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NCI'S PROBLEMS WITH FDA APPEAR TO BE RESOLVED WITH AGREEMENT ON DRUG DISTRIBUTION SYSTEM

The two-year-long battle between NCI and the Food & Drug Administration over supervision of clinical testing and distribution of experi-

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In Brief

DEVITA, FDA CHIEF HELP KILL CALIFORNIA BILL LEGALIZING LAETRILE WITH COMMITTEE TESTIMONY

LAETRILE PROPONENTS received a setback when a California State Legislature committee voted 6-5 to kill a bill legalizing sale of the drug. Vincent DeVita, director of NCI's Div. of Cancer Treatment, and FDA Commissioner Donald Kennedy, testified against the bill at a hearing just before the vote. The committee's action eliminates any chance laetrile will be legalized in California, this year at least. Meanwhile, FDA published in the *Federal Register* Aug. 5 the administrative record it was required by the courts to compile, along with Kennedy's conclusion that laetrile is not generally recognized by qualified experts as a safe and effective anticancer drug, and that it is not exempt from premarket approval by "grandfather" provisions. . . . **ABSTRACTS:** A group of cancer journal editors met earlier this year to ponder mutual problems, one of which was how to improve the abstracts which are supposed to succinctly and accurately describe the contents of each article they publish. Sidney Weinhouse said he considered it the author's responsibility to write the abstract, but John Bailar said "too many can't write." Jonathan Rhoads suggested that it might be better "to get the author back to work in science and get someone else to write the abstract." Philippe Shubik agreed and offered the opinion that those abstracts "would be more objective." But Weinhouse pointed out that Journals usually are not equipped to write abstracts, and one editor said, "I wouldn't want someone else writing my abstract." A French editor said he was having problems translating articles into English for American publication. He was advised to seek help from an American or an Englishman, but John Ultmann said "the worst thing you can do is to get an Englishman to translate for an American journal. Just do the best you can, if you can't find a handy American to help." . . . **NEW PUBLICATIONS:** "The Smoking Digest—Progress Report on a Nation Kicking the Habit" will be available next month, if government printers stay on schedule (which they rarely do.) Written by NCI's Office of Cancer Communications, it includes reports on adult and teenage smoking behavior, biomedical effects of cigarette smoking, information and education programs, smoking cessation programs, legislative restraints, and the tobacco industry. Also, "Pretesting in Cancer Communications—Methods, Examples and Resources for Improving Cancer Messages and Materials," also published by OCC. Write to OCC, NCI, Bethesda, Md. 20014.

CANCER CENTERS TO AID DISTRIBUTION OF EXPERIMENTAL DRUGS TO PHYSICIANS

(Continued from page 1)

mental anticancer drugs appears to have come to an end. The final major hurdle to an agreement was cleared when FDA approved NCI's plan for distribution of drugs to investigators and practicing physicians.

"Our relationship with FDA is going very well, and if it keeps on as it has been, everything will be fine," said Vincent DeVita, director of the Div. of Cancer Treatment. "We owe a large debt to Dick Crout (director of FDA's Bureau of Drugs) for working this out."

When NCI could get nowhere in discussions with FDA's Div. of Oncologic Drugs following a series of FDA interruptions of INDs for petty or illogical reasons, Crout intervened and took over negotiations with NCI which led to the agreement.

There are no current problems with INDs (investigational new drugs which require FDA approval before they can be tested in humans), and the two agencies have agreed on systems for providing annual reports and monitoring of clinical trials.

Crout had promised DCT's Board of Scientific Counselors last March that there would be no more interruptions of INDs because of procedural matters. "If we run into monitoring or communications problems, we hope to elevate those problems to us (himself and DeVita) and not take it out on the IND. If we do interrupt you, you can be sure it will be for reasons of toxicity or pure science. Interruptions will not happen unless there is a very valid reason, and after a high level of communication between NCI and FDA."

