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TAXOL: A CASE STUDY OF BIOMEDICAL RESEARCH

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TAXOL: A CASE STUDY OF BIOMEDICAL RESEARCH AND PHARMACEUTICAL DEVELOPMENT IN THE UNITED STATES.

by

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ABSTRACT

TAXOL: A CASE STUDY OF BIOMEDICAL RESEARCH
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The high cost of new drug development in the United States contributes to the very high cost of health care in this country. The discovery and development of Taxol, a new anti-cancer drug, is described to illustrate practices which contribute to these high costs.

This thesis argues that the natural product search which resulted in the discovery of Taxol in the bark of the Pacific yew tree was too broad and therefore too expensive to justify its results. The author asserts that the continued dependence on yew bark in spite of the availability of less expensive and less ecologically sensitive sources was short-sighted and has resulted in some changes in NCI practices. The argument is also made that the agreement between the National Cancer Institute and Bristol-Myers Squibb, Inc. was a misuse of the Orphan Drug Act and resulted in too high a market price for Taxol.

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PREFACE

I first became interested in the subject of Taxol while preparing a paper on plants used as medicines for an anthropology course. As a registered nurse, who over the years has dispensed thousands of drugs to patients, I was well aware of the fact that many current pharmaceuticals are derived from plant sources. I wished to conclude my paper with information about a plant based drug which was then being developed and showed promise for the future. I remembered reading in the local newspaper of a nearby plant nursery that hoped to become involved in the production of a new anticancer drug, Taxol, and contacted them. The information that I received from the horticulturist at the Nursery, Mr. Ralph Shugert, not only provided me with a fitting conclusion for my paper but inspired an ongoing interest which formed the basis for this thesis.

Through the process of developing this thesis, I have learned much about the pharmaceutical industry and about the treatment of ovarian cancer that is both encouraging and discouraging. I have found particularly interesting the steps involved in bringing a drug from discovery to market and hope the reader finds this story equally intriguing. In this era of widespread health care reform, it is to be hoped that some attention will be paid to the pharmaceutical industry and that reforms in this industry and in the drug development process will help to reduce costs within the overall system.

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ABBREVIATIONS

BLM	Bureau of Land Management
CRADA	Cooperative Research and Development Agreement
DHHS	Department of Health and Human Services
EDF	Environmental Defense Fund
FDA	Food and Drug Administration
IND	Investigational New Drug Application
NCI	National Cancer Institute (Division of National Institutes of Health)
NDA	New Drug Application
NIH	National Institutes of Health
OARDC	Ohio Agriculture Research and Development Center
TAP	Taxpayer Assets Project
USDA	United States Department of Agriculture

INTRODUCTION

It is widely acknowledged that the cost of health care in the United States is exorbitant. The fact that this issue is currently being addressed at the highest levels underscores the urgency of this problem. The high cost of drug development and the subsequent high cost of pharmaceuticals is just one part, but an important part, of this picture. The pharmaceutical industry in this country claims that it costs them, on average, $125 million for each genuinely new drug developed (Weck 1990, see DHHS 53). That compares rather unfavorably with the equivalent of $87 million for the same process in Japan, the only other country for which I was able to obtain this information (Sapporo 1993). In some cases consumers pay twice for this process, with higher drug prices and with tax support for government assisted pharmaceutical development.

Much has been written both descriptively and critically about drug development in the U.S. However, I have not been able to identify any study in the scholarly literature which describes in depth the development process of a recently introduced pharmaceutical. I have chosen to follow a new anti-cancer drug, Taxol, along this route because the story of its discovery and development not only illustrates how a modern drug evolves but how practices within this process contribute to their high cost. Taxol is a plant-based pharmaceutical, and its production has had an ecological impact. This impact will also be discussed since it has contributed to the resultant cost of Taxol production both economically and environmentally.

The literature having to do with the discovery and development of Taxol is varied and relatively recent due to the current nature of the topic. Because Taxol was discovered in the bark of a tree and showed promise against a form of cancer which is particularly difficult to treat, it excited both popular and scientific interest. However, most of these articles, especially those in the scholarly journals, were specialized in nature. Some of the articles, like those of McGuire et al. and Rowinsky and associates of Johns Hopkins, were highly technical and dealt in detail with the mechanism of action or with the conducting and results of the various clinical trials of Taxol. Sufffness and Douros wrote specifically about the natural products program and search conducted by the National Cancer Institute. Other writers were more concerned with the ecological impact of the yew bark harvest. Nader and Love in *The Progressive* and Daniel Newman in the *Multinational Monitor* focused on the economic and political issues raised by the agreement between NCI and Bristol-Myers Squibb. There were also many short articles dealing with attempts by researchers around the country to synthesize Taxol. Articles in popular publications, such as Junod's in *LIFE*, tended to be more general, covering more of the story but in less depth. In addition to these and many other published sources, I have used the proceedings of two conferences on Taxol, a letter from Dr. Saul Shepartz of NCI, and discussions with Ralph Shugert of Zelenka Nursery. In this thesis I have attempted to pull all these disparate pieces together into a coherent whole and by doing so have, I hope, provided the complete story of a modern pharmaceutical from which some conclusions can be drawn.

