A REPORT TO THE PHYSICIANS OF TEXAS

newsletter

THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER

September–October 1980 M. D. Anderson Hospital and Tumor Institute Volume 25, Number 5

Conference Unites Treatment, Science

The 25th Annual Clinical Conference, "Gastrointestinal Cancer," to be held November 5–7 at Houston's Shamrock Hilton Hotel, is designed to bring together current information on the etiology, diagnosis, treatment, and basic science aspects of commonly occurring gastrointestinal cancers. During the meeting, the Heath Award will be presented to an internationally known Canadian physician.

"We believe we have a program that has drawn successfully on local resources and has attracted clinicians and scientists known nationally and internationally for work in specific areas," said John R. Stroehlein, MD, cochairman of the conference program committee. "The program, rather than being strictly 'clinical,' really attempts to bring together scientific developments and prospects for current and future application of these advancements." Program committee cochairman is Marvin M. Romsdahl, MD, PhD, professor of surgery.

Dr Stroehlein, chief of gastroenterology in the Department of Medicine, said it would be difficult to single out any one aspect of the conference. He did say the program was particularly relevant because of the frequent occurrence of gastrointestinal cancers. Researchers estimate that in 1980 large bowel cancer will affect 114,000 Americans and claim over 50,000 lives. In pancreas cancer, there will be 24,000 new cases and 21,000 deaths; in stomach cancer, 23,000 cases and 14,000 victims; in hepatobiliary cancer, 11,600 cases and 9,300 lives lost; in esophageal cancer, 8,800 new cases and 7,600 estimated deaths. He added that a snythesis of clinical and research information is important in order to try to decrease the incidence of gastrointestinal cancer and improve survival rates of patients with it.

The program begins with a general session on current concepts in gastrointestinal cancer, and sessions on recent advances in diagnosis and treatment of esophageal, gastric,

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Interferon Research Described

(Editor's Note: Jordan U. Gutterman, MD, professor of medicine in the Department of Developmental Therapeutics, was the first American researcher to treat cancer patients with interferon. He now heads the American Cancer Society's 10-institution study on interferon. Here he answers often-asked questions about the research.)*

What is interferon and when was it discovered?

Interferon was discovered in 1957. It is a hormone of the body, and it was first discovered as a natural antivirus substance. Dr Alick Issacs, working in England [London's National Institute for Medical Research] with Jean Lindenmann, found while working with chick cells that he could protect other cells from virus challenge with this hormone, this protein. He named the substance "interferon" because it interferred with the growth of viruses. This discovery immediately created a tremendous amount of excitement in the scientific community because up until that time there had been no way of treating viral infections. This occurred about 14 years after the introduction of penicillin and the tremendous progress that had been made in treating bacterial infections with antibiotics.

In 1962, Dr Kurt Paucker discovered that interferon had an additional property, that is, it slowed down the growth of cancer cells as well as normal cells. He discovered it had an antigrowth or antiproliferative effect that seemed to be independent of its antiviral properties. This stimulated a lot of basic research on interferon as a potential antitumor substance in animals.

How is interferon made?

There are three types of interferon, and virtually every cell of the body can produce interferon. Each cell has its own way, presumably, of protecting itself against virus invaders and perhaps even tumors. The first source that was found in man was leukocyte interferon. That is what we are now using in the clinic. When one exposes white blood cells to viruses, interferon is produced for a very brief period of time. Then the cell is no longer able to produce that interferon. Therefore, enormous quantities of white blood cells are needed in order to produce sufficient quantities of interferon for clinical research. The pioneer in the production of interferon from the leukocyte is Dr Kari Cantell [Helsinki's Central Public Health Laboratory]. Cantell illustrates to me the importance of one individual in research, because in 1963 he

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Jordan U. Gutterman, MD

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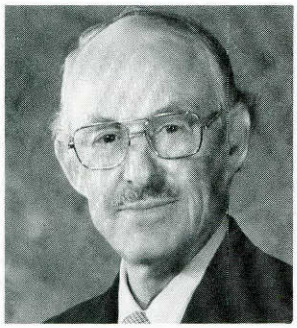
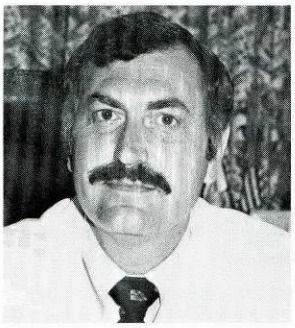


R. Lee Clark, MD



Guy R. Newell, Jr., MD

Noteworthy

The American Cancer Society, Inc. (ACS) will present its Humanitarian Award to **R. Lee Clark,** MD, president emeritus, November 8 at the ACS Board of Directors meeting. According to Lane W. Adams, ACS executive vice president, the award honors Dr Clark for his "far-reaching contributions to the control of cancer as a cancer specialist, with remarkable vision and tireless energy." The nominating committee, in recommending Dr Clark for the award, cited his administrative competence, his contribution to creating and nourishing MDAH, and, above all, his persistent dedication to the welfare of all cancer patients.

