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COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

FEBRUARY 28, 1980

B-197656

The Honorable Edward M. Kennedy
Chairman, Subcommittee on Health
and Scientific Research
Committee on Labor and Human Resources
United States Senate

SRNO 7102

Dear Mr. Chairman:

Subject: Review of the National Cancer Institute's Acquisition and Screening of Plant Extracts (HRD-80-53)

Your January 18, 1979, letter asked us to review selected research management activities of the National Institutes of Health (~~NIH~~). In later meetings with your office, four issues were selected for indepth review. The results of our work will be provided to the Subcommittee in three reports.

This first report covers the portion of your request concerning the National Cancer Institute's (NCI's) Division of Cancer Treatment. As agreed with your office, we focused on two areas within the Division's Developmental Therapeutics Program (DTP):

--Methods for acquiring plants to avoid excessive duplications.

--Efforts to develop more effective and economic screens to identify chemical agents that may be useful in cancer chemotherapy.

INTRODUCTION

NCI's goal is to develop the means for reducing the incidence, morbidity, and mortality of cancer. Through grants and contracts to universities, medical schools, and nonprofit research organizations, NCI uses its research funds to investigate the nature of cancer and its causes and prevention, diagnosis, and cure. NCI was reorganized

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in 1972 to implement the responsibilities of the National Cancer Act of 1971 (42 U.S.C. 281), which increased NCI's authorities and established the National Cancer Program. Under the reorganization four divisions were established, including the Division of Cancer Treatment--the main organizational component of the cancer program responsible for coordinating cancer treatment research within NCI. The major emphasis in cancer treatment research is searching for antitumor drugs and developing and improving combined methods of therapy using drugs singly or in combination with other forms of therapy, including surgery and radiotherapy.

The Developmental Therapeutics Program (DTP), one of the Division of Cancer Treatment's four subdivisions, administers the search for new anticancer agents. Through the collaborative efforts of its four branches and five laboratories, DTP acquires various chemicals and natural products for evaluation as potential sources of new cancer treatment drugs. These may be of synthetic origin or come from microbiological, plant, and animal sources. The review was limited to activities within two branches: the Natural Products Branch (NPB), which arranges for acquiring plants, and the Drug Evaluation Branch, which is responsible for screening new agents for anticancer activity. Obligations for these two branches were $5.9 million and $20.6 million, respectively, in fiscal year 1979.

The investigation of plants as a source of new drugs begins by collecting test samples. These samples are collected largely at random and may consist of any plant part or combinations of parts, such as root, stem, bark, and flower. Once collected, these samples undergo an extraction process to remove the plants' chemical compounds for initial screening in laboratory animals (referred to as in vivo) and cell cultures (referred to as in vitro). Plant extracts exhibiting anticancer activity in screening are considered for further research and development. Those exhibiting little or no activity are not considered.

ACQUISITION OF PLANTS

NPB arranges for worldwide collection of plants. Collections are made primarily under an interagency agreement with

the U.S. Department of Agriculture (USDA) for about $451,000 annually. USDA obtains about 90 percent of its collections from contract suppliers in about 60 countries and the remainder from USDA personnel throughout the world. Other sources include a contract with the University of Hawaii and occasional submissions from research institutes, interested scientists, and universities. In fiscal year 1979 these sources provided about 3,450 plant samples to NPB.

NPB controls for plant duplication

In 1977 DTP found substantial duplication in the plant program because of lack of controls over activities of collection contractors. DTP considers some duplication of plants as being acceptable if they are collected in different seasons or from different countries because plants' chemical composition may vary based on those factors. However, in a review of USDA samples submitted over a 2-year period, from 1975 to 1977, NPB determined that 60 percent were identical to plant species already collected and screened in the past. Therefore, only 40 percent of the samples collected during this period actually went before the DTP screens for the first time.

To improve this situation, NPB established a control system designed to limit the repetitive collecting of plant species. The NPB staff compiled a list of more than 67,000 plant species 1/ and genera 2/ that would no longer be accepted for DTP evaluation. An NPB official estimated that over 250,000 species exist. The list was first made available to the collection contractors in 1978 and is periodically updated as a reference for future collections.