Some background information is important to this discussion of Taxol development. Therefore, I will devote space in the introductory section to material regarding ovarian cancer, the only condition for which Taxol has so far

been approved, and also to general principles of drug development in the U.S. Each section in the body of the thesis will deal with one phase in the evolution of Taxol. Where appropriate within a section, I will describe those practices in the development of Taxol or pharmaceuticals in general which contribute unnecessarily to their cost. In the conclusion I will suggest steps which might have been taken to lessen those costs. In the epilogue I will discuss aspects of the Taxol story from which valuable lessons might be learned about pharmaceutical development and health care in general.

Cancer of the Ovary

Ovarian cancer is the leading cause of gynecologic cancer death in the United States and the fourth leading cause of cancer death among women overall. In 1992, estimates of incidence and mortality suggested that at least 21,000 women are diagnosed with cancer of the ovary every year and another 13,000 women die from it during that same period. Nearly one in every seventy women will develop ovarian cancer and approximately 1% of all female deaths will result from it (Young, Perez, and Hoskins 1993, 1226).

Cancer estimates projected for 1993 illustrate why ovarian cancer is such a challenge for oncologists and such a serious diagnosis for those women unfortunate enough to contract it. Cancer of the ovary accounted for only 4% of the cancer incidence among women, a rather small amount compared to the 32% incidence of breast cancer and even the 8% incidence of cancer of the uterus. The estimates of cancer deaths for the same year present a much different picture; 5% for ovarian cancer, 18% for breast cancer, and 4% for uterine cancer. The five year survival rates for the period 1983 to 1987 are even more telling; breast cancer 79%, uterine cancer 76%, and ovarian cancer 39%. An explanation for this disparity can be seen in statistics giving the percent of cancer cases by stage at diagnosis during the same five year period. Whereas 53% of breast cancer and 61% of uterine cancer are diagnosed while the tumor is still localized, that percentage drops to 23% in the case of cancer of the ovary (Boring, Squires, and Tong 1993).

From a medical point of view, therefore, the major problem with ovarian cancer is that it is difficult to diagnose when the tumor is sufficiently small and localized for effective treatment. There are no obviously discernable signs of

early stage disease: no uterine bleeding, no pain, and no definitive gastrointestinal or urinary symptoms. It is not until later in the disease process, when women often present complaining of vague abdominal discomfort and bloating, that diagnosis is usually made. This is due to the fact that the ovary is suspended loosely in the rather spacious pelvic cavity. The ovarian mass can thus become rather large without causing symptoms of pain or pressure. Compounding the problem is the fact that there has been no reliable screening method devised which will identify an ovarian cancer at an early stage, as the mammogram does for breast cancer and the pap smear does for cancer of the cervix of the uterus. For these reasons 75% of patients have cancer which has spread beyond the ovary at diagnosis and 60% have disease which has spread beyond the pelvis (Young, Perez, and Hoskins 1993, 1231).

The treatment for ovarian cancer, which, due to delayed diagnosis, is so often begun in later stages of the disease, remains a serious challenge to clinicians. Although few women can be treated with surgery alone, surgery is always the first step. It is necessary diagnostically to determine the extent of the tumor on which is based the classification of the disease and subsequent treatment.

> Stage I is tumor growth limited to the ovaries.
>
> Stage II is tumor growth involving one or both ovaries with pelvic extension.
>
> Stage III is tumor involving one or both ovaries with evidence of extension outside the pelvis and/or positive lymph nodes.
>
> Stage IV is growth involving one or both ovaries with distant metastasis.

Surgery to remove as much as possible of the tumor is also necessary because the success of subsequent treatment, and therefore survival rates, has been

shown to be directly related to the extent of residual disease left after the initial surgical procedure (Young, Perez, and Hoskins 1993, 1234). In most cases chemotherapy is required following surgery and in the United States, at least since the early 1980's, a combination platinum based therapy has been the standard treatment. Currently, in this country, a combination of cisplatin and cyclophosphamide is considered the appropriate first-line therapy. Other drugs have shown activity against and been approved for use to treat relapsed or refractory ovarian cancer. Taxol is one of these and is available at NCI designated cancer centers. Patients must have disease which is persistent or progressive while on a platinum based chemotherapy or have a recurrence within three months of completion of that therapy and have failed at least three prior chemotherapy regimens to be eligible for treatment with it (Runowicz 1992, 336).