So far, Crout has been able to keep that promise. Some NCI staff members are a little concerned about what will happen when the standard routine is resumed, that is when both Crout and DeVita move away from their intense scrutiny of day to day problems and let their subordinates handle them. It was one of Crout's subordinates, R.S.K. Young, group leader for oncology, who started the whole affair with wholesale interruptions of INDs.

Although any of Young's superiors, right on up to the FDA commissioner, could have vetoed his actions, the FDA hierarchy is always reluctant to overrule a subordinate because of a highly developed concern for their own necks in case he turns out to be right. Survival and advancement at FDA frequently has depended on an individual's ability to avoid such situations.

DeVita said that "Young is no problem now," indicating that Crout has persuaded Young to go along with the new systems and the promise not to interfere with INDs without Crout's personal approval.

DeVita also gave credit to Vincent Bono, chief of the Investigational Drug Branch, for smoothing out the problems with FDA.

The primary feature of the drug distribution system is the use of cancer centers to dispense certain drugs to individual investigators who are not affiliated with any Cooperative Group, NCI contract, or NCI supported task force or study group. NCI has traditionally provided investigational drugs to those physicians because it was the only way many cancer patients would have any chance of receiving effective treatment.

FDA had objected because many physicians were not following investigational procedures—drugs could be used only in approved protocols, adverse reactions had to be reported immediately, and results should be reported regularly.

NCI suggested that the centers could help provide better monitoring and followup of the use of those drugs by physicians in their respective communities, and FDA has now agreed.

DeVita said that center directors have agreed to undertake that role and feel that it will help improve cancer care. They were concerned that it would put a further drain on their shrinking budgets, "but it is my feeling it won't," DeVita said. If it does, NCI will have to provide the money to cover the costs. NCI will continue to provide the drugs at no cost to physicians, patients, or the centers.

The distribution system and drugs that will be available were reported in ***The Cancer Letter*** March 25. That system remains essentially as described then, with some modifications:

- Two drugs have been added to Group C, those that will be available to "qualified registered investigators" without going through the centers. The two are platinum, for non-seminomathous testicular tumors and ovarian carcinoma, and hexamethylmelamine, for ovarian carcinoma. The other Group C drugs are BCNU, methyl-CCNU, daunomycin, 5-azacytidine, and streptozotocin.

Group C drugs are those of proven efficacy against certain forms of cancer but for which NDAs (approval for marketing as prescription drugs) have not been obtained. To qualify as a registered investigator, a physician must submit form 1573, available from DCT. Drugs will be sent on written request, and physicians are required to use them only as suggested by the guidelines and only for the conditions in which clinical efficacy has been shown.

- Not all Group B drugs will be available through the centers. NCI is preparing a list of 20 drugs selected from Group B which will be available (and which will be published in ***The Cancer Letter***). Reasons for exluding are lack of availability; the fact that a drug had been studied extensively and found ineffective, or that a pharmaceutical company is developing the drug, may be secured from the company, and that NCI does not feel it warrants further study.

Group A drugs are those in phase I and limited early phase II studies. They will be available only to members of the Phase I Working Group which consists of seven contract supported investigators, nin non-funded investigators who are supported by their own institutions, and investigators on the DCT intramural staff.

Group B drugs are those in broader phase II, phase III and phase IV studies. They are available now to the Phase I and II Working Groups, phase III investigators on contracts with NCI, members of the Cooperative Groups, and NCI supported study groups and task forces.

- Distribution will be done only through the recognized comprehensive cancer centers and the clinical centers with NCI core grants. Center directors have been notified that they must submit letters of intent to DCT, signifying their willingness to participate. Letters of intent will be accepted from Sept. 1 on, and distribution of drugs will start soon thereafter.

Each center director may decide on the scope and magnitude of his participation. He may choose to provide drugs only for those protocols in use within his own center; for those within his center and affiliated institutions; or he may agree to supply drugs to independent investigators not affiliated with his center.

Some physicians may find themselves in an area in which the center does not want to distribute drugs to them. In that case, "we're willing to give them the option of going to another center," Bono said.

