Canadian Cancer Conference

Volume I

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Edited by

R. W. BEGG

Department of Medical Research
University of Western Ontario
London, Canada

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Contributors to Volume I

CLAUDE ALLARD, *Montreal Cancer Institute, Notre Dame Hospital, Montreal, Canada*

HOWARD B. ANDERVONT, *National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

M. I. ARMSTRONG, *Department of Anatomy, University of Toronto, Toronto, Canada*

R. W. BEGG, *Department of Medical Research, University of Western Ontario, London, Canada*

ANTONIO CANTERO, *Montreal Cancer Institute, Notre Dame Hospital, Montreal, Canada*

ROGER DAOUST, *Montreal Cancer Institute, Notre Dame Hospital, Montreal, Canada*

J. ENGELBRETH-HOLM, *University Institute of Pathological Anatomy, Copenhagen, Denmark*

W. R. FRANKS, *Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada*

JACOB FURTH, *The Children's Cancer Research Foundation, Boston, Massachusetts*

ROGER GAUDRY, *Ayerst, McKenna & Harrison, Ltd., Montreal, Canada*

J. P. W. GILMAN, *Division of Biology, Ontario Veterinary College, Guelph, Canada*

E. S. GORANSON, *Department of Biology, University of British Columbia, Vancouver, Canada*

A. F. GRAHAM, *Connaught Medical Research Laboratories, University of Toronto, Toronto, Canada*

CHARLES S. HANES, *Department of Biochemistry, University of Toronto, Toronto, Canada*

W. STANLEY HARTROFT, *Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada*

W. C. HUEPER, *National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

H. E. JOHNS, *University of Saskatchewan, Saskatoon, Canada*

GASTON DE LAMIRANDE, *Montreal Cancer Institute, Notre Dame Hospital, Montreal, Canada*

J. A. MCCARTER, *Department of Biochemistry, Dalhousie University, Halifax, Nova Scotia*

H. D. MCEWEN, *Department of Pharmacology, Queen's University, Kingston, Canada*

A. McGregor, *Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada*

E. W. McHenry, *Department of Public Health Nutrition, University of Toronto, Toronto, Canada*

G. A. Meek, *Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada*

G. Burroughs Mider, *National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

Robert H. More, *Department of Pathology, Queen's University, Kingston, Canada*

Raymond C. Parker, *Department of Experimental Cytology, School of Hygiene, Connaught Medical Research Laboratories, University of Toronto, Toronto, Canada*

A. J. Phillips, *National Cancer Institute of Canada, Toronto, Canada*

Van R. Potter, *Department of Oncology, McArdle Memorial Laboratory, University of Wisconsin Medical School, Madison, Wisconsin*

J. H. Quastel, *Research Institute, Montreal General Hospital, Montreal, Canada*

R. J. Rossiter, *Department of Biochemistry, University of Western Ontario, London, Canada*

Hans Selye, *Institute of Experimental Medicine and Surgery, Université de Montréal, Montreal, Canada*

M. M. Shaw, *Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada*

L. Siminovitch, *Connaught Medical Research Laboratories, University of Toronto, Toronto, Canada*

Howard E. Skipper, *Biochemistry Division, Southern Research Institute, Birmingham, Alabama*

Stanley C. Skoryna, *Department of Experimental Surgery, McGill University, Montreal, Canada*

J. Skublics, *Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada*

Paul E. Steiner, *Department of Pathology, The University of Chicago, Chicago, Illinois*

Jules Tuba, *Department of Biochemistry, University of Alberta, Edmonton, Canada*

S. Vesselinovitch, *Division of Biology, Ontario Veterinary College, Guelph, Canada*

A. Cameron Wallace, *Collip Medical Research Laboratory, University of Western Ontario, London, Canada*

Foreword

The National Cancer Institute of Canada was founded in 1947 as a voluntary organization which has as its principal aim the stimulation and financial suport of fundamental cancer research in Canada. It is supported very generously by our sister organization the Canadian Cancer Society, and also receives substantial support through Federal-Provincial grants coming from a number of the Provinces. The work of the National Cancer Institute had rather modest beginnings, but the number of investigators receiving grants has grown markedly in the interval, and the number of Cancer Research Fellows has increased greatly as well.