Because of the difficulty in treating ovarian cancer, the search continues for other more effective drugs or more effective ways of using already known therapies. Other treatment approaches being studied include the use of some second-line drugs, including Taxol, as part of first-line treatment, intraperitoneal chemotherapy, in which drugs are instilled directly into the peritoneal cavity instead of being given intravenously, and hormone therapy. It is also hoped that advances in molecular biology and molecular oncology during the coming years may provide insight into the causes and prevention of cancer of the ovary as well as more effective treatments for it (Runowicz 1992, 336).

Development of New Drugs in the United States

Pharmaceutical development in the U.S. is a lengthy and expensive process. The discovery, testing and government approval of a new drug takes an average of eight years. Most of this time is spent in testing the drug on animal and human subjects. Such testing is not conducted by the Food and Drug Administration (FDA) but by the pharmaceutical manufacturer in conjunction with the National Institutes of Health (NIH) and other research institutions across the country. After a pharmaceutical company or research institution has completed its initial animal testing of the new drug and is ready to begin tests in humans, it submits an initial application to the FDA for approval. This is an Investigational New Drug Application (IND) which presents a plan for the study on human subjects, as well as a complete picture of the drug, including its structural formula and animal test results. Upon approval of the IND by the FDA, clinical trials may begin (Flieger see DHHS 1990, 11). Figure 1 illustrates phases of drug testing in humans.

How Experimental Drugs Are Tested in Humans

	Number of Patients	Length	Purpose	Percent of Drugs Successfully Completing*
Phase 1	20 - 100	Several months	Mainly safety	70 percent
Phase 2	Up to several hundred	Several months to 2 years	Some short-term safety, but mainly effectiveness	33 percent
Phase 3	Several hundred to several thousand	1-4	Safety, effectiveness, dosage	25-30 percent

*For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70 will successfully complete phase 1 trials and go on to phase 2; about 33 will complete phase 2 and go to phase 3; 25 to 30 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

Figure 1 (DHHS 1990, 12)

It is not until the safety and effectiveness of the drug is ascertained through these trials and a New Drug Application (NDA) has been prepared and submitted to the FDA that the approval process begins. It is then the FDA's responsibility to review the test results, making sure that they do, in fact, show the drug to be both safe and effective for its proposed use. This review takes an average of twenty-four months (Flieger see DHHS 1990, 15). Figure 2 illustrates the time required for the various stages in this process.

