with the Health Physics group would be most promising. It is expected that the work with microorganisms will give results in a relatively short time.

5. Experimental Radiology

Present Staff: Chief Experimental Radiologist
2 Zoologists
2 Assistant Zoologists
10 Technicians

The Experimental Radiology section is the only one which was functioning at Oak Ridge at the time the Director took over. Dr. Henshaw was in charge. He is the last of the biologists who were connected with this laboratory during the war. The work which Dr. Henshaw is conducting concerns itself with

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the determination of tolerance dosage and the damaging effect of pile radiation on whole animals. Especially has the work on high intensity beta radiation been most fruitful. It is planned to continue the work in tolerance dosage and beta radiation. A very limited amount of work will be done on the production of cancers by radiation. Other work which Dr. Henshaw has initiated is the effect of radiation on the work function of rats.

6. Cooperative Section - under the direction of the Biology Director

Minimum Staff: 3 Technicians

Permanent Staff: 2 Assistant Scientists
4 Technicians

The study of the effects of radiation requires not only a knowledge of the basic functions of the individual cell and the whole animal, but also a good understanding of the physical aspects of radiation energy, measurements, penetration, etc. The implication of radiation effects are so profound that it requires many disciplines to follow them up. It is not possible to have all the different disciplines included in a Biology Division. Cooperation will have to overcome the handicaps which limit the single worker and the individual group.

A. Cooperation with other Divisions at the Clinton Laboratories.

1. A major and essential part of the cooperation work will have to be with Dr. Morgan's group (Health Physics), as has been mentioned before. It is hoped that the cooperation with this group will be intimate enough to permit co-authorship on publications.

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2. The Chemistry Division has not only available plutonium as a source of radiation but also a variety of other radioactive compounds which might turn out to be very important in our work. The Physics group will have to advise and help us in connection with the use of the pile. The contact with the Medical group will depend on the interest of the men who will be connected with this group in the future.

B. Cooperation with the National Institute of Health.

The plan for the development of the Clinton Biology Division is based on the close cooperation with the different Divisions of the National Institute of Health.

1. The Radiobiology Laboratory which the Director has developed during the last nine years at the National Institute of Health will be maintained at Bethesda. Dr. Carlson and Dr. Zolle will continue their work with Dr. Hollaender's cooperation. Both of these men will become involved in the work at Clinton as soon as arrangements for space and equipment have been made.

2. It is hoped that the different members of the Industrial Hygiene Research Laboratory (Medical Director Paul A. Neal) will become interested in taking advantage of the opportunities at Clinton. For instance that Dr. Stannard and Dr. Horecker will use the general facilities at Clinton. This also applied to Dr. Yagoda, Dr. Hoppel, etc.

3. It is hoped that several members of the National Cancer Institute become interested in the possibilities at Clinton. Especially is it hoped for Dr. Andervont to take over the cancer aspects of this work. It is also

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hoped that Dr. Eschenbrenner, Dr. White, Dr. Greenstein and others become involved in cooperative work.

4. Similarly it is hoped that the Physiology and the Zoology Divisions become interested in the Clinton Laboratories.

C. Cooperation with Universities and Research Institutions.

The Director's close contact with several Universities and Research Institutions will be most helpful in setting up cooperation work with these different groups. Close cooperative arrangements exist with Johns Hopkins University Biology Department and Medical School, Washington University and the Carnegie Institution's Genetics Laboratory at Cold Spring Harbor. It is planned to establish similar relationship with Vanderbilt University and the University of Cincinnati and a number of other Southern Universities. Personal contacts with several investigators in these institutions will make cooperation very probable.

Conclusion:

The development of the Biology Division will depend very much on the space and facilities which may be made available at Oak Ridge for this work. The Director has found a wide interest and an intense eagerness of many outstanding biologists to join in the work planned at Clinton in connection with the basic aspects of the effects of radiation on living cells. It is believed that a carefully planned program in the field of Radiobiology will not only help to understand the effects of radiation, give us the material to set up safeguards, suggest measures to counteract radiation effects but also supply information in regard to the structure and function of living cells, the mechanisms of inheritance and many other aspects of basic biology.