Guy R. Newell, MD, director of the Division of Cancer Prevention, has been appointed to the Mesa Petroleum Co. Professorship in Cancer Prevention. T. Boone Pickens, Jr., member of MDAH's Board of Visitors and founder and president of Mesa Petroleum Co., recommended creating the professorship, which is based on a $300,000 gift from Mesa. Dr Newell, a 1962 graduate of Tulane University's medical school, served as deputy director of the National Cancer Institute from 1973 to 1979, including some 10 months as acting director, before coming to MDAH.

Scientific Abstracts

V. L. Ng, J. J. Kopchick, W. L. Karshin, T. G. Wood, and R. B. Arlinghaus: "The Structural Relatedness of the Virus Core Proteins of Rauscher and Moloney Murine Leukemia Virus"

The virus core proteins p30, p15, pp12, and p10 of Rauscher murine leukemia virus (R-MuLV) and Moloney murine leukemia virus (Mo-MuLV) were purified. Two-dimensional peptide maps of ^{3}H-leucine-containing tryptic peptides, as well as elution profiles from ion-exchange chromatography of tryptic peptides derived from ^{3}H-tyrosine-labeled R-MuLV core proteins and ^{14}C-tyrosine-labeled Mo-MuLV core proteins, were compared. The results show that the p30 and p10 proteins are very similar but that p15 and pp12 exhibit significant differences (*J Gen Virol* 47:161–170, 1980).

P. E. Barker and E. Stubblefield: "Ultrastructure of Double Minutes From a Human Tumor Cell Line"

Double minutes (dm) have been isolated from human tumor cells by zonal centrifugation and by differential pelleting of chromosome suspensions. These methods allowed collection of dm in sufficient quantity and purity for visualization with electron microscopy. Ultrastructurally, the chromatin fibers in dm resemble those in metaphase chromosomes. No evidence of attached membrane fragments was found. When the two isolation protocols were compared, differential pelleting was shown to increase purity twofold to 85% dm by mass. The differential pelleting procedure enables easy collection of dm in sufficient quantity and purity for chemical analysis (*J Cell Biol* 83:663–666, 1979).

Department Celebrates 15th Anniversary

The Department of Developmental Therapeutics celebrated its 15th anniversary with a program July 18. The program, "M. D. Anderson and Developmental Therapeutics—The First Fifteen Years," consisted of presentations by MDAH staff members from several departments and by three speakers from other institutions.

The presentations spanned a range of topics pertinent to developmental therapeutics. Some of the subjects addressed included chemotherapy, infection, supportive care in cancer management, pharmacology and drug development, testicular cancer, cure of advanced cancer in experimental animals, biological therapy of cancer, and clinical statistical research. Department head Emil J Freireich, MD, concluded the program with a presentation entitled "The Next Fifteen Years."

Among the program's speakers from outside MDAH was Emil Frei, MD, first head of the Department of Developmental Therapeutics and current director of the Sidney Farber Cancer Center in Boston. Frank M. Schabel, Jr., MD, director of chemotherapy research at the Southern Research Institute, Birmingham, Alabama, and recipient of the Department of Developmental Therapeutics Jeffrey A. Gottlieb Memorial Award in 1978, also spoke. Lawrence Einhorn, MD, an MDAH fellow in oncology 1972–73 who is now at the Indiana University School of Medicine, headed the second half of the program with a lecture on testicular cancer.

