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FDA BACKS DOWN, RELEASES INDs, BUT REVIVES CONTROVERSY OVER CLINICAL TESTING GUIDELINES

The Food & Drug Administration, bowing to pressures from cancer investigators, clinicians, NCI and Cancer Program leaders, has backed down and released the seven investigational new drug applications it has held up since mid-1975.

Four of the INDs were sponsored by NCI—for maytansine, thiadiazole, hycanthane, and neocarzinostatin. The others were from Sloan-Kettering, for tetrahydrouradine; from Sidney Farber Center, for amenopterin; and from M.D. Anderson, for peptichemio.

FDA previously had, after much argument, permitted NCI to proceed with phase I studies with maytansine, but only by NCI clinicians at the NIH Clinical Center. Investigators at other major cancer clinical research centers may now apply to NCI for the drug, as well as for the others

(Continued to page 2)

In Brief

MDA TREATS ONLY 9% OF TEXAS CANCER PATIENTS; CLINICAL DIRECTOR SEARCH NARROWS TO THREE

M.D. ANDERSON, one of the largest cancer centers in the country, treated 21,235 patients in 1975. Seventy percent of those were from Texas, yet that number was only 9% of the total number of cancer patients treated in Texas. Only 13% of new cancer cases in the state received treatment at the hospital. R. Lee Clark, president of the Univ. of Texas System Cancer Center, MDA's parent institution, said those figures "demonstrate dramatically" the need for cooperation among everyone involved in cancer care—primary physicians, community hospitals and cancer centers, the university and comprehensive centers. "It is an impossibility for any comprehensive cancer center to care for more than a small percentage of the total number of cancer patients in any region," Clark said. . . . **SENATE HEW** Appropriations Subcommittee abruptly canceled hearings on the NIH budget when HEW budget office failed to deliver on time data the subcommittee had requested. Subcommittee staff chief Harley Dirks sent NIH units, including NCI, copies of letter he sent to HEW saying, "We regret we did not receive your cooperation needed to implement the new Budget Control and Impoundment Act." The subcommittee apparently intends to stick to the deadlines established by the Act. NCI has sent Dirks all material requested, so the cancelation probably will not affect the amount the Senate will give NCI. . . . **ROSWELL PARK** has released data from a 10-year study which shows that women who use alcohol and tobacco develop oral cancer as much as 15 years earlier than women who use neither. . . . **SEARCH COMMITTEE** screening prospects for the NCI clinical director job has submitted names of three candidates to DCT Director Vincent DeVita. DeVita has been holding down the job himself for several months while the search was in progress.

FDA BACKS DOWN, RELEASES INDs, REVIVES GUIDELINES CONTROVERSY

(Continued from page 1)

sponsored by NCI, FDA indicated.

R.S.K. Young, group leader for oncologic drugs in FDA's Div. of Oncology and Radiopharmaceutical Drug Products, told ***The Cancer Letter*** that release of the INDs does not relieve the sponsors from the requirement to correct what he said were the "deficiencies" in the applications which caused all the problems originally.

Those "deficiencies" had nothing to do with the quality of science in the applications nor the qualifications of the investigators. Young previously had admitted they were more matters of form rather than substance—such items as incomplete information on investigators, animal tests and chemical composition of the drugs. These were matters FDA in the past had not bothered with too much when the sponsors were the major cancer centers or NCI, whose qualifications were known and whose judgment the agency trusted.

Richard Crout, director of FDA's Bureau of Drugs, told the agency's Oncology Drugs Advisory Committee last week that the sudden reversal of FDA's policy and subsequent difficulties with NCI followed the Senate hearings last year "in which the commissioner (of FDA) was embarrassed" (when some drug manufacturers were found to be supplying incomplete, inaccurate and perhaps falsified data in support of new drugs).

Crout also said the difficulties were related to personnel changes, "in which new, young people came in, both with a sense of pizzaz. It happened on both sides." He was referring to Young, on FDA's side, and NCI Div. of Cancer Treatment Director Vincent DeVita.

