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I am privileged to have the opportunity to discuss with you the possibility of recognition for major contributions to chemotherapy, and to do so in a confidential manner, since my secretary who is typing this is absolutely trustworthy and discreet.

There are many men who have made contributions to chemotherapy of great importance. George Hitchings synthesized 6-mercaptopurine, thioguanine, imuran, daraprim and discovered the significance of differential binding to the folic acid related enzymes which has allowed for treatment of toxoplasma, pneumocystis and bacterial diseases. He also led the team that synthesized allopurinol. His coworker in much of this activity was Gertrude B. Elion. Surely, Hitchings in terms of his contributions to human welfare must be high on anyone's list.

If one looks at chemists in the cancer chemotherapy area after Hutchings, Heidelberger's synthesis of 5-fluorouracil, 5-trifluormethyldeoxyuridine (trifluorothymidine) and his work in the chemistry of carcinogenesis merits recognition.

Umezawa, in Japan, has been the prime chemist associated with antibiotic development for cancer, and aside from anthraycyclines has dominated the field.

Among those who on experimental levels made the telling contribution to chemotherapy of neoplastic disease, one must mention Lloyd Law, who isolated the L-1210 tumor, performed the first Luria-Delbruck experiment on the origin of resistance in tumor cells, and first undertook combination chemotherapy with aminopterin and azaguanine.

Abraham Goldin tenaciously demonstrated the characteristic of the complex pharmacology of anticancer drug and the tumor, in a legion of critical studies on how to use the antifols in leukemia. His research is the most complete treatise on the pharmacology of an anticancer drug extending over twenty-five years.

Howard Skipper and Frank Schabel revolutionzed the concepts of chemotherapy for cure, laying stress on residual cells and the necessity for treating them. Their work has profound influence on clinical chemotherapy and in a systematic corpus has underlay some of the clinical events which have occurred.

W. Robert Bruce merits consideration also for the significance of his work showing the difference in impact of several cancer drugs on tumor and normal cells, using the clonal colony forming unit technique for normal and tumor cells.

You asked about clinical candidates. I doubt that there are clinicians whose accomplishments have the same importance that Hitchings or Law have contributed, for example and thus I give you this assessment with moderate reluctance. The four leading American chemotherapists, as contenders, I believe, would be Frei, Freireich, Burchenal and myself.

Frei succeeded me at the Cancer Institute and chaired with me the organization of the first study of combination chemotherapy in childhood acute leukemia. He and Freireich undertook the first multi-combination chemotherapy, VAMP, in acute lymphocytic leukemia and he organized the trial of combination chemotherapy of Hodgkin's disease. He postulated the first successful treatment for Burkitt's tumor using Skipperian techniques, and has generally had a pervasive influence on American cancer research.

Freireich conducted the first trial proving the activity of a drug during remission of acute leukemia in a study of 6-mercaptopurine by the Acute Leukemia Group B, and is the senior author of the VAMP multidrug partially curative regimen in acute lymphocytic leukemia.

Burchenal is one of the earliest students of acute lymphocytic leukemia and with Karnofsky, now deceased, inaugurated much of the early research in alkylating agents in broad scale application. He introduced 6-mercaptopurine to clinical practice. He was contemporaneous with Law in demonstrating the effect of combination chemotherapy in mouse tumors.

Holland initiated the first trial of combination chemotherapy in acute lymphocytic leukemia, which became the substance of the work which he and Frei published. He demonstrated the effect of intensive courses of chemotherapy on acute myelocytic leukemia for induction and demonstrated with Bekesi successful immunotherapy of acute myelocytic leukemias. He recognized the effects of adriamycin on osteosarcoma and conducted a successful surgical adjuvant trial with it. He introduced platinum for the treatment of testicular tumors, and demonstrated the curability of ovarian cancer with adriamycin and platinum.

You specifically asked about Hertz and the antifol treatment of trophoblastic neoplasia. Condit was conducting clinical pharmacological studies with methotrexate at the National Cancer Institute, extrapolating some of Goldin's pharmacology experiments with high-dose intermittent methotrexate. Patients with trophoblastic neoplasia were lying on Hertz's service without specific therapeutic plans and were permitted to participate in this clinical pharmacologic trial. M.C. Li recognized the decrease in gonadotropin levels, and interrupted the pharmacologic trial to convert it to a therapeutic one. The original report was Li, Hertz, and Spencer, and shortly thereafter Li's association with the project was terminated. Hertz and his colleagues went on to define the optimal treatment approaches. Since the initial observations were not purposeful and were not made by Hertz, I have always had some reservations about its prizeworthiness. I have been disturbed by Li's sometime exclusion from the recognition that has already accrued. Hertz and his collaborators did systematically introduce orthparprimg dichlorodiphenyl, dichloroethane (O, P' DDD) for the treatment of adrenal carcinoma, which is a notable accomplishment.

