NEWS LETTER

The University of Texas at Houston
M. D. Anderson Hospital and
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Environment and Cancer
Topic of Spring Symposium

The exciting and controversial topic of environmental elements and cancer was the concern of participants in the MDAH 24th Annual Symposium on Fundamental Cancer Research, held March 3, 4, and 5, 1971. According to co-chairmen, Dr. Roger Hewitt, dept. of biology, and Dr. Marvin Romsdahl, dept. of surgery, who arranged the program with the aid of their committee, scientists from as far away as Tübingen, Germany, concentrated their Symposium efforts on three main areas in five sessions. These were: Identification of Hazards in the Environment I and II, Mechanisms of Cancer Induction I and II, and Host-Dependent Factors in Environmental Carcinogenesis.

In addition to lectures and panel discussions, the Bertner Foundation and Wilson Stuart Stone Memorial awards were presented. Drs. Elizabeth C. and James A. Miller of the McArdle Laboratory in Wisconsin received the Bertner Award jointly, and Roberta M. Palmour, Ph.D., was given the Stone Award for outstanding achievement in the biomedical sciences. Jesse Steinfeld, surgeon general of the U. S. Public Health Service, gave the keynote address, "Detecting and Eradicating Hazards in Our Environment."

Among papers presented was one by Johannes Sander of the Hygiene-Institut der Universität Tübingen on the possible formation of cancerogenic nitroso compounds under the influence of biological conditions. Ernest Wynder from the American Health Foundation of New York considered the preventive aspects of the problem of carcinogenic hazards in the air. John Higginson from the International Agency for Research on Cancer in Lyon, France, assessed the effect of certain environmental chemicals in an effort to outline more valid legislative controls. John Gofman of the

Dr. Jesse Steinfeld, surgeon general of the U. S. Public Health Service, was keynote speaker at the March Symposium.

Donner Laboratory of Medical Physics in Berkeley evaluated, in terms of biological cost, the current standards of radiation allowable for U. S. Atomic Energy Programs.

Additional presentations centered on mechanisms of cancer induction. Methodology for the induction, selection, and characterization of point mutations in cultured mammalian cells was discussed by E. H. Y. Chu, Oak Ridge National Laboratory. Leonard Merkow from the Allegheny General Hospital in Pittsburgh reported on a study of environmental carcinogens. According to Merkow, these manifest their activity by finite and predictable morphologic cellular responses which are as yet incompletely understood. In vitro transformation of human cells by several oncogenic simian adenoviruses was the subject of the lecture by Malcolm Slifkin from the Allegheny General Hospital, and A. Clark Griffin of the MDAH dept. of biochemistry considered possible interactions between chemical carcinogens and transfer RNA. R. J. Huebner from the National Institutes of Health discussed the possibility that RNA virus-specific antigenic expressions could be activated in tumors induced by chemical carcinogens; such activation has already been observed in spontaneous tumors and in normal prenatal and postnatal tissues of mice.

Three reports in the area of host-dependent factors in environmental carcinogenesis were: the difficulty of assessing the exact role of hormones in tumor induction in human beings (Robert Huseby, American Medical Center at Denver); spontaneous and induced neoplasms in germfree rats (Morris Pollard, University of Notre Dame); and the role of host-defense impairment in the development and progression of cancer in man (Evan Hersh, MDAH dept. of developmental therapeutics).

The University of Texas MDAH sponsored the Symposium. Co-sponsors were The University of Texas School of Public Health at Houston, The University of Texas Graduate School of Biomedical Sciences at Houston, the Texas Division of the American Cancer Society, and the National Cancer Institute. The Advisory Committee included Dr. Isaac Berenblum, Weizmann Institute of Science, Rehovoth, Israel; Dr. Alexander Hollaender, Oak Ridge National Laboratory; Dr. William Poel, University of Pittsburgh Graduate School of Public Health; Dr. Phillipe Shubik, Eppley Institute for Research in Cancer, Omaha; Dr. Reuel A. Stallones, dean, The University of Texas School of Public Health at Houston; and Dr. John Weisburger, National Cancer Institute. The following MDAH staff were members of the Symposium Committee: Roger R. Hewitt (chairman), Marvin M. Romsdahl (vice-chairman), James M. Bowen (dept. of virology), Edmund A. Gehan (dept. of biomathematics),

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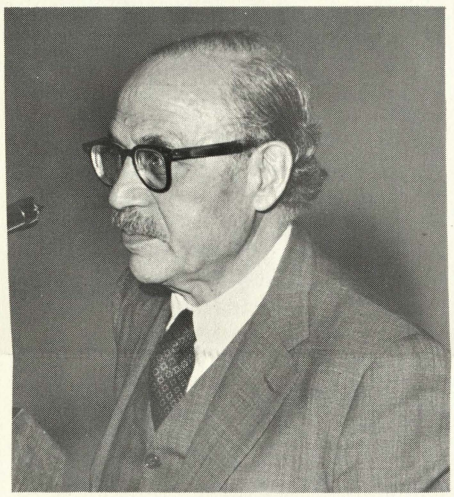
A. Clark Griffin (dept. of biochemistry), Felix Haas (dept. of biology), Ronald M. Humphrey (dept. of physics), Joseph P. Kennedy (UT Environmental Science Park), Gerald LePage (dept. of dev. therapeutics), and Eleanor Macdonald (dept. of epidemiology).