"Would you say the level of disagreement with NCI has been reduced?" asked Michael Shimkin, chairman of the committee.

"I don't know about that," Crout said. "But we're still working to reach an agreement."

"Then at least the level of cholemic rage has been reduced," Shimkin said.

"There never was, at FDA," Crout responded.

Crout said FDA recognized that "you've got, in the cancer business, a somewhat different system" than other investigators developing new drug therapies. "It's more of a closed shop, with the same people who work up the drug handling the patients. A good deal of medical care occurs under the IND process. That's not the usual procedure with most other diseases, in which drug testing is solely investigational. . . The source of tension between FDA and NCI lies in the Food, Drug & Cosmetics Act, and in the way you do your business. . . That's at the heart of some of our problems with NCI."

Crout said "We're in excellent communication with NCI," and noted that a meeting had been scheduled for this week involving top executives of both agencies. Incidentally, that meeting was set up under the rather silly procedure in which FDA Commissioner Alexander Schmidt has to talk with his counterpart —not NCI Director Frank Rauscher, but NIH Director Donald Fredrickson. Crout is Rauscher's opposite number, since both head "bureaus" (NCI was declared to be a bureau by HEW about two years ago).

Crout pointed out that NCI is heavily involved in its own drug development program. "In a legal sense, the Bureau of Drugs regulates NCI drug development. It's a fact of life, not one that NCI welcomes," he said. "But we have some bending to do, and so does NCI. NCI is in effect a regulated drug development company.

"No one is angry at each other," Crout insisted. "We're trying to work out our problems. I hope this committee can help both institutions to stay cooler."

Crout said that FDA's complaints have to do with record keeping, by NCI and investigators elsewhere; monitoring of drug clinical trials; "especially the reporting of trials data to NCI and by NCI to us."

Without saying so, Crout admitted that some of the problems (such as unconscionably long delays in responding to investigator queries—see ***The Cancer Letter,*** Feb. 6) was in inadequate staffing at FDA. "And it may require some staff changes, here and at NCI." That last comment did not come across as a threat that someone may lose his job but that assignments may be shifted to provide closer coordination with NCI and more manpower devoted to the oncology group.

Crout said that "as a matter of policy, we are not at the present time stopping phase I INDs unless there is a serious safety factor. INDs will be held up only if they are signed by Dr. (William) Gyarfas, Dr. (Marian) Finkel and Dr. Young." Gyarfas is director of the division, Finkel associate bureau director for new drug evaluation.

Committee member Charles Moertel, Mayo Clinic, pointed out to Crout that the abrupt policy change last year "held up programs for several months and affected a number of us adversely." He said he hoped such changes could be handled with more "gradualism."

So ends, for the moment, one controversy between NCI and cancer clinical investigators on one side and FDA on the other. Another disagreement, dormant since last fall, surfaced again when Crout told the committee that FDA intends to proceed with developing guidelines for clinical tests of anticancer drugs over the objections of the committee and NCI.

FDA had floated a previous draft of proposed guidelines last fall, but withdrew them in the face of stiff opposition from DeVita and Shimkin's committee (***The Cancer Letter,*** Dec. 5). Young passed around copies of a new draft last week (which will appear next week in ***The Cancer Letter***). An effort was made to meet some of DeVita's objections; the

statement that phase I studies were not intended to have any therapeutic effect was removed, and references were made in the phase I guidelines to observation of therapeutic effects. Patients should be fully informed that there may be no therapeutic benefit, but that "should in no way be construed as abridging the investigator's right to a personal conviction that he only administers drugs with a therapeutic intent on his part," the proposed guidelines say.

Shimkin referred to the committee's meeting last November, when "we felt it was a waste of time to discuss guidelines until FDA and NCI settled their differences and could agree on them. We want the working people to get together, then we could try to assess whether guidelines they agree upon can be useful. I don't think our opinion has changed. I want to see FDA and NCI come up with a common document. Bring us draft No. 25 if necessary, but not before you have that agreement."

Committee member Philip Schein, Georgetown Univ., told Crout that "we voted that new guidelines are not needed, and accepted the current general guidelines as all that are needed."

