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THE TAXOL SUPPLY CRISIS. NEW NCI POLICIES FOR HANDLING THE LARGE-SCALE PRODUCTION OF NOVEL NATURAL PRODUCT ANTICANCER AND ANTI-HIV AGENTS

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ABSTRACT.—Over the past 30 years, the National Cancer Institute has been involved in the preclinical and/or clinical evaluation of the majority of those agents approved for the treatment of cancer. Many of the new agents under consideration in the NCI program are either natural products or derivatives of natural product leads, and of critical importance to their development is the issue of drug supply. In responding to the drug supply crisis which emerged with the demonstration of the clinical efficacy of taxol, the NCI has identified several important lessons for those interested in natural product drug discovery and development. As a result, the NCI has developed plans to avert similar supply crises in the future by initiating exploratory research projects for large-scale production of promising agents at the earliest possible point following the demonstration of confirmed antitumor activity. These plans, together with a review of the development of taxol, are presented in this paper.

Despite the major advances that have been made in the treatment of malignancy, many patients still die either from initially unresponsive tumors or recurrent disease. In general, malignancies that are either unresponsive to initial chemotherapy or those that reoccur are less amenable to control with standard anticancer drugs. Therefore, there is an unquestionable need for new therapeutic products for the treatment of cancer. The processes of cancer drug discovery and development are complex, arduous, and time consuming. The National Cancer Institute (NCI) has played an extremely important role in supporting, sponsoring, and carrying out major efforts to facilitate the discovery and development of those agents worthy of clinical investigation.

The Developmental Therapeutics Program (DTP) is the preclinical program at the NCI responsible for the discovery and preclinical development of new agents, including the conduct of those investigations necessary to define the safe and optimal method for introducing new agents into the initial clinical trial (phase I) in humans with cancer. Furthermore, the NCI's Cancer Therapy Evaluation Program (CTEP) has both the expertise and resources to conduct the entire spectrum of clinical evaluations needed to prepare an agent for consideration for final approval by the Food and Drug Administration (FDA). Thus, the government has made a substantial and comprehensive investment to evaluate novel therapeutic products that may benefit patients with malignant disease. Extensive efforts have been made over the past few years to establish collaborative research programs with academic investigators and the pharmaceutical industry.

Over the past 30 years, the NCI has been involved with the preclinical and/or clinical evaluation of the overwhelming majority of those agents currently approved for the treatment of cancer. Many of the exciting new chemical entities under consideration are either natural products or the derivatives of a natural product lead. There has been growing interest at the NCI in exploring natural products as an untapped source of even more promising new agents. Furthermore, efforts have been made to expedite the processes of drug discovery and development. Critically important to these efforts is the issue of drug supply. Whether the task is to expand on exciting preliminary in vitro observations of a natural product observed in a drug discovery screen or to secure sufficient material to establish the in vivo therapeutic index of a new agent, supply is

frequently a limiting factor. While extensive in vitro testing can be accomplished with milligram quantities of an agent, usually gram quantities are needed (depending on the potency of the agent) to fully determine if a promising in vitro observation is likely to produce a viable drug candidate.

Drug supply can again become a major limiting factor in the complete clinical evaluation of an anticancer agent at the other end of the developmental process. In fact, the observation of efficacy in the clinical setting can produce extraordinary demands for the drug both for completion of those studies needed to define the optimal method of administration and for those patients not on clinical protocols who are dying from their disease.

The demonstration of the clinical activity associated with the administration of taxol has tremendously enhanced interest in exploring other natural product sources for potentially effective antineoplastic agents. There are many instructive elements in the taxol story. The prolonged period of development encompasses many of the problems encountered with the preclinical and clinical investigation of poorly soluble and potentially toxic agents. Although some have been critical of the time involved with the development of taxol, issues relating to the safety of its administration and difficulties in drug supply have both contributed significantly to delays in demonstrating its broad potential clinical application. In fact, the dedication of those early clinical investigators to circumventing the problems posed by the drug's vehicle and the ultimate commitment of the NCI to solving the supply crisis for this promising agent are important factors to understand if future problems are to be avoided with similar natural product leads. Cooperation and communication among many individuals from diverse backgrounds, including those from academic institutions, the pharmaceutical industry, nonmedical scientists with expertise in the procurement and processing of the raw material, and government scientists committed to drug discovery and development, have contributed to easing the current drug supply shortage with this agent. This accomplishment expedited the final FDA approval of this drug for the treatment of advanced ovarian cancer in December 1992 and will potentially enable its full clinical evaluation.

