At the beginning of this century cancer research was extremely unpopular. It was only after Gaylord brought the Jensen mouse carcinoma to the United States early in 1908 that experimental tumor material became generally available in this country. Systematic charting of transplanted tumors was introduced, and, as a result, it was soon recognized that a large number of tumors regressed spontaneously; in 1904 investigators in this country discovered that mice that had recovered spontaneously were immune to subsequent transplants of the same tumor strain. Insignificant as this discovery may appear in the light of our present knowledge, it was apparently the trigger mechanism which led to the expansion of cancer research, not only in the United States, but throughout the world, an expansion which, as a result of numerous additional discoveries, has proceeded with accelerating velocity ever since.1

Professor Paul Ehrlich, who had previously expressed to the writer the opinion that there was no future in cancer research and that more reputations had been ruined in this field than in any other, was only one of the prominent investigators who began to experiment with transplantable mouse tumors in an effort to determine the nature of the immune mechanism involved and to secure information regarding the biological and chemical characteristics of these animal tumors. The tendency of a tumor to regress appeared to bear an inverse relation to its rate of development and to the size attained by the tumor. However, all unmistakable spontaneous recoveries conferred immunity against repeated transplants of the same tumor. Furthermore, a tumor which had already reached a considerable size appeared to interfere markedly with the development of a subsequent transplant of the same tumor. Great irregularity in development was occasionally exhibited. A tumor might reach a weight of a gram or more, then regress for 3 or 4 weeks to a tenth of its previous size, and then once more develop and cause the death of the animal; this suggested an antagonism between the tumor and host as a result of fluctuations in the development of immune reaction and of tolerance. The preliminary report by Graham and Graham that antigens are produced by human cancers in the intermediate but not advanced stages is in agreement with the above observations. These experiments on mice led to a careful investigation of the cancer literature, and Gaylord accumulated evidence regarding unquestioned spontaneous recoveries from cancer in a small number of human subjects. As much as 50 years ago Ewing recognized that spontaneous recovery occurs occasionally, and he stated that the course of development of cancer in man might be highly irregular, the period of maximum growth of human tumors varying from less than 3 months to more than 20 years.

The tumor experiments on mice were carried out with animals of unknown origin. The work of Little, Loeb, Tyzzer, Strong, Bittner, Snell, and others with inbred mice and the development of the genetic theory of transplantation were still in the future. Regret has been frequently expressed that pure-strain mice were not available at the time that these initial experiments on immunity against cancer were carried out. The writer, who remembers this period well, can only say that the experiments were honestly interpreted in the light of existing knowledge and at least had the effect of increasing interest in and support for cancer research. As a result, many additional important discoveries were made, and by the time that the First World War was over there was no longer any question regarding the future of cancer research. If the original experiments had been carried out with pure-strain mice, Bashford’s subsequent attempts to immunize against cancer transplants by means of homologous red corpuscles would probably have been uniformly successful, and Barrett’s demonstration that the intact ghosts of the red corpuscles exerted a similar antigenic effect, while ghosts which had been broken up by freezing or mild sonic vibration failed to do so, would have reduced this particular problem to one of maintaining the architectural integrity of what Barrett believes to be a lipoprotein complex (personal communication). This
complex is presumably a specific component of the membrane, the antigenic effect of which would depend not only on the nature and proportion of the various lipids and proteins involved but also particularly on the orientation of these molecules in relation to one another. This would presumably have nothing to do with a possible inciting agent within the cell. When Rous found that cell-free, filtered extracts of chicken sarcomas, when injected into chickens, produced a sarcoma of the same type as that from which the extract was derived, he also found, as might be expected, that immunity induced against the inciting agent did not necessarily confer immunity against transplants of the original tumor. The tendency of certain tumors to develop, then for a brief period to regress, and subsequently to develop once more—ultimately causing the death of the animal—would have been attributed, as a result of more recent work, to spontaneous mutant change within the tumor itself, giving rise to a secondary and more resistant tumor which was developing at the time that the original tumor was regressing. An alternate explanation might well be a variation in the activity of an inciting agent.