Crout objected, insisting that the general guidelines did not fit the requirements for cancer drug tests. Moertel argued, "We felt the current writeup was ample, applied to cancer drugs, and left room for initiatives."

Committee member Julian Ambrus, Roswell Park, said that "it is impossible to develop universal guidelines to cover all cancer clinical tests. There are entirely new approaches, in a rapidly moving field."

Committee member Melvin Krant, Tufts Univ., said, "There are two approaches here in conflict. We say, 'leave us alone.' You say, 'I can't. I'm a regulatory agency, I've got a law to uphold'."

"The fact of life is, we get INDs," Crout said. They have in them toxicological data. We have to make a judgment. These come from a variety of places, not just NCI or the top research institutions. For some places, you want harsh regulations, backed by the full weight of the law–have had INDs for laetril, for example, and other hoax remedies. What are the correct ways to develop drugs? There are correct ways. Some involve procedural matters, some general things like informed consent. Sometimes we say it is proper to hinder research. We're asking you to lay down the procedural rules for working up drugs in the cancer field."

Crout said once guidelines were adopted, FDA would consider itself "bound" by them. Submissions following those guidelines would be speeded through the review process.

Moertel said he interpreted that as meaning that "if you have a creative protocol, review would require months. If you follow the guidelines, FDA action will come promptly."

With Shimkin insisting on prior agreement with NCI for any guideline proposal, and other committee members maintaining that more guidelines are not needed, Crout ended the discussion, saying, "Okay, the ball is in our court," and agreed to try to work out a draft in cooperation with NCI.

SHUBIK GROUP HAMMERS OUT DOCUMENT ON "CARCINOGENICITY CRITERIA"

The National Cancer Advisory Board's Subcommittee on Environmental Carcinogenesis has finally hammered out a document, after six months of agonizing over every word and nuance, which probably will have an enormous impact on the effort to remove carcinogenic chemicals from the environment.

The document, entitled "General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances," is certain to become embroiled in controversy. The regulatory agencies charged with controlling substances in the environment endangering health--primarily the Food & Drug Administration and the Environmental Protection Agency–certainly will rely heavily on it in their deliberations, as will those they seek to regulate.

It probably will wind up in more courtrooms than Perry Mason and F. Lee Bailey combined, as attorneys wrangle over countless interpretations and try to use it to prove conflicting points of view.

The document probably will be the working bible–although one subject to regular revision and updating–for the new committee being chartered to advise the NCI director on what actions NCI should take regarding the determination of the carcinogenicity of a substance. This is the committee which one NCI executive said is needed so that "scientific data can be evaluated by scientists in a committee room rather than by lawyers in a courtroom."

Arnold Brown, chairman of the Dept. of Experimental Pathology at the Mayo Clinic, has agreed to chair the committee if Mayo will give him the time off the job will require. Brown has been a consultant to the subcommittee all through the process of writing the document. He also chaired the ad hoc committee which evaluated the studies relating to the carcinogenicity of cyclamate.

The new committee's deliberations will be open and thus will afford "instant release of carcinogenicity information," an NCI executive said. The public then, theoretically, would be aware of potential hazards and could act accordingly, even if the regulatory agencies did not. And the committee's discussions–scientists talking about results of scientific studies–would be available to the agencies and the courts for their use in evaluating a substance.

The "general criteria" document may be criticized for alleged shortcomings by both consumer groups and their adversaries in industry, and possibly by other scientists. Those criticisms may have some validity, if they are based on the language of the document and not on the motives of those who wrote it.

Subcommittee Chairman Philippe Shubik has been the target recently of some environmentalists and at least one politician (*The Cancer Letter*, March 5) who contend he has been unduly influenced by the fact that he and the Eppley Institute which he heads have performed various research and consulting tasks for private industry.

If that charge is meant to discredit Shubik as a leader in the environmental carcinogenesis field, it's a bum rap. As a member of the National Cancer Advisory Board, Shubik has fought for a larger share of NCI's budget for environmental studies. He and his subcommittee were successful in persuading NIH to establish a special study section to review grants in that field, hoping to overcome a major shortcoming in the funding of those grants. He has argued for increased training of epidemiologists, the shortage of which is hampering environmental research.