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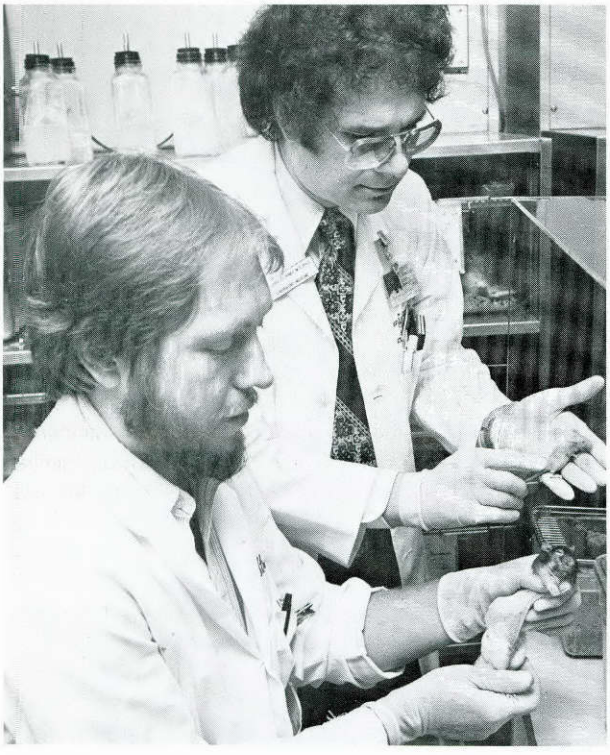

James J. Stragand, PhD (foreground), holds a Rowett athymic rat, commonly called a nude rat, and compares it to a nude mouse held by Benjamin Drewinko, MD, PhD. The investigators are using nude rats to expand their tumor research.

Nude Rats Expand Research Horizons

Researchers at MDAH are working with one of two nude rat colonies in the United States. The rats provide an in vivo system for studying human tumors equal to that of nude mice while expanding the spectrum of studies by their larger size and hardier constitution.

Benjamin Drewinko, MD, PhD, and James J. Stragand, PhD, Department of Laboratory Medicine, have been experimenting with Rowett athymic rats since March. Like nude mice, these rats accept xenografts of human tumors and provide an in vivo system for the study of human tumor growth, immune response, and anticancer drug effects.

The rats weigh 300-400 grams (the average nude mouse weighs 20 grams) and are not as susceptible as nude mice to low-grade infections or the murine Sendai virus. Because of this, researchers can perform experiments such as surgical procedures, hyperalimentation studies, and serial blood samples—all impractical or impossible with nude mice.

Dr Drewinko has worked for about 10 years with human cells grown in vitro. When he began in vivo studies, tumors induced in normal mice were problematic. "Mouse tumors are not like human tumors—the metabolism is different, the speed of growth is different, and the response to drugs is different. So now we use transplanted human tumors for in vivo studies in nude mice," he said. Nude mice will accept the transplants, according to Dr Drewinko, but the mice are very expensive and very sensitive to contamination.

"For two years the work has been complicated and expensive. These rats were an alternative. They were sturdier, not as easily affected by contamination, and not as susceptible to infection," Dr Drewinko said. Although each nude rat costs $70 and each nude mouse $13, the researchers say the rats are less expensive because the rats can be bred under controlled conditions. Dr Drewinko and Dr Stragand rejected the idea of breeding their own nude mice after determining the number of breeders necessary to guarantee 20 offspring a month and deciding that the high newborn mortality rate and the high cost of maintenance made the proposal economically infeasible.

According to a report published by Michael Festing and co-workers of the British Medical Research Council, the rats were first recorded at the Rowett Research Institute, Bucksburn, Aberdeen, Scotland, in 1953, and thus were called Rowett athymic rats. This original mutation died out but reappeared in 1975 when two females were produced in a randomly bred colony of hooded rats. Festing developed a breeding nucleus at the Medical Research Council's Laboratory Animals Centre in Carshalton, Surrey, England, and began skin grafting and xenografting experiments. Dr Drewinko and Dr Stragand asked Festing for rats to begin a breeding colony, but some of Festing's rats were contaminated by Tyzzer's disease—what Dr Stragand calls the "black plague" of rats. They were able to obtain 20 nude rats from the Oxford Laboratory Animal Centre in England, whose colony originated with rats from Festing. About 25 rats are produced monthly at MDAH from these 20 breeders.

Work that was limited because of a nude mouse's size and vulnerability can now be expanded. Dr Drewinko and Dr Stragand found that serial blood samples of the size required to monitor carcinoembryonic antigen production were impossible with nude mice, but nude rats can support the testing. "A milliliter of blood is all a nude mouse would have," Dr Stragand explains, "but with rats, you can take one milliliter per week for a couple of months without harming them."

With nude rats, researchers can begin to look at therapy responses in tissue culture from tumor and bone marrow. A biopsy can be performed on a mouse's tumor, but problems are magnified, according to Dr. Stragand. "Sedation is a problem, there is blood and fluid loss, and the size of the needle—even a 1-mm needle—poses problems," he says. Rats in the MDAH laboratory colony have tolerated sedation, cardiac puncture, and intrafemural withdrawal of bone marrow, the latter without even a limp, Dr Stragand says.