EARLY DEVELOPMENT OF TAXOL.—The first sample of *Taxus brevifolia* (Pacific yew) bark was collected by the United States Department of Agriculture (USDA) in 1962 as part of the exploratory plant screening program of what was then called the Cancer Chemotherapy National Service Center (CCNSC) of NCI. Activity of an extract was confirmed by the KB cytotoxicity assay in 1964, and a re-collection was assigned to Dr. Monroe Wall at Research Triangle Institute for fractionation in 1965. Taxol was isolated as the active constituent in 1969, and the report of its isolation and structural elucidation was published in 1971 (1). An analysis of the KB cytotoxicity of various plant parts collected by the USDA in 1969 showed that extracts of the bark were consistently more active than those of any other part, although needles and roots showed substantial activity. Wood was inactive. Like many other agents, taxol initially exhibited moderate in vivo activity against the P-388 and L-1210 murine leukemia models, but observation of strong activity against the B16 melanoma system in 1975 further enhanced interest. In 1977, it was accepted as a drug candidate for preclinical development. Taxol was subsequently shown to exhibit significant activity against several human tumor xenograft systems including the MX-1 mammary tumor. Further interest in developing this agent was generated in 1979 by Horwitz's demonstrations of its unique mechanism of action in promoting tubulin polymerization and stabilization of microtubules against depolymerization (2). Formulation studies were completed in 1980, and toxicology studies initiated. Following completion of these preclinical studies, approval was granted for initiation of Phase I trials in 1983.

CLINICAL DEVELOPMENT OF TAXOL.—The very precipitous changes in the demand for taxol are somewhat unusual in the context of other drugs which the NCI has developed. While it is always the case that demand for drug increases substantially going from Phase I trials (human safety and evaluation of alternative doses and regimens) to Phase II trials (efficacy in various cancer types) to Phase III trials (large trials to confirm efficacy leading to a New Drug Application), many drugs never reach Phase III trials, and for those that do, their promise is usually apparent fairly early in the clinical trials. This was not the case for taxol. The initial trials were fraught with serious problems of toxicity, particularly allergic reactions including anaphylaxis, and the drug was very close to being dropped from clinical study for reasons of safety. This can be traced back to the extremely poor solubility of taxol in aqueous systems and its relatively high dose requirements compared with other antitumor natural products such as the Vinca alkaloids. Development of a suitable formulation for parenteral administration was extremely difficult and ultimately required the use of a surfactant formulation in which Cremophor EL, a polyethoxylated castor oil derivative, is a major component (3). Cremophor is known to cause histamine release in dogs and is believed to be implicated in hypersensitivity reactions to other drugs where it is a component of the formulation (4). The concentration of Cremophor EL in the taxol formulation developed for clinical trials results in a dose of Cremophor EL that is at least twice that used with any other experimental drug.

Early Phase I clinical trials of taxol began with a variety of schedules including single 1-h, 3-h, or 6-h iv infusions repeated every 21 days; daily 1-h to 6-h iv infusions for 5 days repeated every 21 days; and 24-h continuous iv infusions every 14–21 days. The incidence of serious hypersensitivity reactions was more frequent with the shorter infusion times, perhaps related to the peak level exposure to Cremophor EL, and eventually the 24-h infusion schedule together with premedication with anti-allergy drugs was found to greatly reduce the incidence of allergic reactions and provide a sound basis for moving to Phase II trials.