Canada is a large country. The recipients of research grants and the young research fellows working with them are scattered across the country from Halifax to Vancouver, some of them in locations that isolate them from others who are interested and active in cancer research. The desirability of close communication between investigators working on allied problems is obvious, and the difficulties that exist in Canada in this respect has caused the Board of Directors of the Institute a good deal of concern. For several years the Board has provided support to enable the attendance of our Western grantees at the meetings of the Western Regional Group of the National Research Council, but it was realized that this did not meet the requirements fully.

A little more than two years ago we invited three of our senior investigators to visit, among them, all of our cancer grantees across Canada, partly to make a survey of the progress of cancer research with a view to making recommendations for the improvement of our program, but partly also because it was thought that the visits themselves would be stimulating to the individual grantees. Each grantee has by now been visited by at least one, if not two, of these men who have now been formed into what we have called a Research Advisory Group consisting of Dr. Arthur Ham of the University of Toronto, Dr. Charles Leblond of McGill University, and Dr. Robert Noble of the University of Western Ontario. Dr. Harold Warwick, our efficient Executive Director, is also a member, ex officio.

As a result of their survey the Research Advisors brought in a number of recommendations to the Board, among which was the strong recommendation that our cancer research workers should be brought together periodically at least for regional meetings or, better still, for a national

meeting at which all of our investigators could meet together for their mutual benefit and stimulation. This Canadian Cancer Research Conference is the first fruit of that recommendation. While they have had the enthusiastic support of the Board of Directors, the Research Advisory Group has been entirely responsible for the organization of the Conference. They have done all the work and deserve all the credit. I am very glad to have the opportunity to say this and, on behalf of the Board of Directors, to express to them our thanks and congratulations.

G. Lyman Duff, *President*
National Cancer Institute of Canada

Preface

In Canada, cancer research is a relatively new field of endeavor. It has engaged the attention of a number of our more experienced scientists, along with a growing number of younger investigators. As in other countries the group represents a number of scientific disciplines In making arrangements for the Conference, our research advisors felt that the most helpful type of program would be one that was educational as well as informative and which, at the same time, would encourage a discussion of principles, and indicate avenues of research.

In choosing the subject matter for this conference it was decided that only a few topics could receive adequate consideration, and that one day should be assigned to each. It was further decided not to restrict the Conference to either multiple short papers, or a few major ones, but rather to intersperse the two. In this way it was felt that a greater number of our grantees would have an opportunity of expressing themselves, while at the same time deriving benefit from the deliberations of the senior investigators.

The first day of this conference was devoted to the "raw material" of cancer research, experimental tumors. The biological and pathological aspects of tumors were considered, and a number of papers dealt with such practical points as tumor induction and transplantation.

It seemed natural, the following day, to discuss the effect of a tumor upon its host. The metabolic and endocrine aspects were stressed, and some short papers on normal metabolism were added to give better understanding of the abnormal reactions of the cancerous animal. The informal discussion of lung cancer was introduced as a result of widespread interest in this subject.

The general consideration of metabolism led to the more specific discussion, on the third day, of enzymes and nucleic acids. This was not an exhaustive discussion, but served the purpose of introducing the subject to grantees not already familiar with it.

The nature of ionizing radiations and their biological effects were chosen as the subject matter for the last day of the Conference. Because the ramifications of this subject are becoming so important in cancer research it was felt that this topic should be introduced at this time, and explored in greater detail at a later date.

The proceedings should not be considered as an all-embracing record of recent research developments, or as a comprehensive review of the subject. Such was not the purpose of the meeting. The various papers do, however, bring together the more general thoughts of distinguished investigators on particular aspects of cancer research.

March, 1955

O. H. WARWICK, *Executive Director*
National Cancer Institute of Canada

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EXPERIMENTAL TUMORS

Biological Background for Experimental Work on Tumors

HOWARD B. ANDERVONT

National Cancer Institute, National Institutes of Health, Bethesda, Maryland

This conference is being held when the problems of cancer have aroused the interests and resources of medical and all allied sciences. Concrete evidence of this interest was provided during the past year in the appearance of three volumes totaling over 2100 pages—and there is promise of more to come. A considerable portion of these volumes deals with experimental work on cancer, and you, as cancer workers, must have been impressed by the diversity of disciplines involved in our problems—a diversity which inevitably leads to specialization in an already specialized field. To the novice this high degree of diversity is confusing and presents a complex picture. This is true when cancer is regarded as an over-all problem but, in common with other scientific problems, it becomes much simpler when broken down into its component parts. It is my pleasure and honor to review with you the biological components which provide a setting for most cancer research. The biological background for experimental work on tumors has evolved from studies of host-tumor relationships and the response of hosts to inherited and environmental influences capable of eliciting tumors. Consequently, a discussion of this background falls into two main divisions: (1) contributions from biological studies of the hosts; (2) contributions from similar studies of the tumors.