NCI will prepare a map showing which regions are covered by centers willing to distribute drugs to individual investigators "when we know who's covered and who's not," Bono said. "Right now, it's unclear what will happen."

NCI does not plan any effort to inform individual unaffiliated physicians about the availability of drugs and where they may be obtained. That information will be published in ***The Cancer Letter*** as it becomes available.

NCI SCHEDULE AIMED AT CLEARING UP BIOASSAY BACKLOG BY MID-FEBRUARY

The infamous backlog of bioassay reports, which has brought down the wrath of Congress, consumer groups and anyone else out to take a swing at NCI, will be cleared up by the middle of next February, according to the director of the Carcinogen Bioassay Program.

Richard Griesemer told the Clearinghouse on Carcinogens Data Evaluation/Risk Assessment Subgroup that reports are being produced at the rate of three a week. If that schedule is maintained, the backlog of reports that accumulated when NCI substantially increased the number of chemicals going on test in 1972-74, will be brought up to date about six weeks into 1978.

Griesemer said that reports on bioassays presently under way will be completed within six months after terminal sacrifice of the animals. That will include three months required for histopathologic evaluation of the animals, Griesemer said.

It became apparent more than two years ago that reports on carcinogenesis tests of suspect chemicals were piling up. Labor groups concerned with occupational exposure and consumer groups, notably the Nader-affiliated Health Research Group, picked it up and began a barrage of criticism that is still going on. Some of the critics hinted darkly that NCI was sitting on the reports because of pressures from industry.

It was a matter of extreme embarrassment for then Director Frank Rauscher and Div. of Cancer Cause & Prevention Director James Peters. They in turn put the heat on Umberto Saffiotti, director of the Carcinogenesis Program.

Saffiotti claimed that he was denied the staff and other resources needed to conduct the program and get the reports out. When Rauscher and Peters decided to take bioassay out of Saffiotti's program, leaving him with carcinogenesis research, Saffiotti quit as program director, remaining as chief of the Experimental Pathology Branch.

Rauscher and Peters felt that Saffiotti was not properly managing the bioassay effort, that it was more than a matter of giving him additional staff.

Congressman David Obey got into the fray by writing into the appropriations bill last year an order giving NCI additional positions and earmarking them for carcinogenesis. That was more than Peters felt was needed, but he absorbed them anyw ay and put some of the new staff to work on the backlog.

The additional staff undoubtedly has helped speed up elimination of the backlog and probably will prove to be even more useful in other aspects of the Carcinogenesis Program, especially environmental epidemiology (also receiving earmarked positions from Obey) and carcinogenesis research. But resolution of the backlog problem was already under way without those positions. Cancer prevention, which Obey says NCI has neglected, might have been better served if that money had been used to initiate some of the excellent grants which were left unfunded this year.

Sidney Wolfe, medical director of Health Research Group and a member of the Data Evaluation/Risk Assessment Subgroup, brought up an interesting aspect of the bioassay reports at the subgroup's last meeting. Wolfe noted that Melvin Reuber, a member Litton Bionetics staff at Frederick Cancer Research Center, had reviewed the pathology findings from a number of the bioassays. Reuber found a number of scientific anomalies which he considered worth reporting but had been denied permission to publish until after the contract lab staff had had the opportunity to report the study.

Wolfe said he felt Reuber and others should be

able to report those findings without having to wait an indeterminable time for the contractor to publish. Reuber, who was at the subgroup meeting, pointed out that his interest was in reporting findings of scientific value which were outside the immediate bioassay results.

Griesemer commented that the bioassay data are the findings of primary concern and that they are being reported as fast as possible. Since publication of scientific anomalies would not be related to regulatory decisions, Griesemer said delay in their publication would not be detrimental to public health.

Arnold Brown, Clearinghouse chairman, suggested that a contractor be given six months from the issuance of a bioassay report to publish any findings from a study. Subgroup member Henry Pitot agreed. NCI staff member Kenneth Chu suggested that it would be more desirable if the six month period would start following completion of the backlog reports. This would allow those contractors who were busy meeting their commitment to the backlog more time to consider manuscripts for publication.