Rowinsky *et al.* (5) have written an excellent review of the preclinical studies and early clinical trials with taxol. Due to the slow progress of taxol through Phase I trials, doubts that Phase II trials would show activity, if indeed they were conducted at all, and other program priorities, sufficient bulk taxol was produced for only a moderate number of Phase II trials. This later became a problem when important antitumor activity was found in Phase II trials in ovarian cancer and interest in the drug greatly intensified. The observations of responses in patients with ovarian cancer resulted in a tremendous increase in the demand for taxol. The preliminary reports indicated that the response rate was approximately 30% with a few patients actually achieving a complete remission (6). Although it is important to emphasize that a complete remission does not equate to a cure, it is somewhat unusual to observe this degree of activity in patients who have been previously exposed to other chemotherapeutic agents. Shortly after the original report of activity in ovarian cancer, three additional clinical trials provided confirmation that responses are observed (mostly partial remissions) in 20% to 50% of patients with this disease. Approximately 12,500 women die annually in the United States from advanced ovarian cancer. Thus, there was a strong sense of urgency to obtain more drug for those patients not responding to standard therapy, and to explore the potential value of moving this therapeutic agent into a front-line position in an effort to further improve on the therapeutic outcome. Due to the efforts of Bristol-Myers Squibb, the USDA Forest Service, the Bureau of Land Management, and Hauser Northwest, the supply situation has been alleviated and taxol is now available on a compassionate use basis through the NCI to all ovarian cancer patients meeting defined disease criteria. Clinical studies are

ongoing to define the activity of taxol in combination with cisplatin and other drugs active in ovarian cancer.

In addition to responses in patients with ovarian cancer, a preliminary report by Holmes *et al.* (7) showed that this new drug produced responses in patients with metastatic breast cancer. The patients had symptomatic improvement in bone pain concomitant with objective evidence of tumor reduction. Two additional studies confirmed that taxol was effective in producing responses in patients with metastatic breast cancer (8,9). Therefore, it was reasonable to conclude that there would be an enormous increase in the demand for this agent which further increased the severity of the supply crisis. While the actual response rate for taxol in breast cancer has not yet been firmly established and its role in combination therapy also requires further study, it is clear that taxol may be of benefit to many of the more than 40,000 women who die from this disease each year. Finally, responses have also been observed in patients with other forms of advanced malignancy including lung cancer (10), cancer of the head and neck region (11), malignant melanoma (12), and lymphomas (13).

The importance of securing an adequate drug supply must never be underappreciated, as patients suffering from terminal disease do not have an option to wait for these shortages to be rectified. Furthermore, critically important studies cannot be done to ensure that the optimal approach to drug delivery, combination regimens, and overall use clinically have been adequately defined if there are insufficient quantities available for testing. The approval process may also be delayed by difficulties in defining the source of drug for commercial distribution. Therefore, it is essential that good communication be continuously maintained during the early clinical evaluation of natural products to avoid the inordinate delays that might occur if the preclinical scientists capable of assisting to enhance supplies are unaware of responses being observed. Likewise, recommendations of the natural product experts to fully explore alternative sources of promising agents must also be given adequate consideration and support.

Much remains to be learned about the clinical use of taxol, including: additional active cancer types; optimal schedules of administration; dose-response relationships; effectiveness in combination with other drugs for active disease types; sequencing with other drugs in combination therapy; and additivity of toxicities in combination regimens. It is clear, however, that taxol will receive wide use and, at present, based on just the ovarian and breast cancer utilization, the worldwide need will be hundreds of kilograms per year. This need for additional drug supplies has mandated the development of alternative sources in addition to the bark. If data for additional cancer types in which taxol has shown preliminary activity to date continue to be promising, much larger quantities will be needed.

TAXUS BREVIFOLIA BARK AS A SOURCE OF TAXOL.—Unpublished surveys in the 1960s by the USDA Forest Service (USDAFS) cited *T. brevifolia* as being common on the Olympic Peninsula in Washington and on Vancouver Island in British Columbia; in addition, vegetation studies indicated that it was common along the western slopes of the Oregon Cascade Range in association with *Pseudotsuga* (Douglas fir) and *Tsuga* (western hemlock) species. A later limited survey in 1977 reported *T. brevifolia* as being common in the National Forests of southern Oregon and as a major understory tree in northwestern Montana (C. Edson, unpublished report; USDA). The taxol supply needs for preclinical and early clinical studies were easily met by bark collections in Oregon between 1976 and 1985, ranging in size from 2000 pounds to 15,000 pounds, which yielded a total of approximately 1.3 kg of the drug. The clinical demand started to escalate with the observation of the tumor responses in the treatment of patients with a variety of solid tumors, including malignant melanoma and ovarian cancer, in Phase

I trials. Consequently a 60,000-pound collection was undertaken in 1987–1988. Except for periodic closures of the Oregon National Forests because of fire danger, no apparent difficulties were encountered in fulfilling this collection. The minimal lead time for production of bulk taxol following recognition of increased needs was at least 18–24 months and depended on the time of year. Bark collection from *Taxus* is extremely difficult except in spring and summer when the sap is running and the bark is readily peeled off the trunk. After award of contracts, collection and drying of bark took several months, and then the process of extraction, solvent partitions, multiple chromatographic steps, and recrystallization took nine months to a year. The limitation on supply also reflected the fact that drug production was being conducted on a pilot plant scale during the early clinical trials. Formulation of taxol into finished vials together with the time needed for quality control assessment consumed another three months before the vials could be shipped for patient use.

