A Pilgrim’s Progress in Cancer Research, 1918 to 1974: Autobiographical Essay

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Lymphocyte

Immediately after graduation in biology (Ph.D., Cornell University, 1918) I joined the scientific staff of the Rockefeller Institute for Medical Research (now Rockefeller University), New York, as assistant to Dr. James B. Murphy. The armistice of World War I was declared toward the end of that year, and the normal research activity of the Institute was then resumed.

At that time, Dr. Murphy was holding fast to the idea that the lymphocyte was an important factor in tumor resistance, and the research activity of his small group was concentrated on this theme. A series of elegant experiments, such as tumor implantation in developing chick embryos, association of marked lymphocytosis with tumor graft rejection in mice, abrogation of tumor resistance by lymphoid destruction through exposure to X-rays, etc., had already established for him a high reputation in experimental cancer research. A part of my contribution was in showing that, accompanying the state of tumor resistance, there was a stimulation of the general reticuloendothelial system, as indicated by the enlargement and increased mitotic activity in germinal centers of lymphoid organs. The work culminated in Murphy’s monograph, which appeared in 1924 as Monograph of the Rockefeller Institute, No. 21.

As I look back upon those early days of experimental cancer research when pure strains of mice were not available and the distinction between syngeneic and allogeneic tumor transplantations was scarcely appreciated, it is apparent, although very regrettable, why some of Murphy’s extensive work on tumor resistance has become overshadowed. His suggestion sufficiently explains the contradictory results. It is true that the spontaneous-tumor mice of the old Rockefeller Institute days were of an outbred population, but so were the spontaneous tumors of mice can be drastically suppressed by means of oleic acid injections. This important finding was originally allowed to appear as my debut paper! Returning to Japan in 1925, I immediately repeated this experiment with the intention of trying out a whole series of unsaturated fatty acids which were then available at the Institute of Physical and Chemical Research, Tokyo. Mice bearing spontaneous tumors were purchasable from dealers in Tokyo, although only a few were available at a time. However, the data laboriously collected over a period of about 3 years failed so completely to show any inhibition of local recurrence or autografts that it discouraged an anticipated extension of experiments to other fatty acids.

Alexander cited the early oleic acid experiment in his 1968 review and stated that he and Delorme failed to confirm the result using a pure line of mice with high tumor incidence. A possible explanation for this difference, he felt, was that the high-tumor-strain lines were more tolerant than the outbred colony mice, in which only a small fraction of mice developed tumors. I seriously doubt whether this suggestion sufficiently explains the contradictory results. It is true that the spontaneous-tumor mice of the old Rockefeller Institute days were of an outbred population, but so were the spontaneous mammary tumors of my Tokyo series. Inasmuch as the mice, designated as bearing spontaneous tumors, were given to me from the “mouse room” of the Rockefeller Institute, tumor autografts had to be considered as strictly autochthonous. I still have no explanation for any other source of error which apparently must have entered into our experimental system.

It was fortunate for me that my stay at the Institute (1918 to 1925) was its most active period, when giants like Jaques Loeb, P. A. Levene, and Alexis Carrel were the leading figures on the staff. Hideyo Noguchi was at the height of his career. Peyton Rous, Oswald Avery, James B. Murphy, Michael Heidelberger, John Northrop, and E. V. Cowdry, among others, belonged to the rising generation. The atmosphere created by the active work at all levels was very...
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stimulating. The sustained high-pressure research activity, generated from the Director of the Institute, Simon Flexner, was to push and pursue, without providing time to rest. One's output, in terms of the number of papers published in a year was often used as a measure of achievement; this resulted in a tendency for rapidly published papers which the authors may have given further consideration, if allowed sufficient time. All this, however, is my reflection at the vantage point of half a century; I myself have been a victim of an “Output = Achievement” delusion for a long time, as attested by a large number of inferior papers that I published in the past and am still producing from force of habit.