Peters told the subgroup he felt it was time to review the mission of the Clearinghouse and specific objectives of the subgroups. He said this would be discussed with program staff and brought up at the next meeting of the Executive Subgroup, scheduled for Sept. 12. Another matter for consideration by the Executive Subgroup is NCI's continued responsibility for routine bioassay testing, particularly in light of the Toxic Substances Act, Peters said.

ADVISORY GROUP, OTHER CANCER MEETINGS FOR SEPTEMBER, OCTOBER

General Oncology and Hematology—Sept. 1, Roswell Park continuing education in oncology; contact Claudia Lee.

Committee on Cancer Immunodiagnosis—Sept. 2, NIH Bldg 10 Room 4B14, open 1—1:30 p.m.

Committee on Cancer Immunotherapy—Sept. 6-8, Landow Bldg Room C418, open Sept. 6 7:30—8 p.m., Sept. 7 & 8 8:30 a.m.—11:30 p.m.

Conference on Human Values & Cancer—Sept. 7-9, American Cancer Society, Palmer House, Chicago.

Current Concepts in Good Lab Animal Practices—Sept. 7-8, Cockeysville, Md. Contact Gene New, NCI.

Large Bowel Cancer Working Cadre—Sept. 8-9, Anderson Mayfair, Houston, open Sept. 8 7:30—8:30 p.m.

Cancer Research Manpower Review Committee Subcommittee on Manpower Needs—Sept. 12, NIH Bldg 31 Room 7, open 9 a.m.—3 p.m.

Clearinghouse on Carcinogens Executive Subgroup—Sept. 12, NIH Bldg 31 Room 10, 8:30 a.m.—5 p.m., open.

Bladder Cancer Project Working Cadre—Sept. 12-13, Logan Hilton, Boston, 8:30 a.m.—5 p.m., open.

Developmental Therapeutics Contract Review Committee—Sept. 14-16, Blair Bldg Room 110, open Sept. 14 8:30—9:30 a.m.

NIH Mammography Consensus Meeting—Sept. 14-16, NIH Bldg 1 Wilson Hall, 9 a.m.—5 p.m. each day, all open.

Virus Cancer Program Scientific Review Committee B—Sept. 15-16, Landow Bldg Room C418, open 9—9:30 a.m.

National Cancer Advisory Board Subcommittee on Construction—Sept. 18, NIH Bldg 31 Room 10, 7:30 p.m., open.

NCAB Subcommittee on Special Actions—Sept. 19, NIH Bldg 31 Room 6, 10:30 a.m.—noon, closed.

NCAB Subcommittee on Planning & Budget—Sept. 19, NIH Bldg 31 Room 6, 8 p.m., open.

National Cancer Advisory Board—Sept. 19-20, NIH Bldg 31 Room 6, open Sept. 19 1-5 p.m., Sept. 20 9 a.m.—noon.

Diet & Cancer Scientific Review Committee—Sept. 21, NIH Bldg 31 Room 9, open 8:30—9:15 a.m.

Cancer & Nutrition Scientific Review Committee—Sept. 22, NIH Bldg 31 Room 9, open 8:30—9:15 a.m.

The Roswell Park symposium on the chronic leukemias—previously scheduled for Sept. 22, was canceled due to Yom Kippur. It will be rescheduled later.

Committee on Cancer Immunodiagnosis—Sept. 25-26, Landow Bldg Room C418, open Sept. 25, 7—7:30 p.m.; Sept. 26, 8:30 a.m.—11:30 p.m.

Clearinghouse Data Evaluation & Risk Assessment Subgroup—Sept. 26, NIH Bldg 31 Room 10, open 8:30 a.m.—5 p.m.

Biometry & Epidemiology Contract Review Committee—Sept. 27-28, Landow Bldg C418, open Sept. 27, 1—3 p.m.

Committee on Cytology Automation—Sept. 28, NIH Bldg 10 Room 1A21, open 1—1:30 p.m.