Initiation of a second 60,000-pound collection in 1989, however, raised concerns about the impact of collections of this size on the continued existence of the tree. A petition requesting classification of the tree as a threatened species was rejected by the Fish and Wildlife Service of the U.S. Department of the Interior in 1990 on the grounds that stand information and satellite imagery indicated that an estimated 130 million yew trees occur on 1,778,000 acres of National Forest lands in the Washington and Oregon Cascades and the Oregon Coast Range. In early 1991 Bristol-Myers Squibb (BMS) signed a Cooperative Research and Development Agreement (CRADA) with NCI after being selected in an open competition involving a number of pharmaceutical companies interested in collaborating with NCI in the development of taxol. Under the terms of the agreement, BMS is responsible for the continued production of taxol, doing whatever is needed to market the drug, and for developing alternative sources as soon as possible. Later that year BMS entered into cooperative agreements with the USDAFS and the Bureau of Land Management whereby BMS agreed to fund an inventory of *T. brevifolia* on government land. Meanwhile, bark collections have continued in the Pacific Northwest under contract to BMS, mainly under the direction of Hauser Northwest, a subsidiary company of Hauser Chemical Research (HCR) of Boulder, Colorado. Harvesting on government lands is strictly controlled and is permitted only from areas designated for clear-cutting. The Pacific Yew Act establishing an Interagency Yew Committee to develop a rigorous harvesting and management scheme for *T. brevifolia* was signed into law by the President in August 1992. In 1991, over 1.6 million pounds of bark were harvested from government and private lands, and a similar quantity was anticipated for 1992. In 1992, HCR produced 130 kg of taxol, and 230 kg is projected for 1993 (14). These substantial increases in the supplies of taxol have resulted not only from the increased harvest of bark but also from the improvement of the isolation and purification procedures achieved by HCR. The amount of dried bark required to yield 1 kg of taxol has now been halved, from 30,000 pounds to 15,000 pounds (14). In addition NCI and USDAFS are collaborating in an extensive survey and analysis of *T. brevifolia* samples collected throughout the Pacific northwest to identify high-yielding trees; these are being propagated in USDAFS nurseries, and are being used as seed stock for replanting programs on both government and private land.

ALTERNATIVE SOURCES OF TAXOL.—NCI officials have always realized that alternative sources of taxol would need to be developed in the event of its becoming a candidate for marketing as a clinical drug. The annual demand to treat patients with ovarian cancer exceeds 20–25 kg for the U.S. alone and, with promise being shown in the treatment of breast and other cancers, the annual demand will increase substantially. Both NCI and BMS have embarked on intensive studies of alternative methods of bulk production and

alternative sources for procurement of taxol. A workshop organized by NCI in June 1990 brought together 200 investigators involved in all areas of taxol research and development. This meeting spawned new ideas and collaborations, and NCI is now supporting a variety of research endeavors through the funding of 35 grants totaling over $4.3 million annually. Projects that have been funded include studies of plant genetics and propagation, tissue culture, biosynthesis, semi and total synthesis, and improved analytical and isolation methods, as well as alternative formulations,, metabolism, drug resistance, and factors affecting binding of taxol to microtubules. Meanwhile, BMS is involved in its own research and development program and is also sponsoring research by other organizations. Results of many of these studies were reported at the second NCI workshop on taxol and *Taxus* held in September 1992.