The proceedings of the three-day Symposium will be collected and published under the title, "Environment and Cancer."

Drs. Elizabeth C. Miller and James A. Miller from the McArdle Laboratory were joint recipients of the Bertner Foundation Award.



Dr. Alexander Hollaender from the Oak Ridge National Laboratory was a member of the advisory committee.

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First Annual Wilson S. Stone Memorial Award Presented

The first presentation of the newly established Wilson S. Stone Memorial Award was made during the 1971 Annual Symposium on Fundamental Cancer Research. The award, which is given for outstanding achievement in the biomedical sciences, was presented this year to Roberta M. Palmour, who received her Ph.D. degree from The University of Texas at Austin in 1970.

Dr. Palmour was recognized for her work in the field of biochemical genetics which she pursued under the direction of Dr. H. Sutton, chairman, dept. of zoology at Austin. More specifically, Dr. Palmour showed unusual technical ability and originality, in the opinion of the Award Committee, in selecting organisms and adapting methods for her studies on the amino acid structure of transferrin.

The Wilson S. Stone Memorial Award was established by MDAH's staff to encourage young scientists in the United States to reinforce and augment the legacy of scientific work and academic traditions left by Dr. Stone at his death.

During most of his career, Dr. Wilson Stuart Stone (1907–1968) was associated with The University of Texas at Austin, first as professor and chairman of the dept. of zoology, and then as Vice Chancellor of the University in 1965. He was instrumental in the establishment of the Genetics Foundation, an important branch of the University. His research was centered on the areas of genic action, irradiation genetics, and microbial genetics.

In addition to membership in the National Academy of Sciences, the Genetics Study Section of the National Institutes of Health, the American Society of Human Genetics, and many other scientific societies, Dr. Stone was Consultant in Genetics to MDAH from 1955 to his death and was a guiding force in the creation of the Graduate School of Biomedical Sciences, another component of The University of Texas at Houston. Dr. Stone also worked to achieve the success and refinement of the Annual Symposium.

Besides publishing many scientific papers, he served as co-editor, with Dr. C. P. Oliver, of the journal *Genetics* from 1957 to 1962, and was associate editor of *Radiation Research* from 1960 to 1963. At the time of his death, Dr. Stone was planning a trip to the Soviet Union where he had been invited to present the results of some of his most recent investigations.

Point mutation in mammalian cells was discussed by Dr. E. H. Y. Chu from Oak Ridge Nat. Lab.

Dr. John Higginson from Lyon, France, spoke to Symposium participants.

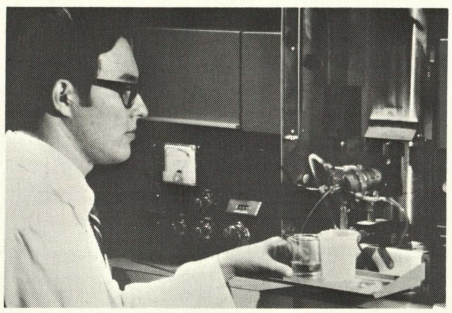
Serum Copper A Possible Predictor of Neoplasia

Investigators in the sec. of exper. pathology at MDAH are in the process of establishing the value of serum copper levels in following and predicting the clinical course of Hodgkin's disease. Serum copper is high in untreated disease and in cases in which treatment has not effected control or favorable response. Studies show that a rise in serum copper levels precedes clinical evidence of active tumor growth. Normal levels are present when the disease is in complete remission, but levels rise if relapse occurs. This promises to be a simple chemical test for tumor activity, something which has not been available to clinicians.

The study of serum copper forms a substantial part of the general trace elements study program set up in the late 1950's in an effort to determine the significance of trace elements in malignant disease. Interest focused on copper after the observation, made in Europe in the early 1960's, that copper levels were high in malignant disease of the reticuloendothelial system, particularly Hodgkin's disease, and were related to the extent of disease. Research, under the direction of Dr. Carl F. Tessmer, chief, sec. of exper. pathology, was designed to extend the observations on the value of serum copper determinations as a predictive guide to disease activity and to the therapeutic response of patients.