If the accusations against Shubik are intended to discredit the document his subcommittee has so laboriously developed, they are both unfair and unfounded. Shubik had no more to do with the actual writing of the document than other members of the subcommittee and its consultants, actually less than some. Throughout the numerous and lengthy deliberations, Shubik never attempted to impose his will and only insisted on achieving a consensus.

The person who was responsible for most of the language in the document was Bernard Weinstein, professor of medicine at Columbia Univ. He wrote the original draft, then patiently rewrote it after each meeting to incorporate the vast number of changes recommended by other consultants and subcommittee members. The group went over each new draft word by word, keenly aware that language interpretation in regulatory and legal proceedings demanded that they carefully consider all shades of meaning.

NCAB members of the subcommittee, in addition to Shubik, are Edward Burger, senior policy analyst for the National Science Foundation; Irving London, director of the Harvard-MIT Program in Health Sciences & Technology; William Powers, director of the Div. of Radiation Oncology at Mallinckrodt Institute of Radiology; and William Baker, president of Bell Telephone Laboratories.

Consultants in addition to Brown and Weinstein were Hans Falk, National Institute of Environmental Health Sciences; Arthur McGee, Stanford Research Institute; Norton Nelson, director of the Institute of Environmental Medicine at New York Univ.; Irving Selikoff, director of the Div. of Environmental Medicine at Mt. Sinai School of Medicine; Michael Shimkin, professor of community medicine and oncology at the Univ. of California (San Diego); Gerald Wogan, professor of Food Toxicology at MIT; Ernst Wynder, president of the American Health Foundation; Roy Albert, deputy assistant administrator of the Environmental Protection Agency; Herbert Blumenthal, Div. of Toxicology at FDA; David Clayson, Eppley Institute; Jerome Cornfield, Biostatistics Center, Bethesda, Md.; Peter Magee, professor of biochemistry at Courtauld Institute of Biochemistry, London; Henry Pitot III, McArdle Laboratory; David Rall, director of NIEHS; and Takeshi Hirayama, chief of the epidemiology division at the National Cancer Center Research Institute in Tokyo.

All contributed in varying degrees to the development of the document; if it is to be attacked on the basis of motives, then the motives of all must be considered.

The document leaves open scientific questions the group agreed have not yet been resolved. It came to grips with the sticky question of when is a neoplasm malignant and when is it benign (and concedes that a benign neoplasm is a health hazard). It insists that animal studies must show a "statistically significant" increase in incidence of neoplasms to establish the carcinogenicity of a substance, a point certain to be argued over by consumer advocates who feel any increase should be sufficient.

The document might be criticized for attempting to cover too many bases. Marvin Schneiderman, who heads NCI's Field Studies & Statistics Program, had this suggestion:

"Why don't we just say that a carcinogen is something that increases the incidence of cancer in animals or man? And then list, one, two, three, the steps that are necessary to prove an increase."

That suggestion came too late, however; the subcommittee had completed its work.

The complete document follows here (without the appendix), as the subcommittee left it last week. It is still subject to editing, and possibly to further revisions, but this is how it stands now:

A. Introduction

The National Cancer Institute of the United States is frequently asked to advise on the possible carcinogenic hazards of substances that might be introduced into, or already exist in, the human environment. On Sept. 19, 1975, National Cancer Program Director, Dr. Frank Rauscher, therefore, asked the National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis to develop general criteria for use in the assessment of whether specific environmental agents constitute a carcinogenic hazard in humans. This document represents this subcommittee's current formulation of these criteria. In assembling these criteria, the subcommittee clearly recognized that at the present time there is no simple and universal definition of either carcinogenesis or neoplasia. The criteria which are described should, therefore, be considered as general guidelines and not rigid, universal criteria. The complexity of the problem dictates that in the final analysis, the evaluation of the potential human hazards of a given agent must be individualized in terms of the chemical(s) and metabolic aspects of that agent, its intended use(s), the data available at the time that the decision must

be made, and other factors pertinent to the case under consideration. Each case must be considered on its own and the criteria appropriate for one agent may not necessarily apply to another.