In 1977, analyses of samples of the combined roots, stems, and leaves of *Taxus baccata*, the roots and wood of *Taxus cuspidata*, and the bark of *T. brevifolia* indicated that the *T. brevifolia* bark was the best source of taxol by at least a factor of two (unpublished results; NCI). In 1980, analyses of the needles of *T. brevifolia* showed that anticipated yields of taxol would be less than half of that of the bark (unpublished results; NCI). These data, together with lower relative abundance of the needles and the more difficult isolation process, led to the decision not to pursue the development of the needles of other *Taxus* species at that time. In 1988, French workers demonstrated that the precursor, 10-desacetylbaccatin III, isolated from the needles of *T. baccata*, can be converted to taxol and related active agents by a relatively simple semi-synthetic procedure (15), and alternative, more efficient processes for this conversion have recently been reported (16–18). The availability of millions of ornamental *Taxus* plants representing a variety of species and cultivars in U.S. nurseries, as well as the abundant supply of several other wild *Taxus* species in other countries, makes the isolation of taxol from the needles an attractive proposition for long-term bulk production. Needles and twigs can, in contrast to bark, be harvested without damage to the plant and thus represent a renewable resource.

Analytical surveys of needles of a number of *Taxus* species are being undertaken by NCI and Program Resources, Inc. (PRI) in collaboration with various organizations (names in parentheses). They include *T. baccata* from the Black Sea–Caucasus region of Georgia and Ukraine, and *T. cuspidata* from Siberian regions of Russia (T. Elias, Rancho Santa Ana Botanic Garden); *Taxus canadensis* from the Gaspe Peninsula of Quebec (Canadian Ministry of Forests); *Taxus globosa* from Mexico and *Taxus sumatriensis* from the Philippines (R. Nicholson, Smith College); and various *Taxus* species from the U.S. Department of Agriculture (USDA) in Beltsville, Maryland (J. Duke). In a number of samples, the taxol content of the needles is comparable to that of the dried bark of *T. brevifolia* (approximately 0.01%; unpublished results; NCI). The taxol content of fresh needles of 35 different *Taxus* cultivars from different locations within the U.S. has been analyzed, and at least six contain amounts comparable to or higher than those found in the dried bark of *T. brevifolia* (19). These observations have resulted in the initiation of a study of the nursery cultivar, *Taxus* × *media* Hicksii, as a potential renewable large-scale source of taxol (20). A mechanical harvester for clipping and collecting Hicksii clippings has been developed, and the factors influencing large-scale drying processes are being evaluated. This project, funded through an interagency agreement between NCI and USDA, has provided approximately 30,000 pounds of dried clippings to NCI and BMS for research on extraction and processing methodology.

Unlike the bark of *T. brevifolia*, the method and duration of drying of *Taxus* needles appears to be critical to achieving optimum yields of taxol (20). Small-scale experiments indicate that drying of the needles attached to the stems at temperatures of 40–50°

provides superior yields of taxol (21). The drying process is also critical in optimizing the yields of the key taxol precursors, baccatin III and 10-deacetylbaccatin III, from needles of *T. baccata* and *Taxus wallichiana* (22). The efficient isolation of these precursors on an industrial scale has been developed by the Italian company, Indena S.P.A., which will be providing them in large quantities to BMS for conversion to taxol by a semi-synthetic procedure developed by Holton *et al.* (16). BMS has also signed a research agreement with Weyerhaeuser Company for the mass propagation of high-yielding *Taxus* cultivars identified through an extensive analytical survey performed by Weyerhaeuser in collaboration with NCI and PRI (23). Production by the semi-synthetic route from the baccatin III precursors will increasingly replace the bark of *T. brevifolia* as the major source of taxol over the next 2–3 years, and it is anticipated that the use of bark will be eliminated by 1996. Since the spectrum of minor impurities (<1%) present in the new product is likely to differ from that isolated from the bark, the new needle-derived taxol product requires approval of the Food and Drug Administration (FDA) prior to use in the clinic. The necessary Supplemental New Drug Application is expected to be filed with the FDA by BMS in 1993.

Another potential long-term source of taxol is plant tissue culture. The advantages of the process are that cell suspension cultures can be established from high-yielding plants, and the growth medium can be varied so as to optimize production of the desired compound; in addition, a variety of stress conditions, such as addition of metal salts and certain microbial pathogens, can be applied in order to enhance production. This approach is theoretically attractive, but difficulties have frequently been encountered in isolating stable cell lines with other species and in inducing high-level production of the desired compounds. In 1977 NCI awarded contracts for the investigation of plant tissue culture as a source of anticancer drugs, and two of these studies related to taxol production. Unfortunately, these contracts were terminated in 1980 before any positive results had been obtained. Considerable research effort has once more been focused on the application of this technology to taxol production, much of it supported by grant funding from NCI. There were eight presentations on progress in this area at the Second NCI Workshop on Taxol and *Taxus* held in September 1992, and two companies, ESCAgenetics Corporation and Phyton Catalytic, are planning scale-up production of taxol in the near future.