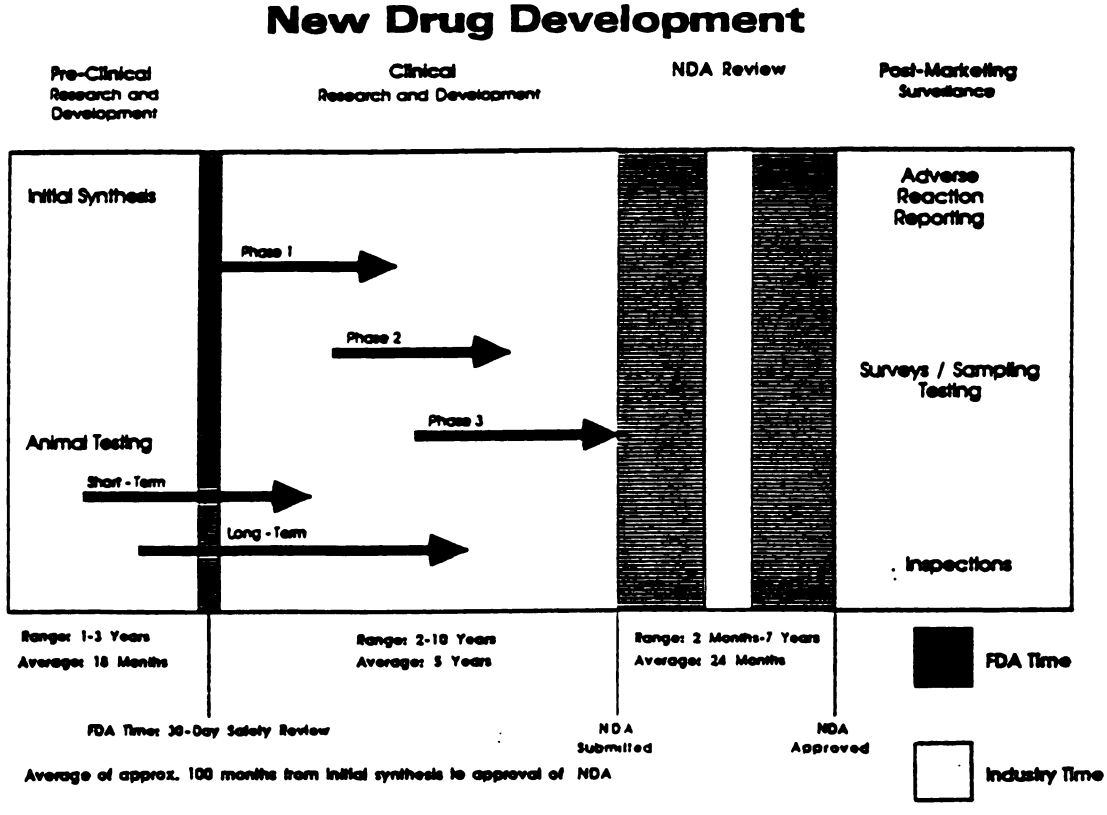

Figure 2 (DHHS 1990, 3)

The FDA asserts that this is time well spent. Dr. Frank Young, Commissioner of Food and Drugs from 1985 to 1989, stated that "the vast majority of chemicals tested are discarded as possible new drugs turn out to be either

unsafe or ineffective for their proposed uses. In fact, the drug development process can be viewed as a series of progressive steps, each designed to highlight drugs of real promise and to weed out those that could be harmful or simply don't work" (Young see DHHS 1990, 2).

Criticism has been leveled at the pharmaceutical industry and especially at the FDA for taking too long to develop and approve new drugs. Dr. Young, who relates this information, says that this criticism is particularly vocal where it concerns drugs with potential use in life threatening illnesses. He says that is has been argued that patients with such conditions would often not survive long enough to benefit from a new medication approved by the usual route, and had little to lose, and perhaps much to gain, from being given a less than thoroughly tested drug. Partially in response to such criticism, the FDA issued a new regulation in 1987 allowing for the use of experimental drugs to treat life threatening illnesses (Young see DHHS 1990, 22-23). For an illustration of when such medications can be made available during the drug development and testing process, see Figure 3.

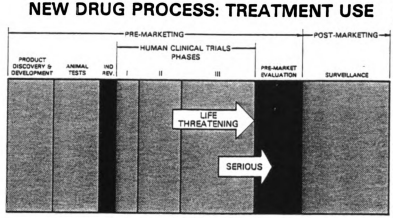

Figure 3 (DHHS 1990, 23)

The arrows on this chart show when a promising experimental drug can be made available to additional desperately ill patients, under a rule issued in 1987 by FDA. With drugs for immediately life-threatening conditions, expanded availability can begin near the end of the second phase of human testing—that is, after the drug's initial safety testing has been done and the proper dose determined (phase I), and after some evidence of therapeutic benefit has been obtained (phase II). For serious but not immediately life-threatening illnesses, approval for expanded treatment availability can occur sometime during the third and final phase of testing. During phase III, early evidence of safety and effectiveness is being verified before marketing approval of the drug is finally sought from FDA. Once granted, FDA approval of an investigational drug for treatment use will normally continue until regular marketing of the drug begins. ("IND Rev." means FDA review of an investigational new drug application, approval of which is necessary before a drug can be tested in people.)

Another problem in the pharmaceutical industry has been the development of drugs for the treatment of rare diseases. The industry claims that it costs on average $125 million for each genuinely new drug that it brings to market. In the past there has been little financial incentive to undertake this costly process if the client population is small. It is true that drug companies did develop some of these drugs as public service products on their own initiative. However the need was far from being met. By the early 1980s, there was growing realization that the government was going to need to become more involved and share the burden of developing these treatments if more patients who were suffering from rare conditions were to be helped. One attempt to answer this problem was the passage in 1983 of the Orphan Drug Act. An orphan drug is defined by the FDA as a drug intended for a rare disease or condition "which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (Patrick 1988). The act encourages the development of these orphan drugs by several means:

1. The orphan drug developer has seven years of exclusive use or license, during which no one else may market the drug in the United States unless permitted by the sponsor.
2. The developer of an orphan drug may claim up to 63 percent of the cost of clinical studies as a tax credit.
3. The FDA can assist sponsors of orphan drugs in developing the protocol, or guidelines, for conducting clinical studies.
4. The FDA can modify certain drug approval requirements for specific orphan drugs. For example, by allowing testing to be done on a smaller

group of patients.