For purposes of clarity, the general criteria have been classified into three groups in terms of the sources of the data: 1) criteria from human studies, 2) criteria from animal bioassays, 3) criteria from in vitro or short-term tests. This does not imply that human carcinogens are distinct from animal carcinogens. Nor does it imply that carcinogens can be defined absolutely by any of the currently available in vitro or short term tests. Since the extrapolation of data from experimental animals systems to the human is a problem separate from that of establishing the validity of the experimental animal data, the problem of extrapolation is dealt with separately (See Section E) in this document.

A major source of data on carcinogenicity comes from bioassays done in experimental animals. Experience has indicated that, with one or two possible exceptions, compounds that are carcinogenic in humans are also carcinogenic in one or more experimental animal bioassay systems. In addition, several compounds first detected as carcinogens in experimental animals were later found to cause human cancer. The clear demonstration that a compound is carcinogenic in experimental animals must, therefore, be taken as evidence that it is carcinogenic in humans unless there is strong evidence to the contrary. On the other hand, negative evidence in experimental animals does not exclude the potential human carcinogenicity of a substance.

In this document the term carcinogen is used in its broad sense because in most of the current human epidemiologic approaches and animal bioassays it is not possible to differentiate between initiating agents and promoting agents. Any agent which increases the risk of cancer in humans is of concern regardless of its mechanism of action. The criteria listed here apply only to chemical agents since evidence for the induction of neoplasms by physical agents or viruses has not been considered.

This subcommittee has found it useful to state generalized definitions of malignant and benign neoplasms, recognizing that in practice the diagnosis of a particular neoplasm is an operational one based on convention and experience.

A malignant neoplasm is composed of a population of cells displaying progressive growth and varying degrees of autonomy and cellular atypia. It displays, or it has the capacity for, invasion of normal tissues, metastases, and causing death to the host. Benign neoplasms are a less autonomous population of cells and exhibit little or no cellular atypia or invasion of normal tissues and do not metastasize. In particular cases, however, benign neoplasms may endanger the life of the host by a variety of mechanisms, including hemorrhage, encroachment on a vital organ, or unregulated hormone production. It is recognized that the cytologic and histologic criteria utilized in determining whether a lesion is benign or malignant differ depending upon the tissue in which the neoplasm arises. Evaluation of whether a specific lesion is benign or malignant should, therefore, follow standard criteria used by experimental oncologists and pathologists with the emphasis on correlation of the histopathologic pattern with the biologic behavior of the lesion or type of lesion under investigation. In equivocal cases, the diagnosis of a specific lesion may require a panel of experts; recognizing that this may not always give uniform agreement.

Depending upon the particular case, benign neoplasms may represent a stage in the evolution of a malignant neoplasm and in other cases they may be "end points" which do not readily undergo transition to malignant neoplasms.

(For more detailed discussions on the definition of benign and malignant neoplasms and their relationship to each other, the reader is referred to references given in the Appendix)

We must stress that the general criteria listed in this document reflect the judgment of this subcommittee based on its assessment of the current "state of the art". These general criteria should be reviewed on a continuing basis and revised as necessary in the light of new knowledge. For more detailed discussions of principles of carcinogenicity and carcinogen assessment, the reader is referred to specific references on this subject. (See Appendix).

B. Criteria in Human Studies

An agent—which may comprise a combination of chemicals—is a carcinogen in man if it increases the age-specific incidence of malignant neoplasms (or a mixture of benign and malignant neoplasms) in humans to levels that are significantly higher than those in a comparable group not exposed (or exposed at a lower dose) to the same agent. If all the neoplasms are benign, rather than malignant, then for the reasons given elsewhere in this document, the agent must be considered a possible carcinogen and it should, therefore, be very carefully evaluated as a health hazard.