Psycho-Sociological Aspects of Diseases of the Breast—Sept. 30-Oct. 2, Strasbourg.

Third Biennial Medical Oncology Review Course—Oct. 3-7, Pasadena, Calif., American College of Physicians, contact Arlene Ellis, Huntington Memorial Hospital, 100 Congress St., Pasadena 91105.

Clinical Cancer Education Committee—Oct. 5-6, NIH Bldg 31 Room 7, open Oct. 5 8:30—9:30 a.m.

Cancer Research Manpower Review Committee—Oct. 6-8, NIH Bldg 31 Room 7, open Oct. 6, 9—10 a.m.

21st Western Occupational Health Conference—Oct. 6-8, Fairmont Hotel, San Francisco, theme "Carcinogens, Mutagens, Teratogens: Some Delayed Effects of the Occupational Environment," contact Mary Zerwas, SRI, 333 Ravenswood Ave., Menlo Park, Calif. 94025.

Symposium on Malignant Melanoma—Oct. 6-7, Birsbane.

President's Cancer Panel—Oct. 11, NIH Bldg 31 Room 7, 9:30 a.m., open.

Importance of Staging in the Management of Malignant Diseases—Oct. 12-13, Roswell Park continuing education in oncology.

Cancer Control & Rehabilitation Advisory Committee—Oct. 12, NIH Bldg 31 Room 7, 9 a.m., open.

National Prostatic Cancer Project Working Cadre—Oct. 12, Roswell Park, open 8:30—9 a.m.

Biology & Diagnosis Board of Scientific Counselors—Oct. 14-15, NIH Bldg 31 Room 7, open Oct. 14, 9 a.m.—5 p.m.

Australian Cancer Society Biannual Meeting—Oct. 19-21, Melbourne.

International Conference of Radiology—Oct. 23-29, Rio de Janeiro.

Cancer Treatment Board of Scientific Counselors—Oct. 24-25, open 9 a.m.—adjournment Oct. 24 at NIH Bldg 31 Room 6; open Oct. 25 at Frederick Cancer Research Center.

American Assn. of Cancer Institutes—Oct. 24-25, Philadelphia.

Committee on Cancer Immunodiagnosis—Oct. 25, NIH Bldg 10 Room 4B14, open 1—1:30 p.m.

Third Czechoslovak Congress on Oncology—Oct. 26-29, Bratislava.

Committee on Cancer Immunobiology—Oct. 27-28, NIH Bldg 1 Wilson Hall, open Oct. 27, 7—7:30 p.m., Oct. 28, 8:30 a.m.—11:30 p.m.

Clearinghouse on Carcinogens—Oct. 31, NIH Bldg 31 Room 6, 8:30 a.m.—5 p.m., open, plenary session of the full Clearinghouse.

Cancer Control Grant Review Committee—Oct. 31—Nov. 1, NIH Bldg 31 Room 9, open Oct. 31, 8:30—9 a.m.

"WHATEVER HAPPENED TO . . . ?" — ACS FOLLOWS UP REPORTS FIVE YEARS LATER

The American Cancer Society each year conducts a seminar for science writers aimed at keeping them up to date on progress in cancer research. Scientists

present reports on their research projects, which include the entire range of clinical and basic research.

At this year's seminar, ACS staff members Susan Lichtendorf and John Jones compiled a "Whatever Happened To . . . ?" list of projects reported on at the 1972 seminar and followed up on them.

"Because the period of five years often has weighty importance when it comes to cancer, we thought we would backtrack five years," ACS said in describing the work by Lichtendorf and Jones. "They have traced a sizeable number of the ideas, clinical experience and research leads of 1972 and in the process of inquiry, found these developments:"

In 1972 Joseph Bertino, professor of medicine and pharmacology and chief, section of oncology & chemotherapy, at Yale Univ. School of Medicine, described a new approach to a classic rationale that was responsible for some of the first cancer drugs—substances to deprive cancer cells of needed folic acid. This rationale led to the development of aminopterin and a derivative, methotrexate. However, while such drugs are very successful with some forms of cancer, they have little or no effect against most human tumors and there are problems of drug resistence. But because the rationale seemed sound, researchers at Yale searched for a rapid enzymatic means of producing folic acid deficiency. They found an organism in the mud of New Haven green and soil samples of the Long Island Sound which could grow on reduced folate forms and therefore had the capability of breaking down the folic acid molecule. The Yale team purified the enzyme and called it Carboxypeptidase G1. In 1972 further studies were under way in vitro and in human beings.