Though they are only beginning to study the biology of the Rowett Athymic rat's system and characteristics of its growth, Dr Drewinko and Dr Stragand say the similarity of the tumor cell kinetic properties of the rat to those of a human tumor in the patient, including cell cycle time, S-phase length, rate of cell loss, and growth fraction, make cell kinetics studies especially appealing. They anticipate studying cell synchronizing, ways to increase cell kill without increasing toxicity, and methods of protecting normal cells from toxicity.

Other study plans include evaluating nutritional status and its effect on tumor growth and response to antitumor drugs and the effects of drugs in general as related to fasting, feeding, and scheduling.

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The Department of Pediatrics child life worker, Jessica Fitch, MS (above), teaches a pediatric patient how a bone marrow aspiration is performed by assisting him in playing with a doll and a plastic syringe. Proceeds from the Christmas card sales support the child life worker position.

Volunteers Launch 1980 Card Campaign

As the holiday season approaches, the Department of Volunteer Services has once again launched the pediatric Christmas card campaign.

Now in its eighth year, the Christmas card campaign has grown from a small project in 1973 to a Christmas tradition known in many cities throughout Texas. The sales goal for this year is 500,000 cards, says project coordinator Karen Harrison of the Department of Volunteer Services.

The cards are designed by pediatric patients each fall, and five or six are chosen tc be printed for the next year. The contest is judged by members of Volunteer Services. Last year 30 patients participated in the contest.

Proceeds go directly to meet pediatric patients' many nonmedical needs that could not be met otherwise. Supported by the fund are the pediatric cottage (an outpatient residence where children receiving treatment can live in a home-like environment with their parents), art supplies and teaching aids, parties for the children, and salaries for a schoolteacher, child life worker, and Spanish translator.

According to Jan van Eys, MD, PhD, head of the Department of Pediatrics, the most important benefit of the Christmas card campaign is the child life worker. The child life worker is a professional play therapist who oversees a therapeutic play environment, an essential part of the patients' hospital care that would not be possible without the fund.

The translator, another direct benefit of the Christmas card campaign, has "filled an enormous need" in the pediatric unit, according to Dr van Eys. With 40% Spanish-speaking patients, the pediatric unit needs the translator as an important non-passionate intermediary between the doctors and the patients and their parents.

Individuals or groups interested in ordering or helping sell Christmas cards should contact Karen Harrison, Department of Volunteer Services, M. D. Anderson Hospital and Tumor Institute, 6723 Bertner, Houston, Texas 77030.

Pathology Program Follows Conference

The 13th Annual Special Pathology Program will be held November 8 from 8:30 a.m. until noon at Houston's Shamrock Hilton Hotel. As in years past, the program will follow the conclusion of the Annual Clinical Conference and will share its topic, which this year is gastrointestinal neoplasia.

Receiving the Joanne Vandenberge Hill Award and William O. Russell Lectureship in Anatomic Pathology during the program will be Basil C. Morson, MD, director of the Research Department of St. Mark's Hospital in London. J. Leslie Smith, Jr., MD, acting head of the Department of Pathology and moderator of this year's pathology program, calls Dr Morson "one of the world's leading authorities on gastrointestinal pathology." Dr. Morson's lecture, "Prevention of Colorectal Cancer," will open the morning program.

Since 1968 Dr Morson has been a recognized teacher at the University of London at the Royal Postgraduate Medical School and director of the World Health Organization International Reference Center for Study of Precancerous Conditions of the Alimentary Tract. He is president (1978–1980) of the British Division of the International Academy of Pathology and president (1979–1980) of the British Society of Gastroenterology. He has been a grantee of the United Kingdom's Cancer Research Campaign continuously since 1958 and a grantee of the National Large Bowel Cancer Project since 1978.

Dr Morson has authored or helped edit nine books since 1966 on gastrointestinal pathology, systemic pathology, and colorectal cancer. His publication of over 145 papers on pathology and related subjects has spanned almost 30 years.

The award and lectureship, first presented in 1977, was endowed by Ms Hill to honor William O. Russell, MD, first head of the MDAH Department of Pathology. Dr Russell headed the department for 28 years.