Types of evidence suggesting that an agent is carcinogenic in humans include: neoplastic response directly related to exposure (both duration and dose); incidence and mortality differences related to occupational exposure; incidence and mortality differences between geographic regions related to different exposures rather than genetic differences and/or altered incidence in migrant populations; time trends in incidence or mortality related to either the introduction or removal of a specific agent from the environment; and the results of prospective studies of the consequences of human exposure. Clinical case reports may also provide early warning of a potential carcinogen. Since epidemiologic studies have limitations, negative epidemiologic data do not establish

the safety of suspected materials. Negative data on a given agent obtained from extensive epidemiologic studies of sufficient duration are useful for setting upper limits to the rate at which a specific type of exposure to that agent could affect the incidence and/or mortality of specific human cancers.

C. Criteria in Experimental Animal Studies

The carcinogenicity of a substance is established when the administration to groups of animals in adequately designed and conducted experiments results in reproducible increases in the incidence of one or more types of malignant neoplasms in the treated groups as compared to control groups maintained under identical conditions but not given the test compound. (Reproducible indicates that an increased incidence of neoplasms is obtained in different groups of animals and/or different laboratories.) The increased incidence of neoplasms in the experimental groups should be evaluated statistically for significance and the major experimental variable between the control and the experimental group should be the absence or presence of the single test agent. The demonstration that the occurrence of neoplasms follows a dose-dependent relationship further confirms a positive result.

The occurrence of benign neoplasms raises the strong possibility that the agent in question is also carcinogenic since compounds that induce benign neoplasms frequently induce malignant neoplasms and benign neoplasms are often an early stage in a multi-step carcinogenic process and they may later progress to malignant neoplasms; also, benign neoplasms may themselves jeopardize the health and life of the host. For these reasons, if a substance is found to induce benign neoplasms in experimental animals it should be considered a potential health hazard in humans and requires further evaluation. In experiments where the increased incidence of malignant neoplasms in the treated group is of questionable significance, a parallel increase in incidence of benign tumors in the same tissue adds weight to the evidence for carcinogenicity of the test substance.

Certain methods (listed below) are important pointers to potential carcinogenicity and cannot be ignored; however, they may require additional studies before extrapolation to particular conditions of human usage can be made. Examples of these equivocal cases include:

—Many experiments in carcinogenesis employing inbred strains of animals, some of which strains develop high incidences of particular tumors in the untreated state—even 100% levels. In some of these studies the particular characteristics of the animals may require additional evaluation—in other instances such controlled materials may be quite satisfactory for the establishment of carcinogenicity.

—Bioassays in which, in addition to the test agent, animals are treated with a known carcinogen, or some other foreign material which itself may be carcinogenic or co-carcinogenic.

—Bioassays in which the test animals are subjected to grossly unphysiologic conditions, in addition to the administration of the test compound, and there is reason to believe that these unphysiologic conditions may in themselves enhance tumor induction. (Examples include experiments in which the test compound constituted 25% or more of the diet.)

—Bioassays in which the test compound is given by unusual routes of administration (such as bladder implantation) and there is reason to believe that the tumors that occurred may not be due to a specific effect of the test compound. This does not mean, however, that substances should only be tested in animals by the same route of administration as pertains to human exposure.

Statistically significant positive results in the above types of bioassay do, however, raise the possibility that the test substance may be carcinogenic and, therefore, such substances warrant further evaluation.

In the evaluation of carcinogenesis data it is important to consider the composition and identity of the chemical substances tested and their stability under conditions of storage and administration.

As discussed further in Section E, negative results for carcinogenicity in experimental animal bioassays do not exclude the possibility that the substnace in question is carcinogenic in humans.

D. Short-Term or In Vitro Tests for Carcinogens

A major practical limitation in the bioassay of potential carcinogens is the large number of test animals and the long duration required to obtain results. A number of short-term or in vitro tests are currently under development and appear promising. These include assays for: the induction of DNA damage and repair; mutagenesis in bacteria, yeast, Drosophila melanogaster, or in mammalian somatic cell cultures; and neoplastic transformation of mammalian cells in culture. Other assays that have been employed include the dominant lethal test and studies of chromosomal danage. The latter two tests suffer from the fact that they are frequently non-specific and/or difficult to quantify. Of the various short-term tests, the Ames Salmonella mutagenesis system has been studied the most extensively.