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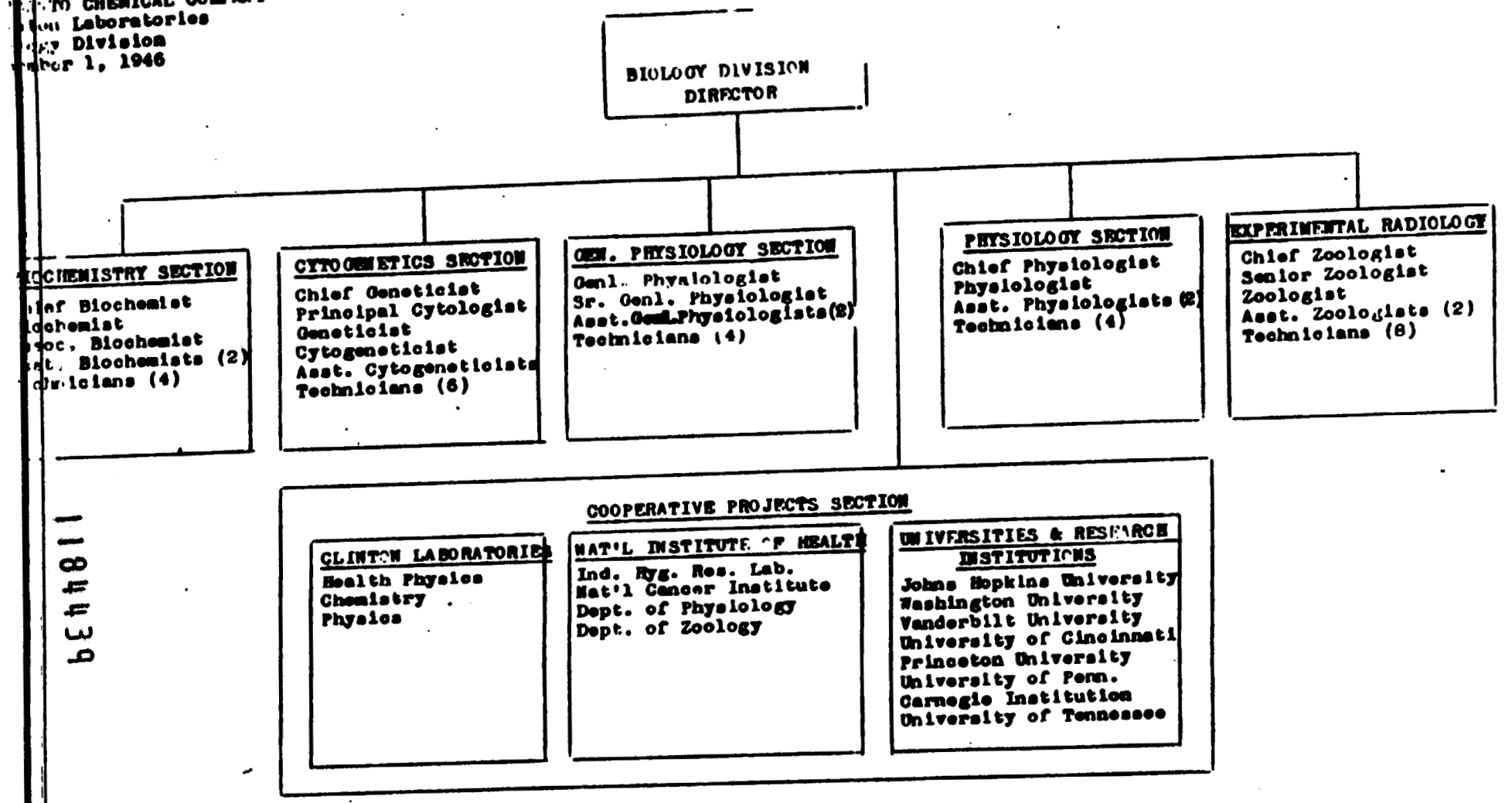