My association with Murphy was fateful in that the resolution to take up cancer research as my life work was made during this period. It was in Murphy’s laboratory that I first became acquainted with spontaneous mouse mammary tumors, in which I have still retained interest during subsequent years.

On the whole, my days at the Rockefeller Institute were most pleasurable and profitable. Among the friends I made were two visiting scientists from Europe, Albert Fischer (Copenhagen) and Joseph Maisin (Louvain), who remained my close associates until their deaths.

**Rous Chicken Sarcoma**

Upon my return to Japan in 1925 I was given joint appointments at the Government Institute for Infectious Diseases, where Professor Mataro Nagayo was Director, and at the Institute of Physical and Chemical Research, where I was assigned to the laboratory of Professor Umetaro Suzuki. It was my good fortune to have independent positions in Tokyo’s two highest-ranking research institutions under the patronage of two leading scientists in Japan.

The year 1925 was notorious for cancer research, if anyone recalls that year. The world was shaken by the announcement by E. E. Gye in *Lancet* that the viral cause of cancer was discovered. The finding upon which the news was based was merely that the Rous chicken sarcoma filtrate was found to be inactivated by small amounts of chloroform and reactivated by the addition of fresh extracts from all types of tumors. The interpretation was that all the tumor extracts contained the tumor virus. Accompanying these experimental results in the same issue of *Lancet* were Bernard’s UV photomicrographic findings of the alleged tumor virus. The startling news experimental results in the same issue of *Lancet* wereBernard’s UV photomicrographic findings of the alleged extracts contained the tumor virus. Accompanying these experimental results in the same issue of *Lancet* were Bernard’s UV photomicrographic findings of the alleged tumor virus.

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The Gye fiasco soon ended, however. The only striking finding at that time was the fact that tumor tissues other than the Rous sarcoma were not characterized by deficient glutathione content, and our expectation to correlate the glutathione content with tumor cell respiration in general was not met.

We found other biochemical peculiarities of Rous sarcoma tissue, such as an inability to reduce methylene blue and a markedly deficient cytochrome content (paralleling the low glutathione content). These findings tended to separate the Rous sarcoma from the generalities of tumors. These studies on the substances related to cell respiration are noteworthy because they represent the early phase of modern biochemical approaches to cancer, in contrast to the mass of sterile data in the classical chemical pathology of cancer.

At the Institute of Physical and Chemical Research, my studies were directed toward the relationship of vitamins to tumor growth. This work led no further than to confirm that the host tends to support the tumor growth at the expense of its own nutritional resources. There seemed to be no tumor-specific requirement for any dietary element, including vitamins.

The only striking finding at that time was the fact that tumor tissues of all varieties, including Rous chicken sarcoma, rat sarcoma, rat carcinoma, and mouse adenocarcinoma, were almost completely vitamin A free. These tumor tissues were dried at a low temperature and extracted with ether, and tumor oils thus obtained were tested for vitamin A color reactions: sulfuric acid, acid clay, and antimony trichloride reactions. Despite the fact that these color reactions were known to be very sensitive (capable of detecting minute amounts of vitamin A), they all demonstrated consistently negative reactions. It was suggested that cancer may be a vitamin A-independent cell growth system. In fairness, it should be added that Burrow suggested as early as 1923 that tumor growth may be a vitamin A-independent system. In his case, however, it was based upon a single rat bioassay that showed the absence of vitamin A in the sarcoma.

Although the whole problem of vitamin A in connection with the origin and metabolism of the tumor cell is now forgotten, it may be worthwhile to mention that vitamin A deficiency produces hyperkeratosis and proliferation of certain epithelial cells. These phenomena direct my thoughts to Fibiger’s squamous cell carcinoma of the
forestomach of the rat and its association with the local presence of a certain nematode that has also been forgotten by the scientific world. Fibiger did obtain what were unquestionably squamous cell carcinomas in his rats, and the tendency among later investigators to drop the subject without making full investigation into the failure to confirm the original experiments seems unfortunate.