Since then, research has progressed in several directions. First, efforts have been made to determine normal values of copper in a control population. Values have been obtained for a wide range of ages, although more information is needed in the very early age groups.

Tests on patients with Hodgkin's disease have revealed a clear relationship between serum copper levels and the clinical course of the patient. In many case studies, an increasing serum copper level during chemotherapy or radiotherapy was an indication of the subsequent adverse course of the disease even though no clinical signs of disease were present. Marked elevation of serum copper levels during remission preceded clinical evidence of relapse by many months. A correlation between serum copper levels and the course of lymphocytic leukemia patients is also indicated.



Mr. Benjamin Thomas, a graduate student in exper. pathology under the direction of Dr. Carl F. Tessmer, is shown analyzing copper levels in serum samples from mice by means of an atomic absorption spectrometer.

A second phase of research concerns the relationship of copper levels and administration of estrogens. Estrogen is the major substance observed to elevate copper levels above normal; hence, a normal woman who takes birth control drugs will have higher than normal serum copper levels. This correlation is now being developed as a simple chemical test to indicate a positive estrogen effect in hormone therapy of carcinoma of the prostate or breast.

A third area of research involves work in animal systems. At present, no animal has been found that exhibits the same copper value responses as human beings. Mice show the early rise in copper levels following administration of oncogenic viruses; and although they display the same rise during pregnancy which is noted in humans, they have not shown a similar estrogen response.

These pilot studies, which have been supported by small institutional grants, have already demonstrated the value of serum copper levels as a guide in the management of certain neoplastic diseases, particularly Hodgkin's disease.

Group Studies Thyroid Tumors

Special Projects Studied

The Thyroid Study Section at MDAH, composed of physicians from the depts. of medicine, pathology, and surgery, presents a multidisciplined approach to the study of the many clinical and laboratory aspects of thyroid tumors. The members of these depts. are the primary staff persons charged with the clinical responsibility of diagnosis and treatment of patients presenting themselves to the institution with thyroid tumors. Many other disciplines, such as genetics, nuclear medicine, immunology, and biochemistry, are often called on to give support for specific projects.

The latest activity of the group is the study of the efficacy of a recently discovered and synthesized hypothalamic hormone, thyrotropic releasing hormone (TRH), in the treatment of metastatic differentiated (follicular, papillary, mixed papillary and follicular, and Hurthle cell) carcinoma of the thyroid.

The function of this hormone is to stimulate release of the thyroid stimulating hormone (TSH) from the pituitary. In the past, it has been assumed that when a person becomes myxedematous, the endogenous TSH production is at its maximum.

Now it is possible to test this hypothesis with the administration of TRH. If a patient develops metastatic differentiated thyroid cancer after total thyroidectomy because of the primary disease, his replacement thyroid hormone therapy is discontinued and he is allowed to become myxedematous. TSH levels are measured by radioimmunoassay techniques at that time. The uptake of radioactive iodine in the metastatic lesion is also measured. TRH is administered and repeat measurements of TSH and the ^{131}I are made. If further TSH stimulation can be achieved, it is hoped there will be a greater accumulation of ^{131}I in the metastatic deposits and a greater degree of destruction of the tumor tissue.

This study offers the first hope for improvement of the efficacy of ^{131}I in the treatment for thyroid cancer. It may be especially beneficial for those patients whose tumors previously concentrated ^{131}I but for some reason have lost this ability.

In another project, group efforts have been successful within the past year in developing a sensitive radioimmunoassay for detection of calcitonin, a polypeptide hormone produced by medullary (solid) carcinoma of the thyroid gland. (A further report on medullary thyroid carcinoma can be found in Vol. 15, No. 3 of the *News Letter*.) This assay provides the opportunity for early diagnosis and a better method of evaluating the prognosis of this disease. The study group in very interested in receiving any patients that could benefit by being in this study and thus accelerate the accumulation of knowledge for the better care of thyroid cancer patients.

CLINICAL ABSTRACTS

The editors of the *News Letter* hope better to acquaint practicing physicians with research developments at MDAH by previewing articles of direct relevance to the readers. As they are submitted to various journals for publication, selected articles will be abstracted by members of the MDAH publications department for presentation in the *News Letter*.

Adenoid Cystic Carcinoma of the Uterine Cervix: Report of 4 Cases: H. Stephen Gallager, C. B. Simpson, and Alberto G. Ayala.

Four instances of patients with adenoid cystic carcinoma of the cervix seen at MDAH are reported and analyzed. Carcinomas of the adenoid cystic pattern are known best as neoplasms of the major and minor salivary glands.