5. The FDA can put orphan drugs on a "fast track," giving them high priority for review.

6. The FDA can make grants ranging from $20,000 to $70,000 in support of a sponsor's clinical research of an orphan drug.

A rare disease was originally defined as one with a patient population of less than 200,000. In 1984, the act was extended to include products that may be needed by more than 200,000 persons, but have no reasonable expectation of recovering research and development costs from sales in the United States (Weck see DHHS 1990, 53-55). Many new drugs, including Taxol, have been developed under the provisions of the act.

CHAPTER 1

THE DISCOVERY OF TAXOL

The Natural Products Search

There are basically two approaches to drug discovery. One is the more cerebral approach of a scientist conceiving, designing, and synthesizing a new drug. The second is the screening of naturally occurring substances to determine their potential therapeutic effectiveness. This second approach has resulted in some of our most potent anticancer agents. Among these are the vinca alkaloids obtained from the rosy periwinkle, antitumor antibiotics, and the platinum compounds (Rowinsky and Ross 1991).

In fact, long before scientists could even recognize, let alone synthesize, chemical compounds, indigenous peoples recognized the medicinal use of natural products. Over a period of time, early man developed an extensive pharmacopoeia of plant parts. These were eaten or drunk in herbal brews, or utilized through local application as poultices or in steam baths (Harris 1972). In the introduction to his survey, *Plants Used Against Cancer*, Jonathan Hartwell, former head of the Natural Products Section at the National Cancer Institute (NCI), relates that years ago, while studying the chemical agents responsible for the anticancer activity of a new plant based drug, he carried out a routine literature review of the source plant. He found that it had been used by the Penobscot Indians of Maine to treat cancer and that the resin from the plant was recommended over a hundred years ago in an American materia medica for the

treatment of cancerous tumors, polyps, and unhealthy granulations. He also discovered that this resin was in use as early as 1897 by physicians of Louisiana and Mississippi for the treatment of venereal warts. These findings inspired Hartwell to broaden his search for information both in technical literature and from folklore that could provide leads to other plants which might be valuable for laboratory investigation. He found that a surprisingly large number of different plants had been used or recommended for the treatment of cancer in various locations around the world. Hartwell later completed a comprehensive survey which contains the names of over three thousand plant species used to treat cancer and other growths (Hartwell 1982).

In the late 1950s The National Cancer Institute (NCI) initiated a natural products program and in 1960 a major effort was begun to screen plant extracts. Field workers from the United States Department of Agriculture (USDA), under contract to NCI, began to collect random samples from all kinds of natural substances, including moss, fungi, and molds. Over the next twenty years, until 1980, 114,000 plant extracts representing 35,000 species from around the world were evaluated (Suffness and Douros 1982, 1). Among them were plant samples from the American northwest including bark, needles, and twigs from the Pacific Yew tree, *Taxus brevifolia*. Taxol was eventually isolated from this bark.

There is no indication that in the natural products search or in the initial screening of thousands of these substances at NCI there was any attempt to first ascertain a history of use within folk medicine or by indigenous peoples. Several authors, in fact, used the term "random" or its equivalent to describe the search for and collection of these samples (Song and Dumais 1991, Daly 1992, Junod 1992). Suffness and Douros state that there is a fairly extensive literature regarding the use of traditional medicine in the treatment of cancer, much of

which was compiled by Jonathan Hartwell, already referred to, who was formerly with NCI. They also acknowledge that "a retrospective correlation of several groups of medicinal and poisonous plants with NCI screening data had found substantially increased activity for plants used as anthelmintics (substances which expell worms from the intestines), arrow poisons and fish poisons when compared with plants selected at random" (Suffness and Douros 1982, 3). In spite of this, the NCI program had, from its inception, been based on random screening of plants, i.e., "plants that have no reason for being screened other than novelty to the program" (Suffness and Douros 1982, 3). In response to my question regarding this, Dr. Saul Schepartz of NCI's Developmental Therapeutics Program of the Division of Cancer Treatment responded via letter. "Although the majority of materials collected were 'random,' plants of reputed medicinal use were collected in the course of their field trips. However, they did not make specific trips for that purpose" (Schepartz 1993). There is some indication that researchers from NCI now do consider evidence of traditional medicinal use before deciding which of the many hundreds of plant samples still remaining in storage they wish to screen (Daly 1992). One could only wish that this had been done earlier in this long and expensive publicly financed world search. The search could have been considerably narrowed and rendered less costly to the public had this information been consulted initially. It appears that, with the possible exception of some analogues of camptothecin, Taxol is the only anticancer drug to have so far resulted from this search (Schepartz 1993). This does not appear to be a very high rate of return on a very expensive process.