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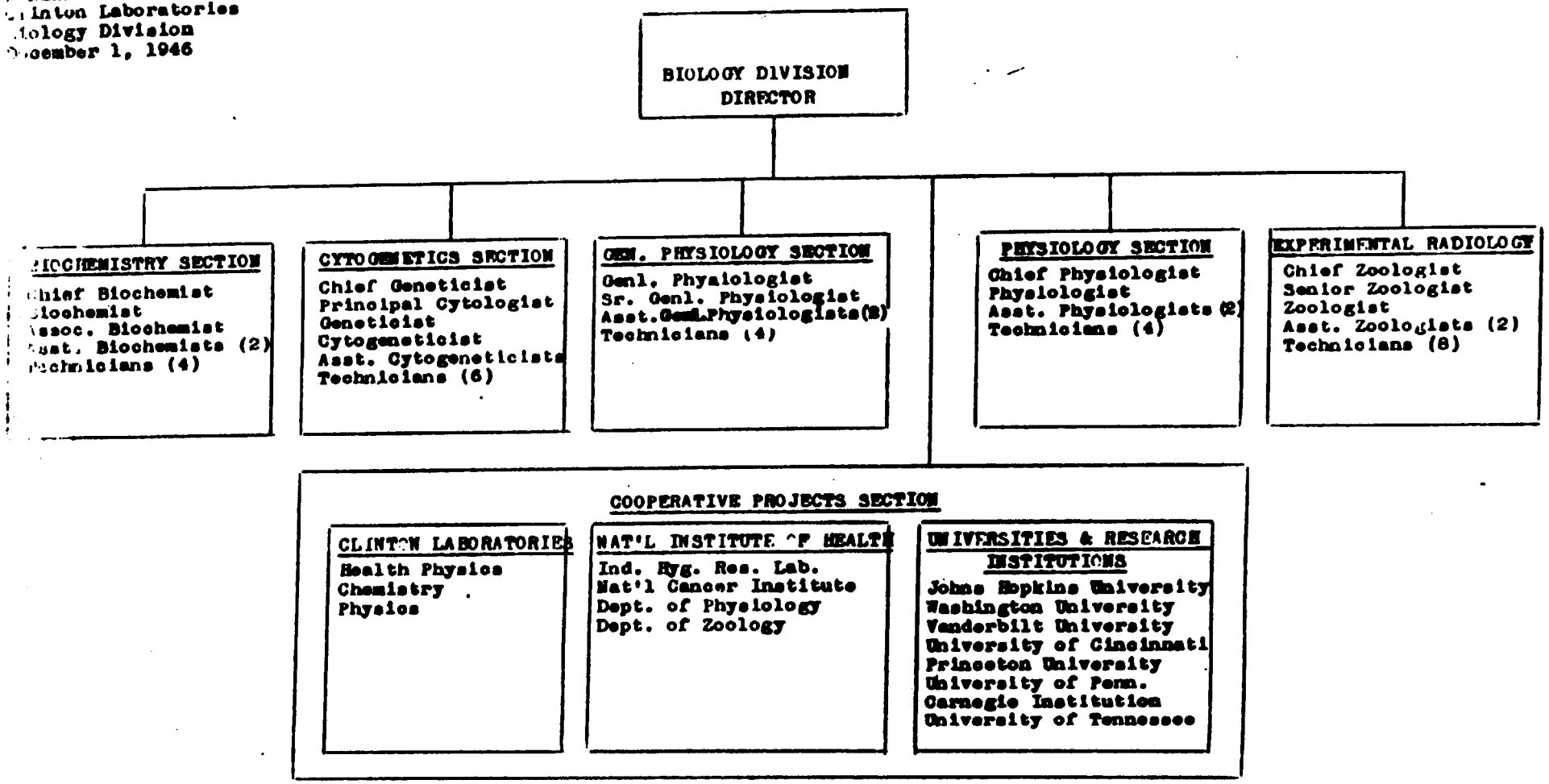
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Clinton Laboratories
Biology Division
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