The four neoplasms were histologically similar. In typical areas, the cells were arranged in circumscribed oval or irregular clusters varying greatly in size. Within the clusters, the cellular arrangement was cribriform with numerous clear spaces or small, rounded areas containing hyalin material or small blood vessels. Cells were not oriented to the spaces in any discernible way.

In other areas of the neoplasms, a more diffuse pattern prevailed. If only these areas had been present, specific histologic diagnosis would not have been made. Often both the diffuse and cribriform patterns could be found within a single tumor nodule.

The authors' experience and six acceptable, previously reported cases indicate that uterine cervical adenoid cystic carcinoma is at least as aggressive as its salivary gland counterpart. Of the six patients followed for more than a few months, only one has survived three years without evidence of recurrence. Available data indicate that a typical patient is likely to be an elderly, multigravid Negro female.

It seems possible that cervical adenoid cystic carcinoma may occur somewhat more frequently than the scarcity of reports implies. It escapes detection as a result of limited biopsy material and and is classed as small cell undifferentiated carcinoma.

Angiographic Demonstration of Hypernephroma in a Polycystic Kidney: Warren L. McFarland, Douglas E. Johnson, and Sidney Wallace.

The paucity of cases describing the coexistence of a neoplasm and polycystic disease reflects in part the difficulty of detecting neoplasms in a kidney already enlarged and a collecting system already distorted.

The most common neoplasm found in association with polycystic disease is renal cell carcinoma, 13 cases having been reported previously. In most instances, the malignant disease was not suspected before surgical exploration or necropsy.

The authors illustrate a diagnostic and therapeutic approach to this problem by a case report of a 45-year-old Caucasian female with known polycystic kidney disease and a pathologic fracture of the middle third of the right clavicle.

Asymmetry in size and shape, palpable mass, and hematuria can be associated with polycystic disease, a neoplasm, or a combination of the two. The presence of any of these findings should precipitate further investigation. Nephrotomography is of value when there is adequate renal function, but renal arteriography is the more definite procedure.

Though renal sonography confirmed the presence of a solid lesion in this patient, continued experience with the technique will be needed before definitive conclusions can be drawn about its efficacy as an aid in the differentiation of renal masses.

A Passive Treatment Verification Device: Earl Van Roosenbeek and Thomas G. Nelson.

The many current models of megavoltage radiotherapy equipment offer a wide range of treatment parameters. When all variables are incorporated into one machine, the possibility of an error in patient treatment is increased greatly. To reduce this possibility on an 18-Mev betatron, a passive treatment verification device was built and installed.

The device is inactive, as opposed to the punch card or tape devices used to automate patient set-up. It is designed around a card translator which "reads" a prepunched card and verifies that at least four of six sets of variables have been set correctly. These are: beam mode (photon or electron); energy (6, 9, 12, 15, or 18 Mev); electron filters (zero to nine); and photon compensators (none, #1, or #2). An error in setting in these variables could mean a large difference in the dose delivered to a patient.

If the parameters are set properly, the machine can be turned on when the patient's prepared card is inserted into the reader. A switch electrically removes the verification unit from the betatron for nontherapeutic use. Among the variables not verified by the card reader are field size, distance, and head and cone angle—all an obvious part of the visual set-up of the patient.

This device could be adapted for use in other therapy equipment in which the many variables pose a potential problem.

Metabolic Changes After Intrauterine Fetal Death Compared with Metabolic Changes During Normal Pregnancy: N. A. Samaan, W. A. McRoberts, and L. G. Myers.

Studies were undertaken to evaluate the role of certain hormones in the changes in carbohydrate, protein, and fat metabolism associated with pregnancy. Hormone levels in normal patients were compared with those of patients in whom one or more hormones were abnormal as a result of intrauterine fetal death, choriocarcinoma, or luteal cyst. Investigations suggested that the level of human placental lactogen (HPL) is a significant factor in these metabolic changes.

Patients were followed through the three trimesters of pregnancy and for 6 to 8 weeks postpartum in order to determine the effects of amino acid infusion and oral glucose administration on the levels of blood glucose, immunoreactive insulin, and growth hormone. Human chorionic gonadotropic hormone and HPL in serum and urinary estriol and pregnanediol were also measured .In normal patients, fasting blood sugar levels fell with increasing periods of gestation. The fasting insulin level increased late in pregnancy while growth hormone levels showed a gradual fall as pregnancy progressed toward term.

All those who had fetal death had metabolic changes (hyperglycemia, hyperlipemia, and hyperinsulinemia) similar to those seen during pregnancy with live fetus in spite of significantly low levels of urinary estrogens. While other hormone levels were abnormal in some respect, serum HPL levels were consistently within normal range for the period of gestation. From these measurements and from results of HPL administration to patients under metabolic balance conditions, the authors have surmised that HPL is of major significance in the metabolic changes occurring during pregnancy.