The potential of molecular biology and bio-engineering approaches should not be overlooked. Very simplistically, the objective here would be to enhance expression of the key enzyme(s) involved in taxol (or taxane) production in either *Taxus* species or in *Taxus* tissue cultures, or to transfer the genes coding for the entire biosynthetic sequence into either a microbial or cell culture system where expression and scale-up would be readily achievable. The first problem with this concept is that the biosynthetic pathway for taxanes is undefined. The obvious precursor of all diterpene biosynthesis is geranylgeranylpyrophosphate, and the isolation and partial purification of an enzyme (a diterpene olefin cyclase) which effects cyclization of this precursor to the taxane skeleton has been reported (24).

Because natural product drugs are often very complex molecules with many chiral centers, large-scale production poses formidable synthetic challenges to even the most accomplished chemists. Taxol is no exception; the agent has 11 chiral centers (and hence 2048 diastereomeric isomers) and, despite years of effort, a total synthesis has yet to be reported. Considerable progress, however, has been made; the synthesis of a tricyclic intermediate having the complete A ring functionality of taxol and the key functionality required to introduce the remaining groups attached to the B and C rings, in eight steps from pinene, has been reported (25). Pinene, a constituent of pine trees and a major

component of industrial solvents such as turpentine, represents an excellent and inexpensive building block for the synthesis of taxol and taxol analogues, and has major implications for the development of an economically viable process.

The synthetic endeavors with taxol could be productive in another sense, however, since the possibility exists that some simpler intermediates might be discovered which are more amenable to large-scale synthesis and retain the desired anticancer activities.

Taxol must be considered as a lead compound as well as a drug. The supply problem as well as problems of formulation and convenience of administration can be obviated by discovery and development of structurally diverse compounds that have the same biological effects as taxol. One approach is detailed characterization of the taxol binding site on microtubules with the aim of determining its spatial and electronic requirements, and then to use this information with molecular modeling programs to design congeners that are much simpler and more readily accessible synthetically. A well-established example of development of simple congeners is the case of morphine, where important drugs such as methadone, meperidine, and propoxyphene have largely replaced the parent compound (26). The amino acid sequences of human tubulin are known, and photoaffinity labeling of the binding site, followed by depolymerization of the microtubules and sequencing of the modified tubulin(s), can define the amino acid residues at the binding site (27). This information can be used for design of congeners and, alternatively, may also lead to synthesis of binding site mimics which can be used in high volume screens for taxol-like activities in natural product extracts or synthetic compounds. Other approaches to screening for taxol mimics are the use of cell lines that are taxol-dependent (28). It is likely that the above approaches will lead to discovery of compounds with taxol-like activities which may be the third or fourth generation of taxol relatives.

NEW NCI STRATEGY FOR THE LARGE-SCALE PRODUCTION OF NATURAL PRODUCTS.—The problems experienced with the development of viable, renewable, long-term sources of taxol prompted the Developmental Therapeutics Program (DTP) of the NCI Division of Cancer Treatment to sponsor a workshop on the large-scale production of natural products in 1991. Over 30 experts in the various areas of natural product drug discovery and development, from the isolation of promising new agents to the eventual clinical trials of potential new drugs, were invited to attend. Short papers were presented on the cultivation of plants and marine organisms (aquaculture); the tissue and cell culture of plants and marine invertebrates; the isolation and culture of marine microorganisms, including symbionts; and the potential of genetic engineering and manipulation for the production of secondary metabolites from plants and other organisms. The synthesis of natural products and the problems associated with the scale-up of bench synthetic procedures were also illustrated and discussed by representatives of academia and industry.

Central to the discussions were the problems confronting DTP in predicting which new natural product agents are of sufficient promise to warrant substantial investment of limited funds, and at what stage of development of a particular agent priority should be given the development of large-scale production capability. Related to these decisions would be the determination of suitable mechanisms for funding such directed studies.