Symposium Scheduled

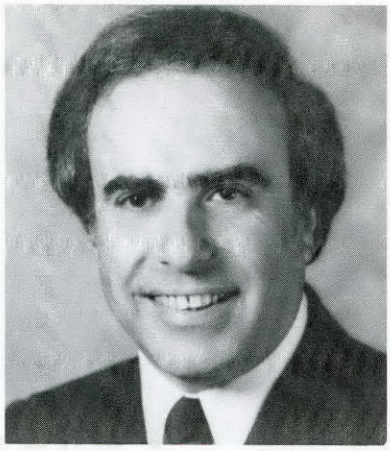
The 34th Annual Symposium on Fundamental Cancer Research, "Molecular Interrelations of Nutrition and Cancer," will be held March 4–6, 1981, at the Shamrock Hilton Hotel in Houston.

Sessions of the symposium will cover the mechanism of carcinogenesis of nutritional components, energy metabolism in tumor cells and nutritional sources, nutrient modulation of carcinogenesis and antitumor drug action, nutritional modulation of cell proliferation, and the biochemical mechanism of the immune defect in malnutrition.

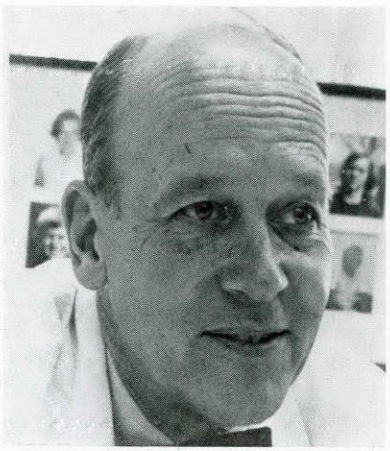
Highlights of the symposium each year include the presentations of the Wilson S. Stone Memorial Award and the Ernst W. Bertner Memorial Award.

Cochairpersons for the meeting are Yeu-Ming Wang, PhD, head of the biochemistry laboratory in the Section of Experimental Pediatrics, Department of Pediatrics; Marilyn S. Arnott, PhD, associate biologist, Division of Biology; and Jan van Eys, MD, PhD, head of the Department of Pediatrics.

Basil C. Morson



Phil Gold



Joseph H. Burchenal

Following Dr Morson's lecture, a panel of MDAH staff members will join Dr Morson in a discussion of selected cases on the conference topic. Panel members will be Bruce Mackay, MD, PhD, associate professor of pathology, Gerald D. Dodd, MD, professor of radiology and head of the Department of Diagnostic Radiology, and Richard G. Martin, MD, professor of surgery and head of the Department of Surgery.

Conference . . .

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pancreatic, hepatobiliary, and large bowel cancer will follow. The final session, which concludes at noon November 7, looks at directions for future research and prospects for control of gastrointestinal cancer.

Recipient of the 15th annual Heath Award, which will be presented during the opening afternoon session of the clinical conference, is Phil Gold, MD, PhD, McGill University professor of medicine and Montreal General Hospital Physician-in-Chief. Dr Gold, known best for his work with carcinoembryonic antigen, receives the award for his outstanding contributions to the development of oncofetal antigens, which many researchers are investigating and many clinicians are finding useful in the care of cancer patients.

A recipient of national and international fellowships, prizes, and awards, Dr Gold is the former director of the McGill University Cancer Centre. He has served as an associate editor of *Cancer Research* and currently is on the editorial board of *Clinical Immunology and Immunopathology, Immunopharmacology,* and the *American Journal of Diagnostic Gynecology and Obstetrics,* while having over 90 publications to his credit.

Session chairmen, all from MDAH, include R. Lee Clark, MD, president emeritus; Murray M. Copeland, MD, vice president of the University Cancer Foundation and director of the National Large Bowel Cancer Project; David A. Karlin, MD, and Josef Korinek, MD, PhD, assistant professors of medicine; Guy Newell, MD, head of the Division of Cancer Prevention; Dr Romsdhal; and Dr Stroehlein.

The conference is cosponsored by the National Cancer Institute and the American Cancer Society, Texas Division, Inc. It is endorsed by the Texas Cancer Coordinating Commission.

Gottlieb Award to Go to Burchenal

The Jeffrey A. Gottlieb Memorial Award will be presented November 5 to Joseph H. Burchenal, MD, director of clinical investigation at Memorial Hospital for Cancer and Allied Diseases in New York, in recognition of his contributions to cancer research. Dr Burchenal will receive the award at 5:30 p.m. in the MDAH auditorium and deliver the Jeffrey A. Gottlieb Memorial Lecture. His topic will be "Alchemy and a Stalking Horse for Solid Tumors."