Inhibition of Liver Cancer Production by Liver Feeding

With the establishment in 1934 of the Cancer Institute and Hospital, by the Japanese Foundation for Cancer Research, Japan had the first institution devoted to cancer research and treatment of cancer patients. Professor Mataro Nagayo was personally responsible for this historic event, and it was under his directorship that the work of experimental cancer research was started. I was fortunate enough to be invited to join the research staff as Head of the Division of Pathology and eventually to succeed Nagayo, first as Vice-Director (1946) and then as Director (1962). My association with the Government Institute for Infectious Diseases was relinquished when I joined the Cancer Institute, but I continued my work at the Institute of Physical and Chemical Research on a part-time basis as an Ordinary Member (1939) and as Chief Member (1946), until I resigned to assume the full-time position of Director of the Cancer Institute.

My fond recollection of the Institute of Physical and Chemical Research is that it was an ideal place to do research. The Institute was what the Japanese law defined as a foundational juridical person, financed by private donations, the profits accruing from inventions made by staff members and, to some extent, from government subsidy. It was operated under the directorship of Vice-Count Masatoshi Okochi, a descendant of an old feudal lord and ex-professor of mechanical engineering, Tokyo Imperial University. Each Chief Member of the Institute was given a fixed annual budget to run his laboratory, and the rules of the Institute provided that he might spend his allocated budget in any way he wished. No restriction was placed as to the subject of research. Each Chief Member chose research projects of his own. This golden age of scientific freedom lasted until World War II came along and commandeered much of the human and financial resources of the Institute for war services.

My Cancer Institute days (1934 to 1963) represented the most productive period of my scientific life, in spite of the interruption of the war years. In 1932 there came Yoshida's epochal announcement of liver cancer development by o-aminoazotoluene feeding. Then Kinoshita discovered the powerful 4-dimethylaminoazobenzene. These pioneering studies served as the starting point for extensive investigations all over the world. For my part, I became interested in dietary effects on liver cancer production.

Diet has long been suspected of having a role in the genesis of human hepatoma, for there has been an apparent correlation between the consumption of rice as a main staple and the incidence of hepatoma; its occurrence was said to be rare except in the rice-eating population of the Far East. This, a priori, aroused a suspicion that there may be some connection between the causation of beri-beri (polyneuritis) and that of hepatoma. By this time it was becoming apparent among experimenters that unpolished rice and wheat bread were not as good as polished rice for a basal diet in azo dye carcinogenesis experiments. It therefore seemed to point to vitamin B deficiency as a possible factor that favored the production of hepatoma. The matter was not so simple, however, and vitamin B₆, which was then becoming widely available in crystalline form, failed to show any sign of inhibiting liver cancer production when added to the azo dye-polished rice diet. More extensive and all-inclusive dietary study was indicated.

Such a study was undertaken in collaboration with Kazuo Mori, using polished rice powder as basal diet and supplementing it with each of the then known dietary factors separately: purified fish protein, butter (as fat and fat-soluble vitamins), crude riboflavin preparation, vitamin B₆, vitamin B₉, nicotinic acid, liver filtrate, MaCollum's salt mixture, and dried beef liver powder. The last was added as a source of possible unknown factors. The hepatocarcinogen used was 4-dimethylaminoazobenzene, which was added to each of the dietary mixtures at the rate of 0.2 g/kg and gradually increased to 0.6 g/kg. At this dosage level, 150 days after the beginning of feeding, 100% of the rats produced extensive nodular hyperplasia with marked cirrhotic changes, and 50% of them showed perfect examples of hepatomas. This happened in all the experimental groups given various dietary supplements, except the group that received dried liver powder. In the liver-fed group, the liver in all the rats was normal to all appearances and the surface of the organ was perfectly smooth with no indication of even early cirrhotic alterations. We published this experimental result in Gann in 1939. To the best of my knowledge, this is the first time that such a remarkable inhibition of experimental cancer production of any sort was demonstrated.