A critical requirement for predicting the potential of new agents is close communication between staff of DTP and the Clinical Therapy Evaluation Program (CTEP). Interactions between the preclinical and clinical programs are essential to ensure the timely identification of promising agents. Another strong recommendation was that DTP should fully utilize the services of extramural consultants with expertise in the

general strategy of drug development on committees dealing with the advanced preclinical and clinical development of specific new agents.

The Decision Network Committee (DNC), composed of senior DCT scientific and clinical staff, is responsible for evaluating preclinical screening and pharmacological data for new agents and making recommendations to the Director, DCT, concerning the acceptance and advancement of such agents through the various stages of the decision process. DNC acceptance constitutes decision point DN2A; at this stage formulation development, preliminary toxicology, and pharmacology studies, as well as the feasibility of large-scale production of the agent, are initiated. Completion of these steps leads to decision point 2B, and approval signals advancement of the agent to INDA-directed toxicology studies. Decision point 3 is reached upon completion of the toxicology phase, and, if approved, an initial new drug application (INDA) is filed, and the agent is advanced to clinical trials.

In considering the stage of development at which priority should be assigned to a particular agent and the mechanisms that might be applied to support developmental studies, the workshop participants recommended that a multiphase strategy be adopted.

1. First, the research community should be notified on a semi-annual basis of new non-confidential compounds of interest to NCI. This will enable scientists to submit grant proposals related to NCI interests. In addition, staff of the DTP Grants and Contracts Operations Branch should keep grantees apprised of the development of those agents relevant to their research efforts and interact with the grantees to promote optimum progress in areas of prime interest to NCI.

2. Once a purified natural product has been approved for the first stage of preclinical development (DN2A level), the DTP Natural Products Branch should identify research groups in the extramural community qualified to perform limited studies aimed at exploring the pilot-scale production of such agents. Such studies could involve the collection and investigation of related species and genera as potentially improved sources of relevant plant, marine organism, or microbial secondary metabolites, or the preliminary investigation of cultivation and/or tissue culture of the source organism(s). In addition, improved analytical and isolation procedures and methods for the scale-up synthesis of the agent could be investigated. The funding of such projects would be in the range of $10,000–$25,000 and would be arranged through mechanisms designed to support small-scale directed research efforts, including Interagency Agreements. An additional mechanism could be that of the Small Business Innovative Research (SBIR) program, whereby proposals are solicited from small businesses for the investigation of selected problems of interest to NCI and other institutes of the National Institutes of Health. The initial Phase I SBIR study can be funded at levels up to $100,000 for 6 months, and contingent upon satisfactory Phase I results and continued program interest, a Phase II development project can be funded at levels of up to $750,000.

3. Satisfactory completion of INDA-directed toxicology studies and approval of an agent to enter Phase I clinical trials (DN3 level) would signal the commitment by NCI of larger resources to its large-scale production. An open workshop may be convened to discuss the best production routes available, and consideration would be given to the preliminary information obtained from the earlier pilot-scale studies. Representatives of academia, relevant government agencies, and the pharmaceutical and other relevant industries would be invited to attend, and based on their discussions, recommendations made to the Board of Scientific Counsellors for appropriate action. The action could take the form of a Program Announcement stating NCI's particular interest in promoting the development of the agent or an RFA (Request for Applications) whereby a sum of money is set aside for research related to the agent's development; proposals addressing

important aspects of its development are submitted, and awards made to those applicants whose proposals are judged to be of sufficiently high technical merit and relevance to the program needs.

Another action could be the issue of RFPs (Request for Proposals), requesting proposals for performance of particular tasks, such as the large-scale recollection or cultivation of a plant or marine organism, the large-scale isolation of the desired agent, or its large-scale synthesis. A convenient mechanism to handle such projects is the Master Agreement Contract (MA) whereby pools of MA holders qualified in particular areas, such as large-scale collection of plants or large-scale isolation of natural products, are established. When a specific procurement need is identified, an RFP for the specific task is issued (i.e., Master Agreement Order RFP), and the relevant MA holders submit proposals tailored to the particular task. A Master Agreement Order (MAO) contract is awarded to the MA holder submitting the best and most cost-effective proposal. Since all the MA holders have already been judged to be qualified to perform tasks in the general area of interest, this mechanism permits a rapid MAO award in response to an urgent program need.