Not surprisingly, the yew does have a history of medicinal use. A form of the plant was used in India to treat cancer (Hartwell 1982). The yew bark has also been used medicinally by Native Americans of the northwest (Moerman

1986). The yew was noted for its toxicity by early Greek and Roman naturalists and has long been known as a poison and associated with death. Even Shakespeare made use of the yew's reputation when he included it in the witches brew in *Macbeth* (Daly 1992, 78).

Statistics indicate that natural products are an important source of potential drugs for use against cancer. NCI screens about 10,000 new synthetic compounds and 400 pure natural products per year plus about 14,000 crude natural product extracts. Of that large number only about six to eight compounds enter clinical trials each year of which about half are natural products (Suffness and Douros 1982, 11). In 1986, NCI re-instituted its plant collection program because of renewed interest in that area and the development of new, more effective screens. The current collection effort is concentrating on tropical and subtropical regions of Southeast Asia, Africa, and Central and South America (Schepartz 1993).

Drugs from natural sources should continue to be pursued, but because of the expense of that pursuit, most serious consideration should be given to those sources with a history of medicinal use. Besides Hartwell's text discussed earlier, there are many resources for information on the history of the medicinal use of plant products. Although these plants are numerous, the list of most promising potential could be narrowed by cross-referencing substances used most often by the most groups which appear to have anticancer type properties.[1]

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[1] Daniel Moerman's Medicinal Plants of Native America is an excellent resource and provides listings of medicinal plants both by species and user group.

Taxol's Novel Mode of Action

The story of the emergence of Taxol from among the 114,000 plant extracts that were tested by NCI for cytotoxic (anticancer) activity between 1960 and 1981 is most interesting. The initial tests were conducted primarily on a series of tumors in rodents. During the late 1960s, the yew bark extract demonstrated activity against several of these including leukemias, sarcomas, and lung tumors (Rowinsky, Cazenave, and Donehower 1990).

During this period, Monroe Wall, a chemist under contract to NCI, and his co-workers at Research Triangle Institute in Durham, North Carolina, were doing studies for NCI on the yew extract along with other extracts that showed similar promise. They were intrigued by the activity that they noted in even a crude extract from the *Taxus brevifolia* bark. By 1969 they had isolated the active agent. (The generic name given to this compound was paclitaxel. However it became known by the common name of taxol which was adopted later by Bristol-Myers Squibb as the trade name Taxol). In 1971, after two years of working on the purified compound, they were able to isolate and describe the very complex Taxol molecule (Daly 1992). In spite of continued interest on the part of Wall and occasional prodding by him, research on Taxol languished for the next several years. The problem was that, not only was Taxol difficult to work with due to solubility problems and expensive to obtain and therefore scarce, but there was nothing to set it apart from many other substances also showing some promise, or any reason to believe that it might be equal or superior to already available drugs like Cisplatin. The NCI has found thousands of chemicals capable of killing cancer cells in test tubes but unless a substance can be shown to be more potent, less toxic, or kill cancer in a new way, using what scientists

term a "novel mechanism," it will probably not be developed (Junod 1992).

Two developments in the 1970's brought Taxol once again to the forefront of cancer research. The first was the development of new, much more reliable animal screens, several of which showed significant activity on the part of Taxol. The second was the discovery that this agent had a novel mechanism of action and induced unique biologic effects. In 1977, NCI contacted Dr. Susan Horwitz, a professor of molecular pharmacology at Albert Einstein College of Medicine in New York City. She was working under a Cancer Research Emphasis Grant from the agency and they thought that she might be interested in investigating how Taxol worked on cancer cells. Horwitz and a graduate student, Peter Schiff, began working with Taxol. What they discovered surprised them. Taxol affected the microtubules of the cancer cells. These are tubular structures which are formed into a framework when a cell is about to divide and are normally in dynamic equilibrium, being constantly formed and dismantled. The Taxol stimulated microtubule formation and stabilized it against dismantling, making cell division impossible, in effect, paralyzing the cancer cells. Horwitz and Schiff's findings were published in 1979 (Daly 1992). Several plant products, including colchicine, and the vinca alkaloids vinblastine and vincristine, which are so useful against Hodgkin's Disease, work by destabilizing microtubules. But Taxol's stabilizing activity is unique. It was the discovery of this novel mechanism, with its potential to damage rapidly dividing cells, such as cancer cells, that so intensified interest in Taxol among researchers (Blume 1989).