The inhibition of liver cancer production by liver feeding has since been confirmed from all sides, beginning with Miller et al., and studies along this line were continued by Maisin. We personally spent much time trying to fractionate and identify the active liver substance responsible for the liver carcinogenesis-inhibiting effect, but without success. In the meantime, Kensler et al. duplicated the original liver feeding effect by the use of casein and riboflavin supplements.

By this time, the war's effect was beginning to be felt by our laboratory personnel, many of whom were mobilized for war services. My competent colleague, Mori, was sent to North Manchuria near the Soviet border. The shortage of all commodities was keenly felt and, finally, the rationing of rice put an end to the hepatocarcinogenesis experiments which required rice for the basal diet. Just before this terminal stage, we had been able to establish two important facts: (a) that addition of blood meal to the azo dye diet resulted in almost as good an inhibition of liver cancer production as the addition of liver powder; and (b) that the liver catalase activity was gradually lowered in the course of the azo dye feeding, until it became practically non-existent in the hepatoma nodules produced, while liver powder or...
blood meal feeding, both inhibiting hepatoma production, effectively prevented this lowering of liver catalase activity. These studies were carried out in collaboration with Fumiko Fukuoka.

I wish to devote some space here for these studies not only because they have biochemical implications in the study of the hepatocarcinogenic mechanism, but also because they appeared in print (Gann) toward the end of the war (1944) and undoubtedly failed to reach readers outside of Japan.

Blood meal was prepared by simply drying the blood clot, from which all the larger lumps of fibrin were previously removed, over a water bath. The blood clot was taken from a horse and was left over after the separation of the serum. The pulverized blood meal was added to the basal diet at the rate of 10%. The inhibiting effect of the blood meal on liver cancer production was of special significance in the study of nutritional factors involved in the liver feeding effect, since blood meal is deficient not only as an adequate source of amino acids but also in its lack of riboflavin. Thus it poses a question as to the inhibiting effect of casein plus riboflavin. This was at a time when increased demethylase activity was not demonstrated, not to mention the protein binding of the amino azo dyes.

Our finding that two different methods (liver powder feeding and blood meal feeding) markedly inhibited liver cancer production, giving rise to the identical reduction of the liver catalase level, may suggest that liver catalase plays an important part in the biochemical process of carcinogenesis and anticarcinogenesis in the liver. Considering the concurrence of all the previous workers that the usual catalase activity of cancer cells is, at best, very weak, it was suggested that the process of cell cancerization may accompany a gradual decrease in the catalase activity. The true biological significance of catalase itself is not very clear, but the enzyme is undoubtedly connected with the process of cell respiration, and therefore it would not be strange if a relationship existed between the process of cell cancerization and decreased catalase activity.

Toxohormone

On the night of April 15, 1945, there was an extensive bombing in Tokyo which completely ruined the buildings of the Cancer Institute and a part of those at the Institute of Physical and Chemical Research. (My private residence was saved.) I managed to acquire a small laboratory space in what was left of the Institute of Physical and Chemical Research and was able to escape being completely burned out of research facilities. The war ended in August of the same year, and the tenuous stream of my cancer research was precariously maintained despite the miserable postwar conditions. Fukuoka remained with me throughout this period.

Access to what was going on abroad in cancer research during the war years enabled us to pick up the work of Greenstein’s group at Bethesda on the tumor effect on liver catalase. It seemed almost a natural continuation of our own last efforts on liver catalase mentioned in the preceding section.

In 1948 Nakahara and Fukuoka demonstrated for the first time that a crude fraction could be isolated from human malignant tumors, which, when injected into normal mice, brought about a marked lowering of liver catalase activity. The term “toxohormone” was proposed for the active principle of the isolated tumor fraction. The word was coined specifically to signify a toxic humoral factor produced by cancer tissue, which may be responsible for some of the biochemical lesions in tumor-bearing hosts. The decrease of liver catalase activity may be said to have been chosen as a salient example of chemicopathological alteration that a growing tumor produces in the host.