A graduate of Princeton University and the University of Pennsylvania Medical School, Dr Burchenal has been affiliated with Memorial Sloan-Kettering Cancer Center and Cornell University Medical College since serving in the Army Medical Corps during World War II. He has served in posts from research fellow to vice president at Sloan-Kettering and in 1973 was named the Institute's field coordinator for cancer and head of the Applied Therapy Laboratory.

He has received numerous prizes and awards including the Albert Lasker Award in Clinical Cancer Chemotherapy, which cited his substantial contribution to developing more effective treatment and better long-term survival rates for acute leukemia patients; the Prix Lepold Griffuel, which described him as "one of the most meritorious pioneers of the chemotherapy of cancer and leukemias"; and the Leukemia Society of America's deVilliers Award, which honored him for initiating laboratory and clinical investigations that led to successful treatment of childhood leukemia. He has also received the Alfred P. Sloan Award in Cancer Research, the David A. Karnofsky Memorial Award of the American Society of Clinical Oncology, and the James Ewing Award.

The Jeffrey A. Gottlieb Award was established in memory of a physician and scientist who initiated the clinical use of combination chemotherapeutic regimens of Adriamycin and bleomycin after joining the MDAH staff in 1970. Before dying of seminoma in 1975, Jeffrey A. Gottlieb, MD, was chief of the chemotherapy service in the Department of Developmental Therapeutics and an associate professor of medicine at MDAH.

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Interferon . . .

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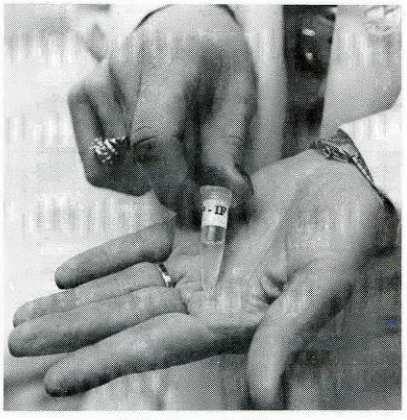
recognized the potential use of interferon in viral diseases and in cancer. He had just worked with Paucker in Pennsylvania, and he went back to Finland in 1963 and organized the Finnish Red Cross to give him the buffy coat, the white cell layer. He wanted to expose the white blood cells to viruses in the laboratory and have them make interferon.

It took him approximately 10 years to perfect the technique up to the point that he could collaborate with Dr Hans Strander in Sweden [Stockholm's Karolinska Institute] in order to see if this material did, indeed, have any potential in the clinic. He was able to purify it up to sufficient quality so it would not be harmful to people. The purity of the material he made in 1973 is one part in 1000. Only one part in 1000 that he gave—that we still give today—is interferon. The remaining materials are contaminating proteins that come out of the white cells.



Interferon in tube

Who did the first interferon study with cancer patients?

The first extensive study prior to our work here at MDAH in cancer patients was made by Dr Strander in Stockholm during the early 1970s. Dr Strander had worked with and received his PhD with Dr Cantell. During the 1960s Cantell was working on methods to purify leukocyte interferon to sufficient quality so he could give it to patients. Dr Strander, who is also an MD and a radiotherapist, went back to Stockholm at the Karolinska Institute and began to do phase I and pharmacological studies with the impure leukocyte interferon. He treated a patient with osteogenic osteosarcoma who had had an amputation for a very large tumor. After the patient got interferon for several weeks and the tumor did not recur, surgeons began to call on Dr Strander. This started a consecutive series, unplanned at the beginning, of treating osteogenic sarcoma patients with interferon.

The percentage of patients achieving a five-year disease-free interval after amputation and radiotherapy varies from institute to institute, but is on the order of 15% to 25%. I don't think people get much better than 25% or 30%. At the current time, 42 patients have been entered in the interferon study; however, only 12 have been followed after five years. The results suggest that 50% will have a five-year disease-free interval. It appears that these results are identical to what one gets with high-dose methotrexate or Adriamycin.

Dr Strander's results have been criticized because this was not a randomized study. I don't think these results are statistically significant because of the small number of patients, but they are very highly suggestive of a beneficial result. If all the evidence that interferon was effective against cancer rested on these studies, I think we wouldn't be very far along. But I think from a historical standpoint they are very important.

How did you become involved in interferon research?

These studies were first reported in 1975 at an international conference on interferon in New York at the Rockefeller Institute. That is where I first heard the results, and I was very intrigued not only by the results Dr Strander was achieving but about the whole possibility of using the various interferons in cancer patients. Here was a nontoxic substance, a natural substance, that not only stopped the growth of viruses but stopped the growth of cancer cells, and it seemed that this material was worthy of further work. The problem was simply one of money.