CHAPTER 2

THE DEVELOPMENT OF TAXOL

Clinical Trials

The Investigational New Drug Application (IND) for Taxol, which had been submitted by NCI, was approved by the FDA in 1982 after two years of toxicology studies had resulted in an acceptable formulation of the drug (Daly 1992). The IND was the preliminary step to clinical trials as it is for all new drugs. In it the sponsor provides the results of laboratory and animal research plus information about any previous use of the drug in humans in this country or abroad. A detailed plan must be furnished for the conducting of the clinical trials, including the number and method of selection of the subjects, where the studies will be done and by whom, how the drug's safety and effectiveness will be evaluated, and what findings would require the study to be altered or discontinued (Flieger see DHHS 1990, 11).

The clinical trials are, as might be expected, the most critical part of the drug development process as they involve the first testing on humans. It is here that most proposed new drugs fail. One major U.S. drug company states that only one out of every twenty compounds that it brings to clinical trial is judged safe and effective enough to merit FDA approval for marketing. The drug's sponsor, whether pharmaceutical company, research organization, public or private agency, or even an individual, is responsible for arranging the clinical trials and compiling the resulting data. The trials are normally done in three

phases in which progressively larger number of subjects are involved (see Figure 1, 7). Physicians and hospitals actually conduct the studies at the request of the drug's sponsors. The FDA than examines these results along with the design and conduct of the study to determine if the results are scientifically valid and free of subjective bias (Flieger see DHHS 1990, 11).

Phase I clinical trials are concerned primarily with the determination of the drug's safety, although some information about the drug's effectiveness may also result. "The various tests determine how the drug is absorbed, metabolized and excreted; what effects it has on various organs and tissues; and what side effects occur as the dose is increased" (Flieger see DHHS 1990, 11). The results of these tests provide essential information about drug dosage and are critical in determining the design of the later trials (Flieger see DHHS, 11). Phase I trials of Taxol were begun in 1983. They were carried out at several hospitals including Johns Hopkins, Memorial Sloan-Kettering, and Walter Reed. There was initially a high incidence of hypersensitivity or allergic reactions, including respiratory difficulty, rashes, and blood pressure changes. Some of these reactions were quite severe. There was one fatality, although that patient had extensive pulmonary metastases from his cancer which may have caused the reaction to be more pronounced. Because Taxol dissolves poorly in water, it is administered in Cremophor, a derivative of castor oil, as are a number of other poorly soluble medications. Initially some investigators felt that the allergic reactions may have been caused by this vehicle but since there was no known suitable substitute for it, Taxol continued to be delivered by this route. Because of the higher incidence of these reactions when Taxol was given in short infusion schedules, those were discontinued and subsequent studies were conducted with 24 hour infusions. Patients were also found to have fewer reactions to

Taxol if they were pretreated with steroids, and an antihistamine (Weiss et al. 1990).

Each of the phase I trials at the various sites used somewhat different drug administration schedules ranging from a one hour intravenous infusion for five days administered every twenty-one days to one twenty-four hour infusion every twenty-one days. One site used Taxol in combination with cisplatin. Neutropenia, a low white blood cell count due to bone marrow suppression, which makes one more susceptible to infections, was the dose-limiting toxic effect in almost every instance. Other toxic side effects included nausea, diarrhea, hair loss, neuropathy, and the allergic reactions discussed above. During the phase I trial antineoplastic (anticancer) activity was noted in patients with several different tumor types both with Taxol alone and with the Taxol/cis-platin combination (Rowinsky, Cazenave, and Donehower 1990). This phase I testing was a slow process with a number of stops and starts due to the allergic reactions and other problems but finally in 1987, NCI was ready to begin phase II studies.

Because of the positive activity seen in the phase I trials and especially because of a very dramatic response noted in a patient with cisplatin-refractory, advanced, and progressive ovarian cancer, phase II trials were initiated (McGuire et al. 1989). These trials usually involve more subjects than do phase I trials and are designed to show whether the drug is effective for treating the condition for which it is intended (Flieger see DHHS 1990, 11). The initial phase II trial consisted of forty-seven women with ovarian cancer who were studied at Johns Hopkins Oncology Center by Eric Rowinsky, William McGuire, and colleagues. The women had to have one or more measurable lesions, normal kidney and liver function, a life expectancy enabling completion of at least two courses of