That the liver catalase activity is significantly lowered in cancer patients and in animals bearing transplanted tumors has been known for some years, but the fact remained almost unnoticed as being a probable part of nonspecific general depletion or system atrophy common in neoplastic diseases. Greenstein and his associates first demonstrated that the depression of liver catalase level in tumor-bearing animals was due specifically to the presence of a growing tumor in the animal body. They showed, among other things, that the lowering of liver catalase level was progressive with the growth of the tumor and that it was reversible to the normal level upon removal of the tumor. They also showed that liver catalase level was not affected by implantation of whole embryonic tissue masses and that the level remained normal throughout the pregnancy up to parturition. All attempts to demonstrate a catalase inhibitor (active in vitro) in the tumor, liver, or sera of tumor-bearing animals were unsuccessful, and Greenstein suggested that the tumor may produce the effect noted either by giving off some toxic product to the circulation or else by removing some material from circulation that was considered essential to normal maintenance of the liver catalase. The isolation of a tumor fraction which, upon injection, markedly lowered the liver catalase level of the normal animal was the substantiation of the first possibility suggested by Greenstein. In fact, Greenstein himself had previously given normal rats injections of a simple aqueous extract of tumor tissue, but he failed to detect any change in liver catalase. This failure was an incentive for us to try to concentrate the hypothetical toxic tumor product from the extract which may not occur in tumor tissue itself in a high concentration, but may be steadily and continuously released into circulation to affect the liver catalase level.

It is easy to extract a toxic substance from tumor tissues. We found, for example, that ether extract in 100-mg doses killed some of the mice in several hr and the remainder within 48 hr with signs of severe general intoxication. A polysaccharide fraction obtained by extraction with 3% trichloroacetic acid, removal of trichloroacetic acid by dialysis, and precipitation with acetic acid (Boivan’s method) killed all the mice overnight after 100-mg doses. In sublethal doses, these toxic fractions did not lower the liver catalase level. Many of the so-called “cancer toxins” in the old literature were of this type and they must be sharply excluded from the toxohormone concept.
There are a variety of heterogeneous materials that actually lower the liver catalase level when injected into normal animals. The list of such nontoxic materials is long: a hopeless jumble of substances, unquestionably not related to the problem of lowered liver catalase level in tumor-bearing animals is seen. For example, how could anyone imagine that talcum powder, which lowers liver catalase in vivo, has anything to do with tumor effect on animals? The bacterial contamination of tumor material can be a serious source of confusion, since some bacterial toxins can depress liver catalase. No experienced worker would think of using heavily infected tumor tissue for any study of tumor tissue. Besides, toxohormone has been isolated from germ-free tumors grown in germ-free animals.

The most insidious possibility that one must guard against may be that some tumor cell components, which are tightly cell bound and not released out of the cell and thus incapable of acting as humoral factors, could be isolated from minutely disrupted tumor cells. Should any such cell-bound substances prove to lower the liver catalase level upon injection into normal animals, they could be easily mistaken for toxohormone.

In some ways it was fortunate that, in the early period of our work on toxohormone, extraction was done by hand with mortar and pestle. Homogenizers were then unknown to us. The result was that we extracted from tumors cells that which was easily soluble in water. Although the cells were intact, they were killed by heating.

Evidence for the humoral nature of toxohormone was rapidly building up. Lucké's ingenious parabiosis experiments, demonstrating that the effect (liver catalase depression) of a growing tumor in one of the parabiotic partners can extend to the other, non-tumor-bearing partner, constitutes clear-cut evidence of the humoral nature of toxohormone. Nakagawa's demonstration of toxohormone in cancer patients' urine would also constitute evidence of the humoral nature of toxohormone, if the urine factor could be established as being derived from the tumor. However, there is no doubt that the demonstration of toxohormone-active material specifically from the urine of cancer patients (but not from normal individuals or from patients with other diseases) strongly indicates that the urine factor may be derived from tumor toxohormone and perhaps is chemically identical to it.