Why was money a problem?

In contrast to almost all other hormones in the body, such as insulin, interferon is species specific. In order to give interferon to a patient with a virus infection or, indeed, with cancer, one has to use interferon from human sources. This makes it very difficult to produce adequate quantities of the material for clinical research, because each cell of the body produces a very tiny amount of interferon.

The cost of production was $150 per dose. The dose Dr Strander was using was 3 million units a day—the same number of units we use of this material. At $150 per dose—he was giving it on a daily basis—it would cost literally several thousand dollars to treat even one patient. The National Institutes of Health and the National Cancer Institute had looked at the situation and said there was very little clinical information and that it was too risky really to invest a large amount of money in further clinical work. . . . Late in 1977, Mrs Mary Lasker, who has been a major figure in the whole area of cancer research, gave a contribution to the M. D. Anderson Hospital and Tumor Institute to allow us to do initial testing in patients with advanced cancer.

What were you trying to determine in MDAH's first interferon study?

We were able to get enough funding to buy leukocyte interferon from Dr Cantell in Finland and begin work. Our objectives were a little different from Dr Strander's. I thought it was very important to determine if interferon could induce regression of established metastasis. We had been working with a variety of immunological agents, and none of them, such as bacillus Calmette-Guérin, levamisole, or thymosin, had the capacity to induce tumor regression. From animal studies, one would not think that this would occur. But I thought it was important, if interferon was going to be effective in early disease, to determine if we could affect late disease. We didn't really expect it, but we have indeed seen the efficacy of interferon against various cancers.

Our first group of patients totaled 38. We evaluated three types of cancer: breast cancer, myeloma, and lymphoma. The dosage schedule we evaluated was primarily 3 million units on a daily basis. We used a daily schedule because in vitro the optimal effects against tumors are seen when the interferon is kept in the cultures continuously. Whether this is the optimal way of keeping the immune response activated we aren't sure.

Basically this was the dosage schedule Dr Strander used in his osteogenic sarcoma series. Because of the limited amount of interferon we had, we really didn't have the opportunity to do dose-response work. It will be quite exciting when we have enough pure material to increase the dose by several factors.

Thirty-four percent of the patients achieved complete or partial remission of their tumors. Seven of 17 breast cancer patients achieved a response. We included a "less-than-partial remission or improvement" category to indicate a patient who did not have 50% reduction of tumor but had a 25% to 50% reduction. I thought it was very important to document these biological effects because of our inability to increase dose.

We have increasing evidence from more recently treated patients that higher doses of interferon seem to be more effective than the lower doses. With more available material, we've begun to escalate dose in certain patients.

These are all patients with quite advanced disease. The breast cancer patients had been treated with virtually everything—surgery, radiotherapy, hormone therapy, and, in most instances, chemotherapy. The same is true for the myeloma and lymphoma patients, although there are some who did not receive chemotherapy.

What side effects do you observe?

This material, as I have indicated, is only one part in 1000 pure. We don't know if the side effects we're seeing are due to interferon or to one of the many contaminating proteins. Most of the patients get a low-grade fever during the initial few days, but by one week, fever is very uncommon. Chills are really minor. Probably the most important side effect we're seeing is fatigue. With the daily injections, particularly with patients in their 70s, fatigue can be a rather prominent symptom, and it's difficult to give interferon to them for more than three months on a daily basis. Loss of appetite occurs in our older patients. Similarly, many of our patients lose weight. A minimal amount of alopecia does occur in some of these patients, particularly if they are on the drug for several months. Interferon does have an effect on the growth of normal tissue. There is a transient rise in SGOT [serum glutamic oxaloacetic transaminase]. We're not sure of the mechanism here, whether it is due to the interferon itself or to the contaminating proteins.

How do your patients' responses to interferon compare to their responses to other treatment?

We correlated the response to interferon to the previous response to chemotherapy to see if there was any biological correlation. Among the nine patients who had never responded to chemotherapy, we had only one patient whose treatment with interferon had an effect. Among the 18 patients who were relapsing after previous remission with chemotherapy, interferon had a biological effect on virtually all. Among patients who had never had chemotherapy, interferon affected about half.

One other fact that is very important to understand is this: no one, I think, right now would imply that interferon *alone* would have a major impact on many of these tumors. But the fact is we've had very interesting effects and very interesting responses—eight partial remissions and complete remissions in patients who are resistant to a whole series of chemotherapeutic compounds. So it is very clear to me at least that adding interferon to conventional chemotherapy, at the minimum, would be something of great excitement for the future.