In 1977 . . . Bertino, now on sabbatical in California, reports that interest in this enzyme is very much alive but that progress has been "really stalled" because it is difficult to get enough of the enzyme. "It works in mouse tumors" he said, noting that the enzyme's action is being studied at both Yale and the Sidney Farber Cancer Center in Boston. There has been some limited work in patients which would justify further clinical trials.

In 1972 Gerald Murphy, director of Roswell Park Memorial Institute, reported on two ways of "taking the toxicity out of chemotherapy." The first was the use of an "extracorporeal chemotherapy unit" on test animals whereby the animal's blood was treated with L-asparaginase outside of its body as the blood passed through a glass perfusion unit. This approach was developed to protect the animal's normal kidney, liver and spleen cells, during cancer treatment. The second area of concern at Roswell Park in 1972 involved the use of a drug called procytoxid (PCO), a natural product of baker's yeast, to offset the depression of respiration in normal cells as a result of chemotherapy (including chemotherapy used to make cancer cells more volnerable to radiation).

In 1977 . . . Murphy reports that regarding approach No. 1, Corning Glass Works engineers have developed the glass unit further to work with very active agents and more clinical trials are due; regarding approach No. 2, purified PCO has gone through additional testing, the biological aspects are hard to characterize, but although there are technical problems, the subject is still being closely followed.

In 1972 Arnold Leonard, associate professor of surgery and head of pediatric surgery at the Univ. of Minnesota School of Medicine, reported the development of a simple inexpensive test for neuroblastoma. It is usually first diagnosed in an advanced stage and is therefore highly fatal. "Yet," Leonard observed, "if patients are operated upon early before spread has occurred, up to 80% long-term survival is possible."

The "dip stick" test developed at Minnesota takes advantage of the fact that almost 80% of children with this form of cancer secrete excess catecholamine or one of its metabolites (VMA) in their urine. By applying a "dip stick" to the diaper, a physician has a rapid chemical reaction test for VMA that can be read in minutes. By using this test several times a year from birth to five years, on a mass screening basis, Leonard said that a "significant impact" on neuroblastoma morbidity and mortality could be achieved.

In 1977 . . . the VMA test is ready to go: a computerized program has been developed to have every newborn in Minnesota be given the test and followed with subsequent tests. But, Leonard is looking for funding. Since the 1972 seminar, the VMA test has been further refined and is now produced in a hermetically sealed form to avoid problems with moisture before the strip is actually used. Cost is down to 12 cents per use. While there is a percentage of false negatives, the VMA test has already picked up totally unsuspected neuroblastoma in an infant.

In 1972 W.B. Gross, professor of veterinary science at Virginia Polytechnic Institute, reported on the effect of social stress on chickens in terms of whether or not they developed Marek's disease tumors. He reported that chickens forced to live under high social stress developed more of these virally-induced tumors. He said that stress caused the pituitary gland to secrete more of the hormone ACTH causing the adrenals to produce more steroids such as corticosterone. He found that birds with high plasma corticosterone levels had a 43% tumor incidence compared with 15% tumor incidence rate among birds with lower levels (these birds, however, were more resistent to bacterial infection).

In 1977 . . . Gross reports that he has continued to work in this field and that he has used metyrapone, a chemical that blocks the production of corticosterone, to treat Marek's disease. Chickens selected has been bred for either high or low plasma corticosterone levels, and were inoculated with Marek's disease virus. At a certain point in their development half were given metyrapone in their feed. The controls died of tumor. Those given metyrapone survived longer, a few at autopsy showed evidence of regressed tumors, two had small tumors and the others were free of tumor. Gross now links reduced plasma corticosterone with increased T-cell responsiveness and increased tumor regression.