The intelligent application and interpretation of the in vitro tests must also take into account species variations of factors related to the pharmacologic distribution and metabolism of the parent compound as well as possible species differences in macromolecular repair and host defense mechanisms. A number of approaches addressed to the metabolic aspects are now available, including "host-mediated" mutagenesis assays; the assay of urine and other biologic fluids taken from animals or humans receiving the test compound; the addition of microsomal enzymes and co-factors to the assay system; and the inclusion of specific cells in the assay.

At the present time, none of the short-term tests

can be used to establish whether a compound will or will not be carcinogenic in humans or experimental animals. Positive results obtained in these systems suggest extensive testing of the agent in long-term animal bioassays, particularly if there are other reasons for testing. Negative results in a short-term test, however, do not establish the safety of the agent.

This subcommittee is enthusiastic about the use of these in vitro tests as part of a screening system for potential carcinogens and believes that their further development and validation deserves high priority.

E. Extrapolation of Experimental Data to the Evaluation of Human Risks

The criteria listed above provide a guide to determining whether a compound is carcinogenic under a specific set of exposure conditions in a given species or subpopulation. Extrapolation from animal studies for the purposes of evaluating human risks cannot always be done quantitatively or with certainty at the present time. Each case must be individually evaluated, taking into consideration such factors as adequacy of experimental design, significance of the data, dose-response relations, duration of exposure, route of administration, metabolism, host susceptibility, co-factors, and other modifying factors. The criteria for extrapolation may vary depending on the agent in question. For example, demonstration that a compound only produces subcutaneous sarcomas in rodents may be relevant to a drug that will be injected subcutaneously in humans, but such animal data may not be appropriate in assessing the risks associated with a substance that humans will only receive orally. Because of the limitations inherent in animal bioassays, a negative result obtained in a particular animal bioassay does not exclude the potential carcinogenicity of a compound in humans. The wrong experimental species may have been chosen; the number of animals tested may have been too small; or the duration of observation may have been too short. Alternatively, test conditions may have been inappropriate in terms of their predictive value for the response of humans. The extrapolation of experimental carcinogenicity data to the human situation is strengthened by obtaining results in more than one species.

For more detailed discussions of the problems of extrapolation and the estimation of safe limits, the reader is referred to references listed in the Appendix.

F. Evaluation of Benefits Versus Risk

In those cases in which a compound has been proved to be carcinogenic there remains the decision to what extent the possible risks to man are counterbalanced by the possible social, economic, or medical benefits of that substance. Scientists should play a role in these decisions by providing and interpreting the available data. The final decision, however, must be made by society at large through informed governmental regulatory and legislative groups.

OCs RELATED TO LIVER TUMORS, SHUBIK GROUP TOLD; STUDIES RECOMMENDED

After wrapping up its work on the carcinogenicity criteria document, the Shubik subcommittee listened to reports that benign liver tumors have been found in from 150 to 200 women who have been taking oral contraceptives.

The subcommittee concluded that there is an unequivocal and undoubted relationship between taking of the pill and the occurrence of benign liver tumors in young women. With an estimated 10 million women in the United States taking oral contraceptives, subcommittee members felt that "we may be seeing just the tip of the iceberg."

Janet Baum, an intern at the Univ. of Michigan in 1970, suspected the relationship between the pill and liver tumors then but could not get her findings published until 1973.

Truman Mays, professor of surgery at the Univ. of Kentucky, said he felt that the fact that the tumors appeared in young women taking the pill, and were never found in young men, was sufficient evidence of the cause and effect relationship.

Wynder pointed out that liver tumors have not been reported in young Japanese women and that Japan has not permitted marketing of oral contraceptives.

Wynder, Brown and others agreed that might be inducing more common cancers. The subcommittee suggested that it may be time now to review whether oral contraceptives are sufficiently efficacious to warrant the risk of tumor induction as well as the previously established cardiovascular hazards.