Comments may be appropriate concerning the extraction of materials with liver catalase depression activity in vivo from normal tissues, although it would be of much lower potency. Greenstein explained this point on a quantitative basis, tumor tissue producing far more of the same toxic substance than normal tissues. Accordingly, that which is a normal metabolite in normal tissues becomes "toxin" in tumor tissues by being produced in an excessive amount. My opinion was that the normal tissue factor could serve only to maintain the normal level of liver catalase where it existed. It could not account for whatever occurred in tumor-bearing animals! Another likely possibility is that these normal tissue toxohormones are not released into circulation. This idea is based on the fact that, although toxohormone can be extracted from embryonic tissues, neither large, growing embryomas nor embryos in utero during pregnancy produce liver catalase decrease, as Greenstein showed a long time ago.

The implication of the toxohormone as a chemical basis of tumor effect on the host is profound. Various enzymatic alterations in tumor-bearing animals are well established, but changes in a host's pharmacological reactions depending upon the enzymatic changes and immunological debility of the tumor-bearing host as related to the involution of the thymus and prevention of differentiation-reversal of lymphocytes by phytohemagglutinins may be traceable to the release of toxohormone from tumor cells. It is likely that toxohormone, similar to ancient vitamins and hormones, may be shown to consist of several chemically different substances, each with its own specific action, but all having identical humoral factors produced by living tumor cells.

4-Nitroquinoline 1-Oxide and Summation of Syncarcinogenic Effects

While our work on toxohormone was going on in the small rooftop laboratory of the Institute of Physical and Chemical Research and news of confirmations was coming in from everywhere, I was depressed over the difficulty of rehabilitating the Cancer Institute buildings. The Board of Directors of the Japanese Foundation for Cancer Research was not in the mood for constructive action. If it were not for the initiative of H.I.H. Princess Takamatsu, the reconditioning of the Cancer Institute buildings would not have progressed as it has. I shall always remember the timely help extended by the gracious Princess.

With the rehabilitation of the Cancer Institute in May 1948, I moved my laboratory there and started to assemble a small but competent research group. Among those who joined this group were Hideya Endo, Tetsuo Ono, and Takashi Sugimura, who now stand as Japan's leading figures in cancer research. My own research turned from toxohormone to chemical carcinogenesis.

During his studies on aromatic amine chemistry, Professor Eiji Ochiai theorized that N-oxygenation of quinoline may alter the reactivity of the aromatic ring system due to the electron-donating resonance effect of the N-oxide group. On the basis of this speculation, Ochiai and his associates synthesized 4-nitroquinoline N-oxide in 1942; it was soon found to be biologically active. It was shown to be mutagenic to certain microbes and also to be tumoricidal in vitro.

Perhaps the most important biological activity of this class of molecules was their carcinogenicity, first demonstrated in 1957 by the production of squamous cell carcinoma and fibrosarcoma of the skin by the conventional skin painting technique using mice. Several related derivatives were then tested by s.c. injections in mice, yielding fibrosarcoma and rhabdomyosarcoma (1958). All of the accumulated data strongly indicated that the nitro group at position 4 and the oxygen atom at position 1 (nitrogen of the quinoline ring) were the essential structural requirements for their carcinogenic activity. These studies first published...
in two papers of Gann (1957 and 1958), built a solid foundation for further intensive studies which have been taken up by many investigators since who have taken various points of view. These investigations are still in progress today. The entire subject is too recent to need recounting here. Enormous amounts of work on chemical properties, quantum biological activities, metabolism, and in particular molecular aspects of the action of the hormone have been compiled by Endo, Ono, and Sugimura in a monograph of the Recent Results in Cancer Research (Springer-Verlag) series of 1971. Contained in it are references to the original publications, which amounted to over 300 during the 10 years following publication of the first two classical papers. A second review of the subject, based upon the work accomplished more recently, is in preparation by Sugimura for Advances in Cancer Research.