In 1972 Dwight Castleberry, associate professor of dentistry and chairman, Dept. of Prosthodontics, Univ. of Alabama, described a regional maxillofacial prosthetic center which was a research and demonstration project program to provide a team approach and training for professionals while better serving patients with head and neck defects, many the result of cancer. The object of concern of the Alabama group was total social rehabilitation of the patient. Castleberry also reported on the development of biomaterials for more natural and long-lasting prostheses for missing noses, ears, etc. Foremost among such materials in 1972 was polyvinyl chloride, a resilient plastic used commercially in upholstered furniture.

In 1977 . . . Castleberry reports that where once there was only his demonstration project to serve an eight-state area, there are now four such regional centers in the same area. Also, the Alabama approach has served as a model for similar prosthetic rehabilitation programs in the cancer centers that have emerged in the last few years. In terms of new materials, Castleberry now thinks that a hybrid silicone, silphenylene, may test and prove to be even better than the material in current use because it may be easier to mold, stain, and may last longer in patient use.

In 1972, Ben Burmester, director, Regional Poultry Research Laboratory at the U.S. Dept. of Agriculture, East Lansing, Mich., discussed the development of a vaccine that protects poultry from a naturally occurring condition, Marek's disease, which most pathologists consider to be a neoplastic disease. It also has been likened to Hodgkin's disease and Burkitt's lymphoma in humans. He said that the vaccine was safe, and was being used in 90% of all commercial poultry kept for egg laying purposes in Western nations.

In 1977 . . . Burmester is now semiretired, but his work is continuing. The vaccine is being used in over 90% of commercial poultry and is 90-95% successful in preventing Marek's disease tumors. However, despite this achievement the East Lansing people are looking for "something better" because the vaccine does not eliminate the Marek

virus and the source of infection for young chickens is virus contaminated environment. It is also not fully understood how the vaccine actually prevents the overt development of this cancer in poultry. Hence, more investigations are under way.

In 1972, Bela Toth, professor of pathology, Univ. of Nebraska, reported that a class of chemicals called substituted hydrazines, was showing carcinogenic activity in both mice and hamsters. He noted that while these chemicals were important to study in order to determine a possible relationship between chemical structure and tumor development, it was also important to call attention to them because they are widely used in our environment for drugs, rocket fuels, corrosive agents, they are used in the aluminum coating process and as agents to ripen pineapples.

In 1977 . . . Toth reports that to date 37 hydrazine compounds have been found to be carcinogenic by laboratories in many countries with about half so identified by his laboratory. At the time of his 1972 presentation Toth had raised the point that these chemicals might have different carcinogenic effect according to the species exposed. In 1977, he noted that there "might be substantial differences but it may be many years before we know the final answer." Most recently, he has reported on the carcinogenic activity of a herbicide, succinic acid 2,2 dimethylhydrazine.

In 1972, David Anderson, professor of biology at M.D. Anderson Hospital & Tumor Institute, presented data that refined thinking about how breast cancer occurs in families. While it was long acknowledged that women with a family history of breast cancer are at higher risk than the general population, Anderson showed that risk varies tremendously depending on two factors: whether or not a woman's relative had breast cancer in one or both breasts; whether or not that relative developed cancer before or after her menopause. Anderson reported that a woman with a mother or sister who had bilateral premenopausal breast cancer could have as high as a 45% chance of developing the disease herself. These findings constituted the highest risk group known for breast cancer which is still the major cause of cancer death among American women.

In 1977. . . Anderson reports that identification of high breast cancer risk goes on but that it is being looked at from a different angle. Anderson now is following three generation groups to see how breast cancer risk can be predicted from a family setting. He is following 600 so-called "mother" pedigrees and has found another genetic constellation in which risk is very high: if a woman (X) has a mother with breast cancer, and she (X) developed the disease, her daughters and sisters have between a 27-30% risk of breast cancer. Anderson and a complete medical team are doing intensive counselling of women found to be at high risk—some are even having prophylactic surgery with plastic reconstruction.