RFPs for the establishment of Master Agreements for the large-scale production of biomass for the isolation of antitumor and anti-HIV agents from natural sources were issued in late 1992. The areas covered include: feasibility studies on the cultivation and tissue culture of plants and marine organisms and the application of these methods to large-scale production; feasibility and optimization studies on the cultivation of phototrophic and non-phototrophic microorganisms and their large-scale cultivation; and the development of improved analytical and isolation methods.

Other mechanisms are the establishment of a Cooperative Research and Development Agreement (CRADA) or an Interagency Agreement with another Government agency. The CRADA mechanism involves an agreement between a pharmaceutical company and the government for the joint development of a promising new agent toward its eventual marketing as an approved drug. CRADAs are awarded on the basis of open competition, and any company may submit a proposal for consideration. In entering an Interagency Agreement, the DTP may decide that another government agency has the necessary expertise for handling a particular procurement, and an agreement for transfer of funds to the other agency is arranged. An example is the survey by the USDAFS of *T. brevifolia* growing on government lands throughout the Pacific northwest; samples of the bark and needles of 500 trees were analyzed by PRI for taxol and related taxane content.

4. The final stage in the strategy recommended by workshop participants represents a major commitment by NCI to the large-scale production of any agent showing objective responses in Phase I or Phase II clinical trials. As stated earlier, maintaining close communications between DTP and CTEP staff is critical to ensure the timely identification of such agents. The best route(s) of large-scale production will hopefully have been established in the earlier studies discussed above, and the most appropriate mechanisms would be selected on a case-by-case basis after discussion by the Decision Network Committee and the Board of Scientific Counsellors. The most suitable mechanisms at this stage of development might be one or more of an RFA, RFP, or CRADA.

Specific timetables for drug development should be defined following observations of efficacy in early clinical trials. The decisions implementing the timetable, however, are never simple. NCI actually has limited funds to commit to the development of a large number of drugs; at present, some 150 drugs are in various stages of clinical development. Despite some clinical responses, early experiences with taxol in Phase I clinical

trials were not encouraging, and indeed it was nearly dropped due to the deaths of several patients as a result of anaphylactic shock (as mentioned earlier, this was later shown to be due to a constituent of the administration vehicle and the method of administration). It was the persistence of a few clinical investigators, and the development of a safe iv infusion route of administration with a premedication regimen, that saved it from elimination (29). The major impetus to its full development resulted from the observation of responses in patients with advanced ovarian cancer (5). Subsequent confirmation of its antitumor activity in additional patients with ovarian cancer and other forms of malignancy (e.g., breast cancer) have emphasized the need for alternative sources of taxol other than the bark of the Pacific yew. The best guarantee to avoid severe drug shortages of promising new agents involves communication between preclinical and clinical investigators committed to the processes of cancer drug discovery and development.

Aspects of this new strategy are already being implemented. With responses being seen in early clinical trials of two relatively new camptothecin derivatives, CPT-11 and topotecan, it appears likely that the demand for camptothecin is going to escalate in the near future (30–32). In addition, NCI is developing 9-aminocamptothecin towards clinical trials. Currently camptothecin is obtained from Chinese and Indian sources and, even though a reasonable supply seems to be available, NCI is initiating an interagency project with USDAFS for the cultivation of the source tree, *Camptotheca acuminata*. In this instance, considerable experience has been gained from USDA cultivation projects in the 1960s when camptothecin itself was a clinical candidate (33). Therefore the problems associated with taxol production are not anticipated. Nevertheless, NCI considers it prudent to act soon so as to preclude the development of a similar supply crisis to that experienced with taxol.

CONCLUSION.—The NCI has exerted extensive efforts to respond to the taxol supply crisis, and in doing so has identified several important lessons for those interested in natural product drug discovery and development. Close communication must exist between those responsible for drug procurement and the clinical investigative team. Drugs that produce objective remissions in early clinical trials should be given sufficient attention to examine supply and potential demand based on the patient population size that may be adversely affected in the event of a shortage.

Therefore, the NCI has outlined plans to avert similar drug supply crises in the future by initiating exploratory research projects for large scale-up at the earliest possible point following the demonstration of confirmed antitumor activity. An extramural panel of experts has made specific recommendations to the program as outlined in this paper. While opinions may vary on the exact approaches that might be optimal, there is no disagreement on the importance of the mission of efficient discovery and development of effective new therapies for the treatment of cancer.

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