NPB established three criteria for determining which plants it does not want for future collections:

--The plant species has been screened six or more times with no anticancer activity observed.

1/Species: a type of plant.

2/Genera: a classification of plant consisting of one or more species.

--For a particular plant genera (a) an extensive number of species within the genera had been screened and (b) in NCI's opinion continued screening within that genera would be of no value.

--Anticancer activity was observed from a previous collection.

NPB policy to limit duplication has unduly restricted plant collections

In the effort to reduce plant duplication by limiting the number of screenings to as few as six, some plants have been categorized as not wanted by NPB after being collected in only one country. To assess the impact of limiting the criteria to six screenings, we randomly selected 56 plants no longer wanted by NPB which had been screened six or seven times with no anticancer activity observed. Of the 56 plants, 28 (50 percent) had been collected from only one country.

Both NPB and USDA officials agree that the chemical makeup of a plant can vary with different geographical areas. Therefore, it is possible for a plant collected in one country to show no anticancer activity while the same plant collected from another country may contain active anticancer agents. For example, we reviewed all screened species of the same genera as the 56 plants. Of these, 32 species contained anticancer active agents, 12 of which had shown no anticancer activity when obtained from other countries.

In commenting on our draft report, NCI agreed, that multiple samples, when they are obtained, should be from different countries. NCI said it had insisted on stopping the collection of one species six or seven times in one country. NCI stated, however, that in view of the limited number of species it can evaluate each year and the desire to discover new types of compounds, it is probably more cost beneficial to use a broad survey of new plant species with fewer samples of a given species tested. This would provide a higher probability of discovering completely new compounds with new structures.

We also recognize that NCI has a limited capability to screen plants and that a broad survey of plant species is desirable. However, NCI is apparently experiencing difficulty in achieving that goal.

For fiscal year 1979 there was a severe reduction in the number of plant samples obtained for DTP evaluation. DTP received only 1,751 of the 4,000 samples desired from USDA. USDA, the principal supplier of plants for DTP, told us that the decline in input was a direct result of the NPB policy to limit plant duplication. This policy has resulted in eliminating more than 67,000 species from any further collection. Many plants dropped were among the most common and thus most accessible to their collection contractors. DTP officials indicated that, despite the elimination of several species, they expect USDA to meet its goal of 4,000 samples for fiscal year 1980 by entering into several new countries where collections have never before been obtained.

NCI has indicated a desire in the past for USDA to obtain plants from new countries. In a March 30, 1978, letter to USDA, NCI indicated its agreement would not be renewed after the expiration date if the conditions that existed were not rectified. Among several problems NCI cited was excessive reliance on a limited number of subcontractors in limited geographic areas. USDA proposed 20 potential new countries or regions for acquiring plants in a June 30, 1979, progress report. A USDA official, however, noted several factors which will affect the collection of plants from these countries

--the availability of qualified botanists,

--the quality of plants in the area,

--the accessibility of the various types of plants, and

--the current political situation in the area.

In view of the potential difficulties in obtaining a broad survey of plant species and given the limited capability for screening plants, we believe it is important to avoid prematurely eliminating potentially active plants from further consideration.

Conclusions

A plant species from one country may not show any anticancer activity, while the same plant species from another

country may show such activity. Thus, NPB's categorization of plant species--when samples came from only one country--as not wanted could result in failure to identify plants with anticancer potential. Although we agree with NPB's policy to reduce duplication of plant acquisition, we believe the policy should be modified so that plants are not categorized as not wanted until samples have been screened from two or more countries.

Once a species has been obtained from an acceptable number of countries, screened, and found to have no anticancer activity, it could be totally excluded from further collection. By assuring that samples are obtained from two or more countries before a plant is categorized as not wanted, the chances of missing plants with anticancer potential would be reduced.

We believe that NPB should review the list of 67,000 plants categorized as not wanted and reinstate those plants collected from only one country. This should increase the contractors' ability to provide the number of plants desired by NPB, minimize duplication, and allow for the acquisition of new plants.

Recommendation to the Director of the National Cancer Institute

We recommend that the Director revise NPB's criteria for deleting plants after six screenings to assure plants are not dropped when samples have been collected from only one country. For those plants in this category, the list of plants not wanted should be modified to identify the specific country from which the plant is no longer desired, thus allowing contractors to collect the plant in other countries.