In 1972, Herbert Wotiz, professor of organic chemistry, Boston Univ., suggested that the estrogen estriol had potential of a "morning after" birth control pill without the implications for breast cancer and the side effects of thromboembolism associated with the widely used pill based on the estrogen estradiol. Studies have provided evidence, Wotiz said, of decreased incidence of breast cancer among child-bearing women. Pregnancy, he said, is characterized by a very high production of estriol, while "women who do not ovulate have a markedly higher incidence of breast cancer." The estradiol based pill inhibits ovulation.

In 1977 . . . Subsequently Wotiz and his associates contracted with a major European drug firm, which cooperated in a study for toxicity and other effects in humans. The estriol based substance proved to be benign, and lived up to its expected effects, he said.

A clinical study of the actual contraceptive use of estriol showed initial excellent results. Unfortunately, Wotiz said, the drug house after appropriate notice, withdrew from the study because tight funds precluded its continuing a contraceptive research division. No further support for the project has developed to date, Wotiz said. Continuing animal studies have confirmed original data, as have independent investigators, Wotiz said.

In 1972 Arthur Herbst, assistant surgeon, Massachusetts General Hospital, reported on the unusual occurrence of a cluster of several cases of vaginal adenocarcinoma in young women 15 to 22 years old who had been born in two Boston hospitals. Herbst and his associates set up a retrospective epidemiological case-control study of the eight patients with vaginal cancer and four controls for each of them. The controls were females born within five days and in the same hospitals as the eight.

Searching familial investigation revealed that the mothers of the eight girls had suffered maternal bleeding and had been treated with diethylstilbestrol during the first trimester of pregnancy.

This was the first demonstration of transplacental chemical carcinogenesis, Herbst said. Within a year more than 70 such cases were brought to their attention. The agents dienestrol and hexestrol were also implicated. Subsequently, a National Reigstry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Women—supported by ACS and NCI—was organized to identify women at possible risk and to consider the pathogenesis of the disease and its appropriate treatment.

In 1977 . . . Herbst, who is now professor and chairman of the Ob-Gyn Dept. of the Univ. of Chicago Lying-In Hospital, has continued the work that has now become a cooperative study. More than 300 cases of the disease—213 vaginal and 120 cervical—in the U.S. and abroad have been reported to the registry. The youngest was 7 and the oldest 27 when the disease was diagnosed. In Denmark where DES and other estrogens are not used in this fashion the disease has not occurred.

In their studies, both retrospective and prospective, Herbst and his associates have found that in comparison to the estimated nearly two million females whose mothers took DES, malignancies are rare. But non-neoplastic abnormalities (tissue changes in the surface lining of the vagina and cervix) have been widespread among the exposed. An earlier Chicago study showed diminished fertility among both males and females, as have the current studies in the case of the females. Although the mechanics of the disease are uncertain, it appears to result from a disturbance in the development of the mullerian ducts.

Most of the patients who developed cancer had bleeding or discharge symptoms, but more than one-tenth had no symptoms when the cancer was diagnosed. Over 90% were 14 years or older "indicating the cancer developed primarily in females who have matured and begun to menstruate. It is during this time that DES-exposed females should begin to undergo screening examinations. Present experience indicates the tumors are curable if detected at an early stage," Herbst said. Of some 304 patients with followup data, 83 or 27% have died or had recurrences, two of which appeared after initial therapy. About 50 have been followed for five or more years. Radiation and surgery have been successful in treating cases of primary and recurrent tumors. Combined radiation and chemotherapy produced regressions in two cases of pulmonary metastases. A combination of 5-FU, methotrexate, vincristine, Cytoxan, and prednisone has produced some partial objective remission and these programs are being evaluated, Herbst said.

—*Editor* JERRY D. BOYD

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