Marian Finkel, director of FDA's Office of Scientific Evaluation, said the agency has directed that package inserts for OCs be rewritten to advise against their use by women over age 40 because of the cardiovascular problems.

ONCOLOGY NURSE SEMINARS SCHEDULED IN APRIL AT NEW HAVEN, ROSWELL PARK

Two seminars for nurse oncologists are scheduled for next month, one in New Haven, Conn., and the other at Roswell Park Memorial Institute.

The Connecticut meeting is a two-day conference April 2-3 sponsored by the Connecticut Oncology Assn., the American Cancer Society Conn. Div., and the Yale Comprehensive Cancer Center. Speakers will include Lisa Marino, president of the Oncology Nurses Society.

Program topics include the nurse and clinical research studies; current status of cancer chemotherapy; practical consideration in patient evaluation and treatment; radiation therapy; the role of the chemotherapy nurse in the outpatient setting; specialized care of the compromised host; cancer immunology; and immunotherapy—a new role for the oncology nurse.

Registration fee is $30, $15 for students; CEU credit has been applied for. Contact Tish Knobf, RN, Yale New Haven Hospital.

The Roswell Park seminar, scheduled for April 8, will focus on surgery, radiation therapy and chemotherapy; the effects of those treatments on patients and the role of the nurse in diagnosing and treating patient responses to therapies.

The seminar is offered free. For further information and to register, contact the Nursing Education Dept. at Roswell Park, 716-845-5712.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg. NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP CDC-99-OSH-105(6)

Title: *Radiation carcinogenesis*
Deadline: *Approximately April 20*

The National Institute for Occupational Safety & Health is soliciting proposals from organizations interested to synthesize from the current literature a report on the carcinogenic properties of ionizing and non-ionizing radiation.

RFP CDC-99-OSH-91(6)

Title: *Toxicity data for establishing "immediately dangerous to life or health" (IDLH) values*
Deadline: *Approximately April 20*

The National Institute for Occupational Safety & Health is soliciting proposals from organizations interested in obtaining additional acute toxicologic data to utilize in establishing IDLH values for 10 industrial chemicals.

Contracting Officer for the above two RFPs:
L.A. Sanders
NIOSH-Room 1-58
5600 Fishers Ln.
Rockville, Md. 20852

CONTRACT AWARDS

Title: Study of the expression of the RNA tumor virus genome in malignant cells
Contractor: Duke Univ., $437,240.

Title: Biological resources management information system support services
Contractor: EG&G/Mason Research Institute, $266,621.

Title: Immunological assays for DNA and RNA viruses
Contractor: Litton Bionetics, $383,350.

Title: Investigations of suspected oncogenic viruses in non-human primates
Contractor: Litton Bionetics, $306,550.

Title: Study role of cyclic AMP mammary gland neoplasis
Contractor: Worcester Foundation, $52,600.

Title: Studies of methods for isolation and characterization of mammary epithelial cell membrane
Contractor: Worcester Foundation, $50,000.

Title: Studies and investigations of new techniques of cell kinetics of breast cancer
Contractor: Papanicolaou Cancer Research Institute, $116,000.

Title: Clinical Oncology Program
Contractor: Allentown, Pa. Hospital Assn., $73,328.

Title: Mechanisms by which tumors avoid destruction by the immune system
Contractor: Weizmann Institute, Rehovot, Israel, $73,000.

Title: Model system for screening agents against spontaneous murine mammary cancer
Contractor: Catholic Medical Center of Brooklyn & Queens, $85,839.

Title: Integrated cancer rehabilitation services
Contractor: Harmarville Rehabilitation Center, Inc., Pittsburgh, Pa., $375,708.

SOLE SOURCE NEGOTIATIONS

Proposals are listed here for information purposes only. RFPs are not available.

Title: Prototype clinical chemotherapy program in cancer control
Contractors: Children's Hospital of Los Angeles, and Children's Hospital Medical Center, Cincinnati.

Title: Research and virus production activities
Contractor: Flow Laboratories.

The Cancer Letter—*Editor* JERRY D. BOYD

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