SCREENING PLANT AND ANIMAL EXTRACTS

The Drug Evaluation Branch (DEB) is responsible for screening new materials to identify those that can kill cancer cells. Screening is performed in two phases

--an initial screen (prescreen) to identify any compounds with the potential to kill cancer cells and

--the detailed screening process which further analyzes those compounds identified in the prescreen as displaying some potential cancer-killing capability.

From April 1, 1978, to March 31, 1979, DEB conducted over 215,000 in vivo and in vitro screenings of synthetic and natural product materials, of which approximately 61,900 were prescreens. Prescreening consists of a series of experimental tumor systems, selected for their ability to eliminate the vast majority of inactive materials and identify those few active compounds having the greatest potential for development into new cancer treatment drugs. The prescreens eliminate about 92 percent of the materials submitted and are performed primarily by contractors monitored by the DEB staff.

DEB uses two test systems simultaneously for initially screening these materials, P388 in vivo and the KB in vitro. The P388 in vivo system consists of a lymphocytic leukemia transplanted in a laboratory mouse. Anticancer activity is measured by the prolonged life of the infected animal and is the principal basis for recommending a new drug for further development. The KB in vitro, which tests for the cell-killing ability of an extract, uses human cancer cells grown in culture media. The KB system is primarily used to isolate the purified agent, but it alsc identifies compounds which have cancer active properties.

An entirely in vitro prescreen could be more effective and economical

DTP and DEB believe the development and application of better in vitro prescreens would have several advantages over the present P388-KB combination screens. More sensitive in vitro prescreens could identify a greater number of compounds. The KB in vitro system used alone only measures for cell-killing activity and is too unstable to be used alone as a prescreen. Studies have shown that the KB system tends to produce numerous false positives--a compound that appears to be active when tested KB but inactive when tested in vivo. At the same time, the KB system has a tendency to overlook some active compounds.

In vitro screens can be designed to detect compounds with specific biochemical activities which cannot be detected by the current screens, such as a compound's ability to kill a specific type of cell. The P388 in vivo screen measures anticancer activity and the KB in vitro screen simply indicates the most cell-killing elements in a compound.

Using in vitro prescreens alone should be less costly, requiring less funds, time, and material. Currently, new products are simultaneously screened against the P388 and the KB at a cost of $80.28 and $19.40, respectively. The estimated cost of in vitro prescreens would range from $15 to $30 each. An NPB official indicated that, while several new in vitro prescreens might be necessary to replace the current prescreen, he believes in vitro will still be less expensive. In a similar DTP program--screening fermentations for anticancer activity--the number of P388 in vivo tests was reduced 93 percent in fiscal year 1979 by applying in vitro prescreens. If plant and animal products were initially screened in vitro, the number of P388 tests could be reduced since only those compounds active in the prescreens would be tested in the animal. Additionally, in vitro prescreens require less time and material. The present P388 test takes 30 days to complete and requires 1 to 2 grams of test material, whereas an in vitro test usually takes 1 hour to 2 days to complete and requires only 5 to 10 milligrams of test material.

In vitro prescreens can be made more sensitive than the current P388 in vivo and KB in vitro screens to detect very low levels of an active concentration that might otherwise be missed. The P388 is used as the primary in vivo screen because of its sensitivity to most clinically effective anticancer drugs. However, some plants might contain an active drug among several thousand chemical components. If the amount of active material is small enough, it can become impossible for the animal screen to detect, because it is not sensitive enough.

DTP's proposed project to develop new in vitro prescreens was given final approval by the Division of Cancer Treatment's Board of Scientific Counselors on October 29, 1979. Since current in vitro prescreens do not perform many of the analyses DTP desires, new in vitro tests must be

developed. The DTP officials plan to issue a Request for Proposals for developing prescreens in February 1980. DTP anticipates that several contracts will be awarded over a 3-year period at an annual cost of about $100,000.

Conclusion

With in vitro's apparent advantages of greater efficiency and effectiveness, we support DTP's project to develop new in vitro prescreens.

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As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the date of the report. At that time we will send copies to interested parties and make copies available to others upon request.

Sincerely yours,

Comptroller General
of the United States