My own interest in chemical carcinogenesis extended from nitroquinolines to pharmacodynamic mechanisms of carcinogenesis in general. It started as an experimental demonstration of the combined effect of two chemically different carcinogens, namely, 4-nitroquinoline 1-oxide and 20-methylcholanthrene. This combination was chosen simply because both chemicals produce skin cancers when topically applied. The first step in the experiment was to determine the submanifestational dose for each carcinogen, that is, the dose at which each carcinogen, if applied alone, fails to produce any visible tumor. Then the two carcinogens were applied on the same skin area, one after the other, using the submanifestational doses. The purpose was to observe the extent of the tumor yields.

As is now known, the application of one carcinogen in its submanifestational dose followed by the submanifestational dose of another carcinogen will always result in approximately the same rate of ultimate cancer incidence, regardless of the order in which the two carcinogens are applied and the time (at least up to 200 days) between the applications of the first and the second carcinogens.

The introduction of the "submanifestational dose" was the empirical principle that led to the clear understanding of the combined syncarcinogenic effects, which now may be said to furnish the basic philosophy of the pharmacodynamic mechanism of carcinogenesis. Basically, it is an extension of the famous summation theory of Druckrey and Küpfmüller in aminoazo dye carcinogenesis to the cases of multiple carcinogens. As Druckrey pointed out, there is no recovery phase in the carcinogenic action of a carcinogen. The latent carcinogenic effect, while invisible, is apparently retained by the cell and its progeny permanently. My work has been to show that such latent effects will combine with carcinogenic effects of all types, to which the cell may be subsequently exposed.

In human cancer etiology, with a few exceptions of some established occupational cancers in which some specific factor plays the major role, the majority of cancers may well be ascribed to a syncarcinogenic combination of many very weak carcinogens of all sorts, including chemical, both exogenous as well as endogenous (hormonal), physical, and viral. We are now in a position to advocate the syncarcinogenic mechanism as an approach to the analysis of epidemiological data in human cancers.

Experimentally, the understanding of the syncarcinogenic combination mechanism made it possible to test the suspected carcinogenic action of agents which, when used alone, may fail to reveal their carcinogenic effects. For such purposes, experiments may be conducted by superimposing the suspected agent upon a submanifestational dose of a standard carcinogen. It has also become possible to accurately evaluate remotely acting carcinogens upon organs that are not generally considered as target organs for the carcinogen. For example, a topically acting carcinogen, such as 20-methylcholanthrene, when applied to the skin, could produce latent (submanifestational) changes in the liver, whereas small doses of hepatocarcinogen feeding, alone too small to induce overt liver cancer, could blend to yield overt liver cancer. Experiments of this kind should form a sound foundation upon which to build the epidemiology of human cancer.


Host Resistance to Autochthonous Tumors

It seems that the plan for establishing a National Cancer Center had been under discussion for some time in Japanese government circles. The plan materialized in 1962 when the Center was officially opened, and I was asked to assume the directorship of the new National Cancer Center Research Institute. At that time I was 65 years old and I naively felt that there should be enough time to do some original work myself, besides organizing the Research Institute.

As to the latter business, I went on bravely according to what I believed to be best, even at the risk of disregarding some of the government's original blueprints for the work of the Institute. I brought together a group of very active young people in their 30's as division chiefs. They were, according to the standards of the Japanese bureaucratic circles, too young to be given the posts of divisions chiefs! It was my idea that the chief of each division was to have complete freedom as to the choice of his research project. He might do whatever he wished in whatever manner he wished. In this, I followed the principle that prevailed at the Institute of Physical and Chemical Research during its golden age, to which I have already referred. To choose the right man for the right post was my only concern then, and I am now proud to see that my "right men" have lived up to my expectations, some having even gone beyond that.

My own major research project was to find a new approach to cancer chemotherapy. Several strains of transplantable mouse tumors were established, including a rare hyalogenic carcinoma of yolk sac origin. We also obtained a transplantable lymphocytic sarcoma that contained an abundance of C-type particles, but which could not be readily transmitted by cell-free material, even to newborn mice of the same strain. These were, however, only by-products of our routine studies on spontaneous mouse
tumors which I proposed to use in our newer research project.