What about the problems with supply?

A remarkable amount of progress has been made in just the last six months on not only the purification but the synthesis of interferon by recombinant DNA. The material has been purified. The amino acid sequence of all these interferons, except immune interferon, are very close to being completed, so we should know the entire structure of leukocyte and fibroblast interferon in the next few months; however, these molecules are too big to chemically synthesize from an economic standpoint—150 amino acids, at least with the current technology, is impractical.

The recombinant DNA in which the gene is inserted into *Escherichia coli* is an alternative route, and leukocyte interferon and fibroblast interferon have been cloned by several groups. There are several potential problems with interferon that comes from the bacteria. We're going to have to go through the same kind of studies with the cloned interferon as we did with the natural materials.

I, for one, am very excited about the cloning. I'm not skeptical, but I think we have to continue the studies with the naturally occurring interferons, because I don't think we should put all our eggs in one basket. But certainly in terms of supplies of interferon we are going to have to depend on some type of synthetic process. It's conceivable that the whole molecule is not required for the biological effects, and maybe only certain fragments are active and these could be synthesized chemically.

These are the types of things that are going on in very basic research laboratories. Of course, this is quite exciting, and eventually we'll be involved with these materials clinically.

What studies are you involved in now?

In the last few months we've begun to explore three additional tumors—cancer of the ovary in collaboration with the Department of Gynecology, cancer of the prostate in collaboration with the Department of Urology, and cancer of the colon. It's too early to say anything by any means definitive. We have some hints of biological effects actually in all three tumors, but we really can't say much at all. I can say one thing about cancer of the colon. We now have had two of eight patients who have had very interesting responses. One patient with a mass that was documented by pelvic and rectal examinations as well as by computerized tomography and ultrasonography had a very interesting response after four months that has persisted well over a year. One young man with extensive documented liver metastasis who had had only surgery had a tumor reduction after six weeks of interferon.

What about the future of the interferons?

I think in the next year or two as we begin to work with all three of the interferons and come to understand them better and perhaps use them in combination, we're going to see even greater effects. We have a lot of work to do to understand how to use them, and then finally we have to integrate

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Relocation Increases Hospital, Research Areas

During the next year several departments currently housed in the MDAH inpatient and outpatient areas, but which are not directly related to patient care, will be moving across Holcombe Boulevard to the former Prudential building, according to William E. Miller, sen or management analyst, Office of Resource Planning and Evaluation. The move is intended to put business functions and other activities that can be performed in an office-building atmosphere in one location, allowing the hospital and clinics to expand patient care and research facilities.

Miller said plans are still being finalized, but the departments currently scheduled to make the move are Biomathematics, Epidemiology, Medical Genetics, and Human Resources. The Physicians Referral Service, Budget Office, Office for Programs Development, and Office of the President are also scheduled to relocate in the former Prudential building, as are the central operations of the mail room and some of the services of the Department of Medical Communication.

This reorganization will free approximately 28,000 square feet of space in the hospital complex, space that will be used for clinical expansion and additional areas for research, Miller said. The Departments of Rehabilitation Medicine and Diagnostic Radiology will be expanding. Diagnostic Radiology will use some of the extra space to house their computerized tomography scanners and other radiologic units and for the new Dunn Laboratory, an experimental diagnostic radiology facility. Some of the space has been allocated for a new immunotherapy research area, according to Miller.

The planned moves will continue at least until August 1981, as the renovation of the former Prudential building is completed and new offices are readied for occupancy. According to Miller, this long-range project will enable MDAH to concentrate related activities in one area and thereby utilize its patient care and research resources to the fullest.

Interferon . . .

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interferons—the whole field—with conventional therapy. Because we are seeing results in patients totally resistant to chemotherapy, I think that at the very least the whole system of interferon will be an important addition to the therapeutic approach in cancer. Cf course, being an antiviral agent, it has the advantage of probably protecting against various types of infections.

I think the final message must be that we now have biological agents that seem to induce regression of cancer, which I think is a new idea. The biolcgical agents that we've worked with over the years have not been able to do this. I think this will open the door to other possible biological approaches. There are agents, of course, that can affect differentiation. I fully expect over the next 10 years that a variety of substances will be coming along that will have very interesting potential, but it's going to take a lot of hard work.

*These comments are drawn from presentations Dr Gutterman made as part of the Fundamentals of Oncology Part II lecture series and Nat onal Hospital Week. (Physicians requiring further information on this subject should contact the author.—ED.)

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