Pinkel introduced cranial radiation for the treatment of acute lymphocytic leukemia. His self-touted "total" therapy regimens for acute lymphocytic leukemia contained cyclophosphamide and were thereby inferior, presumably from immunosuppression, to other regimens used by the Acute Leukemia Group B and many other investigators. When Pinkel finally conducted a controlled trial comparing this phenomenon, he too demonstrated that all his prior research had been conducted with a lesser treatment regimen. For the greater part of his investigation appropriate controls were not used, and now there is substantial fallout of cerebral abnormalities apparently associated with cranial radiation. The costs of this must be [illegible] by others whose research designs were more appropriate. Pinkel also inaugurated the cessation of maintenance treatment in acute lymphocytic leukemia at three years without controls, thus incurring a 20% failure rate (and death). I have never considered Pinkel's research designs to be elegant, or even acceptable. The least one can say is that he and his colleagues publish a lot. Pinkel did innovate a therapeutic approach to embryonal rhabdomyosarcoma integrating chemotherapy, radiation and surgery which is of high quality. He also initiated the use of cancer drugs on a surface area basis, derived from the pediatric practice for fluids and calories.

David Galton of Great Britain introduced many of the alkylating agents that are still in use today, chlorambucil, busulfan and melphalan among them, and has been an influential, meticulous worker his entire life. The corpus of his work deserves consideration.

Two additional names in cancer research that merit your consideration I believe are McCullough from Toronto whose technique of identification of colony forming units has had major impact on quantitative biology.

Last, but by no means least, is the serious omission, I believe, of recognition for Ludwik Gross, whose pioneering iconoclastic studies on viral etiology of murine leukemia provided impetus for a major segment of the world's research in neoplastic diseases. Aside from Joseph Beard who worked in avian leukosis, the concept of viral etiology of cancer had nearly died out when Gross made his observations on the Gross virus. From his research also came the Polyoma virus. The importance of these observations has not yet run out. There is still a possibility that a C-particle of the Gross virus will be shown to impart viral sequences to DNA which are important in their interaction with environmental stimuli to produce cancer. Furthermore, Gross first demonstrated the potential for immune prophylaxis against cancer in his C3H animals who rejected carcinogen induced sarcomas. His contribution to fundamental cancer research in two major spheres are, I believe, reminiscent of the long delay in recognition which characterized the prize for Peyton Rous.

The candidates are many and I believe you would not go wrong to pick among the scientists. I still am not certain in my own mind after dictating this letter that clinicians have yet earned a place on the same honor roll. With every good wish,

Sincerely,

JFH:jb

James F. Holland, M.D.
Professor and Chairman

P.S. It also occurs that among the clinicians the name of George Mathé should be inscribed. Mathé systemically consistently and against considerable odds introduced for major areas of cancer medicine, leukocyte transfusion, sterile rooms, marrow transplantation following intensive chemotherapy in acute leukemia, and immunotherapy using BCG and irradiated cells for children with acute lymphocytic leukemia. All of these have been foundations on which subsequent workers have built, but all were undertaken when the sledding was the hardest.

P.P.S. Delayed submission.

On further reflection, Dr. Bernard Fisher is an additional candidate who merits consideration. Fisher with his brother, Edwin Fisher, undertook a long series of experiments in the sixties relating to transplantability of tumors. Bernard Fisher analyzed the first trial of adjuvant chemotherapy in breast cancer performed with Thiotepa, and although essentially negative in its impact, Fisher gleaned important information from it, and continued with the National Surgical Adjuvant Breast Program, evolving a one, and then two, and then three drug adjuvant chemotherapy for breast cancer. Although none of these chemotherapies per se appears to be the best now available, the scope, quality, and impact of his studies on the practice of surgery in breast cancer is prizeworthy.

Harry Eagle merits consideration on two grounds. His studies on the kinetics of bacterial growth undergoing penicillin treatment was a fundamental treatise in the forties. His systematic delineation of the nutritional requirements of mammalian cells in vitro was a major accomplishment allowing studies of nutritional and drug mechanisms of action to be conducted in chemical terms.