The Hosts

A variety of experimental animals are used in cancer research, but the mouse is often the animal of choice because of its small size, ease of maintenance, and above all, the establishment of inbred strains. From the earliest days of experimental cancer, investigators, especially those in the laboratories of The Imperial Cancer Research Fund and the Harvard Cancer Commission, recognized the importance of the constitution of their animals in the development of spontaneous and transplanted tumors (52). Conclusive evidence of this influence was supplied by C. C. Little, now of the Roscoe B. Jackson Memorial Laboratory, when he developed a high mammary cancer strain of inbred mice. We are indebted to Little and his colleagues, Strong (74) in particular, for the establishment of many inbred strains of mice now used in laboratories throughout the World. Such strains are not only standard research tools for cancer workers, but are rapidly affecting all branches of medical science. All biological work differs from the more precise physical sciences in that it presents many

variables, for all organisms possess individual variations in their reactions to controlled conditions. In inbred strains this variation between individuals is reduced to the minimum. Hence, the use of these strains eliminates a variable which formerly confused the results of much experimental work.

Inbred strains are obtained by brother to sister matings until all individuals are genetically identical and their genetic constitution can change only by mutation (66). In mice this requires at least 20 generations of inbreeding after which we have strains showing high or low susceptibility to the development of spontaneous tumors and a remarkable strain uniformity in reaction to carcinogenic agents and transplantable tissues (51).

Susceptibility of eight inbred mouse strains to various tumors (2) is summarized in Table I. Strain C_3H is the most susceptible and strains Y and I the most resistant to subcutaneous tumors induced by two carcinogenic hydrocarbons. When a standard dose of a carcinogen is injected subcutaneously into mice of strains C_3H and I, the average time elapsing between injection and the appearance of tumors (latent period) is 17–18 weeks for strain C_3H and 30–32 weeks for strain I. Breeding females of strains C_3H, A, and DBA exhibit a high incidence of spontaneous breast tumors whereas the other five strains show a very low incidence. Strain A animals are highly suspectible to the development of spontaneous pulmonary tumors. They are also highly susceptible to pulmonary tumors induced by subcutaneous administration of a carcinogenic hydrocarbon. Susceptibility to induced pulmonary growths is reckoned not only by the number of mice developing tumors, but also by the number of tumors found in individual mice. It is worthy of note that none of the eight strains is completely resistant to spontaneous or induced tumors, despite their striking variations in susceptibility to these growths.

In the last two columns, the strains are listed according to their natural resistance to cutaneous growth of two well known transplantable sarcomas. In every mouse of five strains, sarcoma 37 regressed spontaneously, while in three strains it grew progressively and killed the animals. Sarcoma 180 grew progressively in seven strains, but in strain I the growth regressed. Data in this table reveal that none of the strains is resistant or susceptible to all types of tumor growth. Strain I, however, does possess the strongest tendency toward resistance to all six tumor types.

Table II summarizes the response of five mouse strains to percutaneous administration of a carcinogenic hydrocarbon. Two experiments are included in which different dosages of the carcinogen were applied to the skin of the interscapular region. The occurrence of papillomas is the only part of the experiments included in this table. When the study was started

TABLE 1. *Summary of 8 Inbred Strains of Mice Showing Susceptibility to Spontaneous Mammary and Pulmonary Tumors, Induced Subcutaneous and Pulmonary Tumors, and Two Transplantable Tumors*

Strains listed in order of susceptibility to subcutaneous tumors induced by carcinogenic hydrocarbons	Incidence of spontaneous mammary tumors in breeding females	Incidence of spontaneous pulmonary tumors	Susceptibility to pulmonary tumors induced by subcutaneous injection of lard-dibenzanthracene solutions	Susceptibility to cutaneous growth of sarcoma 37	Susceptibility to cutaneous growth of sarcoma 180
C_3H	100%	<5%	Medium	0%	100%
BALB/c	<5%	>25%	High	100%	100%
$C_{57}L$	<5%	<5%	Medium	0%	100%
$C_{57}Bl$	<1%	<1%	Low	0%	100%
A	85%	89%	Very high	0%	100%
DBA	85%	<1%	Low	100%	100%
Y	<5%	<5%	Medium	100%	100%
I	<5%	<5%	Medium	0%	0%