As a result of the interest created in the problems of tumor growth and immunity, meetings and international congresses were held on the subject, and about 50 years ago a group of pathologists, including Ewing, Gaylord, Leo Loeb, Wood, and Adami, with some surgeons, physicians, biologists, and chemists, started the cancer research society which ultimately became the American Association for Cancer Research. The first meetings never lasted more than 1 day, the main subjects of discussion being (a) whether the pathologists were willing or unwilling to designate certain animal tumors as malignant, a discussion which arose afresh whenever a new transplantable animal tumor was discovered, (b) the nature of the immune forces involved, (c) the possible role played by parasites, viruses, or other extraneous agents in the development of cancer. There was a constant search for possible inciting agents; for a considerable period—before the important discoveries of Rous with chicken sarcomas referred to above and long before discovery by Bittner of the milk-transmitted, filtrable agent, the work with the Shope virus, and Gross’ recent demonstration that filtrable particles are implicated in the etiology of leukemia in certain mouse strains—attempts were constantly being made to induce cancer in mammals by means of cell-free tumor extracts, both unfiltered and filtered. The trout tumor which Gaylord studied in 1907 and believed to be caused by an infective agent was apparently attributable, at least in part, to a metabolic deficiency, since the addition of iodine to the water markedly reduced the incidence of the disease. This does not necessarily exclude an inciting agent.

Turning now to the present day, one may safely say that every field of research bearing directly or indirectly on cancer is being thoroughly explored. The writer has only two suggestions to make: (a) that any and all cell-free inciting agents of animal origin believed to play a role in inducing cancer in animals should be obtained in as pure a form as possible and subjected to the best available procedures for obtaining vaccines against virus diseases in an attempt to produce an antigen which, when injected into susceptible animals, might afford protection against subsequent injections of the cancer-producing agent; and (b) that a greater effort should be made to develop agents capable of blocking energy transfer from the anaerobic glycolytic system. An argument for following this course is the ease with which ascites mouse carcinoma cells take up glucose and convert it into lactic acid, particularly under anaerobic conditions, and the extent to which, under both aerobic and anaerobic conditions, this glucose uptake and lactic acid production are increased by the use of a series of nitrophenols which, at the identical concentrations, completely block oxidative phosphorylation and cell division of fertilized Arbacia eggs and substitute a glycolytic metabolic pathway for the normally preponderant pentose-producing TPN shunt.

In comparing conditions 50 years ago with those of the present, the greatest contrast is to be found in the freedom now granted to research workers in choosing a field of investigation and deciding what course to follow. As late as 1907 it was only through the intervention of Professor William H. Welch, Sir William Osler, Professor Adami, and others that support for certain experimental work was continued. The annual expenditure on cancer research was probably about one-thousandth of what it is today. Leading investigators in this field occupied professorships in universities and medical schools and devoted their spare time to cancer research. There were very few full-time investigators, and it was impossible to embark on any large-scale, long-term experiments because of the uncertainty regarding continued financial support. Now there are numerous institutions and research laboratories devoted to cancer research and provided with the most up-to-date facilities and equipment. There is enlightened leadership and full recognition of the necessity.
not only of engaging able investigators to cover individual fields of research, but also of encouraging them to co-operate with one another, in an effort to bridge the gaps between their respective fields. Fleming's discovery of penicillin has emphasized the fact that many important discoveries have been made more or less by chance and that consequently every possible avenue should be explored.

In conclusion, it may be said that, whereas 50 years ago there was little or no incentive to engage in cancer research, today the results being obtained in this field are so important and the opportunities for research are so excellent that able young investigators need have no hesitation about engaging even in long-term projects in this most difficult and at the same time most fascinating field of research.

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Cancer Research Fifty Years Ago and Now

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