Dissatisfied with existing chemotherapy experiments, screening countless numbers of compounds for their tumoricidal activities, my thoughts returned to the old Rockefeller Institute days with Murphy, when tumor resistance of the host was our major concern. I thought about how people currently talk of combined modality approaches to cancer chemotherapy, but the enhancement of host resistance is hardly considered as a modality to be combined. The total kill of malignant cells is an excellent idea, but successful total kill is apt to include the host too. So, half a century after my first participation in the studies on the lymphocyte as a factor in tumor resistance, I find myself involved again in experimental attempts to learn something about tumor resistance: host-mediated antitumor action of noncytotoxic substances. How history repeats itself!

We have done some preliminary experiments to show that the work of Stock, Old, and others on zymosan, Bacillus Calmette-Guérin, etc., can be duplicated by means of other noncytotoxic plant polysaccharides. Waves of research activity arose, especially in Japan, on various polysaccharides isolated from different botanical sources, notably lichens and mushrooms. These studies cannot be underestimated, as they represent contributions to biochemistry in plant polysaccharides and bioassays of the autotumor activity in which Sarcoma 180 played an important role. For experiments of this sort, Sarcoma 180 is much better than the old Bashford Adenocarcinoma 63 since today we have receptive strains of mice that give 100% takes with a rather uniform rate of tumor growth. However, Sarcoma 180 is an allogeneic tumor and, while it can serve as a tumor-specific transplantation antigen and thus may yield informative results. But here I am flying away into future prospects.

Princess Takamatsu Symposia

Before ending this review on my activities in and around the field of cancer research, it is appropriate to refer to The Princess Takamatsu Symposia. I have already mentioned the part that H.I.H Princess Takamatsu played in the rehabilitation of our Cancer Institute buildings. The opportunity for me to work for Princess Takamatsu came when Her Highness established a fund for cancer research in 1969. This is the Princess Takamatsu Cancer Research Fund, the essence of which has been to award prizes and grants-in-aid to meritorious workers in cancer research in Japan and to hold symposia on timely topics on an international scale. To quote from the opening address of the First Symposium, Princess Takamatsu said: “Ever since I lost my mother through cancer many years ago, it has been my earnest desire to do something toward the conquest of this dread disease. . . . It is my strong conviction that, at the present time, our fight against cancer can hope for the best ultimate results by promoting scientific research, . . .”

I have had the honor of serving as a scientific advisor to the Fund. In this capacity, I headed the organizing committee of the first four International Symposia, namely, on Human Tumor Virology and Immunology, 1970; Chemical Carcinogenesis, 1971; Analytic and Experimental Epidemiology, 1972; and Cell Differentiation and Control of Malignancy, 1973. Among some 70 participants from abroad were: M. A. Epstein, K. E. Hellström, G. Klein, D. S. Nelson, F. J. Rauscher, and C. M. Southern for virology and immunology; H. Druckrey, C. Heidelberger, J. Higginson, P. N. Magee, and J. Weisburger for chemical carcinogenesis; B. S. Blumberg, R. J. Huebner, R. W. Miller, and E. L. Wynder for epidemiology; and J. Paul, V. R. Potter, G. Weber, and S. Weinhouse for cell differentiation.

In undertaking these symposia, I was most fortunate in having the cooperation of my very able colleagues, Takeshi Hirayama, Kusuya Nishioka, Tetsuo Ono, Takashi Sugimura, and Shozo Takayama, upon whom I could rely completely, to the point of compiling in book form 400 to 500 pages from each of the Proceedings of the Symposia. It is hoped that these volumes, with many others to come, will build milestones along the path of progress of cancer.
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research. They will be a lasting tribute to the gracious patronage of H.I.H. Princess Takamatsu.

Looking back over more than 50 years of cancer research, it seems as though so much hard and prolonged work should have produced greater results, but such small successes as I have been able to achieve during these years have given me so much joy that I am glad I entered into this difficult and often frustrating field. It is my hope that future investigators may find helpful the few insights about cancer that my colleagues and I were able to dig out.

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