TABLE II. *Occurrence of Papillomas in Inbred Strains of Mice Following Percutaneous Application of 0.25% MCA in Benzene*

20 weekly paintings			10 weekly paintings	
Strains	Incidence	Average time between first painting and Pap.	Incidence	Average time between first painting and Pap.
		Weeks		Weeks
I	100%	15	77%	15
BALB/c	100%	21	88%	28
C_3H	100%	19	92%	34
RIII	100%	24	95%	30
$C_{57}BL$	97%	22	52%	44

there was no clear information in the literature concerning the appropriate dosage for revealing strain differences, so, as a starting point, each mouse received 20 paintings at weekly intervals of a 0.25% solution of methylcholanthrene dissolved in benzene. It is seen that this exposure is far above the critical amount since virtually all the mice developed papillomas. The only measurable difference between strains is in the average time between the first painting and the appearance of papillomas. Strain I showed the shortest latent period for papilloma formation. When the dosage was reduced to 10 paintings the incidences of papillomas are lowered. and the average latent periods increased, but it is evident that for ascertaining the relative susceptibilities of four strains the appropriate amount of carcinogen was not used. Strain C_{57} BL is apparently the most resistant, and for these animals the dosages were appropriate since those of the second experiment showed half the incidence and twice the latent period as those of the first.

Data in Table II are presented for two reasons. First, strain I which, as shown in Table I, is relatively resistant to six types of tumors is now found to be highly susceptible to induced papillomas. Second, and more important, it reveals both the advantages and disadvantages encountered when inbred strains are used as test animals. One advantage is acquisition of knowledge concerning the susceptibilities of the strains to this particular carcinogen, and the use of these variations in susceptibility to study further the mechanisms of the carcinogenic process. One disadvantage is that when testing for an unknown carcinogen the investigator must use a number of inbred strains. Although experimental evidence is lacking, it is reasonable to assume that smaller amounts of the hydrocarbon will elicit papillomas in strain I, while strain C_{57} BL will remain free of tumors. This wide variation in susceptibility to carcinogens among inbred strains together wth

species differences compel those who test unknowns for carcinogen properties to use several inbred strains of different species. Indeed, the choice of test animals for this kind of investigation could be noninbred animals of different species in addition to inbred strains known to possess a high degree of organ susceptibility to the type of tumor under investigation.

Table III is included as evidence that our present biological background for research is not limited to inbred mice. This information on eight stocks

TABLE III. *Stocks of Rats* (Dr. W. F. Dunning)

Strain	Line	Cysticercus infestation	Susceptibility to estrogen-induced breast tumors	Others
Fischer	344	S[a]	S[a]	AAF-induced liver and breast tumors
Zimmerman	61	S[a]	S[a]	—
Marshall	520	S[a]	—	AAF-induced bile duct tumors
August	990	R[b]	S[a]	Estrogen-induced adrenal tumors
August	7322	R[b]	—	Spontaneous breast tumors
Copenhagen	2331	R[b]	R[b]	Spontaneous thymic tumors and estrogen-induced bladder tumors
A x C	9935-A	R[b]	S+[a]	—
A x C	9935-B	R[b]	—	Spontaneous lymphosarcoma of mesentery

[a] = Susceptible
[b] = Resistant

of rats was supplied by Dunning (25), who has, as can be seen, made outstanding contributions. Column 3 of this table is especially relevant to this discussion. The strains are listed according to their susceptibilities to cysticercus *infestation* of the liver, which in turn leads to the occurrence of tumors. When the larvae have become encysted in the liver all strains are equally susceptible to tumor formation. Thus, we have a good example of how inbreeding can lead to a high or low tumor incidence, not through genetic control of tissue susceptibility to the development of tumors, but by controlling the response of the host to a related environmental factor.

The rat has also attained prominence in cancer research through its susceptibility to induced sarcomas, especially those developing around embedded bakelite disks (80) and other plastics (61).