therapy, and no recent cytotoxic chemotherapy or radiation therapy. In this trial, no exclusions were made based on the number of previous treatment regimens which the patient had endured, but these women had been heavily pretreated and most (thirty-two of forty-seven) were refractory to cisplatin as defined by either tumor growth while receiving cisplatin or recurrence of tumor within six months after completion of cisplatin. All patients were hospitalized for each course of Taxol which was administered as a twenty-four hour intravenous infusion and all were pretreated with a steroid, an antihistamine, and an antiemetic. Repeat courses of Taxol were administered every twenty-two days if there was no evidence of tumor progression and blood counts had returned to pretreatment levels. Of the forty women who finished the trial, twelve had at least 50 percent shrinkage of their tumors in responses that lasted from three to fifteen months. These results were considered significant for several reasons. First, Taxol has a novel mechanism of action and was the first of its class to undergo clinical evaluation. Second, the response rate of 30 percent in such a heavily pretreated population of patients with ovarian cancer was remarkable and reminiscent of early trials of cisplatin. Third, the doses used were only, on average, 50 percent of those recommended from phase I trials and still resulted in significant responses. Finally, the toxic side effects were manageable and had little overlap with those of cisplatin, enabling a future broad study of the two agents in combination (McGuire et al. 1989).

Because of shortages in the supply of Taxol, initial phase II trials did not involve as many subjects as would be usual. Instead, smaller phase II studies were performed in specific cancers on the basis of antitumor activity noted in preclinical and early phase I trials (Rowinsky, Cazenave, and Donehower 1990). One of the most interesting of these is a phase II trial of Taxol in the treatment

of metastatic breast cancer done at the M. D. Anderson Cancer Center in Houston, Texas by Holmes and her associates. They treated twenty-five women with the same twenty-four hour intravenous infusion and the same premedication protocol that was used in the ovarian cancer trial at Johns Hopkins. They had a 56 percent positive response rate while disease progressed in only 8 percent of the women. They went on to initiate phase I trials of Taxol with doxorubicin, frequently used to treat cancer of the breast (Holmes et al. 1991). Another phase I trial which may improve the results seen with Taxol treatment, studied the use of granulocyte colony-stimulating factor (G-CSF) with Taxol administrations. G-CSF is given after the infusion of Taxol and helps to lesson the effects of bone marrow suppression, allowing Taxol to be given in much larger, possibly much more effective, doses (Sarosy et al. 1992). As a result of other trials it was determined that Taxol is probably not effective against melanoma or cancer of the colon, cervix, kidney, or prostate. Broad Phase II testing in most other cancer types is in progress. Trials combining Taxol with other anticancer drugs are ongoing and it is felt that this combination therapy may offer women the best hope (Arbuck 1992).

A more complete understanding of a drug's safety, usefulness, and possible long-term side effects is the goal of phase III trials. These studies are usually done on very large groups of patients, hundreds or even thousands. Many drugs never reach this stage. Others are approved before trials are completed because they are intended for life-threatening conditions (Flieger see DHHS 1990, 12). Such is the case with Taxol which is available at NCI approved cancer centers for women with refractory ovarian cancers who meet the stringent criteria (Runowicz 1992, 336).

The NCI/Bristol-Myers Squibb Connection

The National Cancer Institute has carried out, mostly through contract, a comprehensive program of anticancer drug development since 1955. More recently, that program has been extended to include drugs to fight AIDS. "The program includes all aspects of drug development including the acquisition of new agents; screening in experimental test systems; congener/analogue/prodrug synthesis; natural product purification/isolation; large-scale production of bulk drug; formulation development and manufacturing; preclinical and clinical pharmacology; preclinical toxicology in animals; and Phase I, II, and III clinical trials" (Schepartz 1992, 5). In fact, in collaboration with the pharmaceutical industry and academia worldwide, NCI has been involved in the development of almost all of the drugs in our current armament against cancer. "The NCI does not, however, market drugs and thus transfers its technology to the private sector when a drug appears to be destined for commercial use" (Schepartz 1992, 5). The National Cancer Institute, as part of the National Institutes of Health, is federally funded and therefore tax-payer supported. It is important, therefore, to be aware of how NCI uses this publicly funded research.

After Dr. Horwitz and her associates at the Albert Einstein College of Medicine identified the novel mechanism by which Taxol worked and positive reports began to come in from trials at Johns Hopkins, the interest of some pharmaceutical companies was excited. Bristol-Myers Squibb, Inc. of New York, hereafter referred to as Bristol-Myers, the primary U.S. producer of cancer drugs, won, against Rhone-Poulenc Rorer and two smaller American drug companies, an "open competition" conducted by NCI and in January of 1991 signed a Cooperative Research and Development Agreement (CRADA) with the

agency. According to the *Journal of the National Cancer Institute*, "Under the terms of the CRADA, NCI will give Bristol exclusive access to its clinical and preclinical data, so the company can seek marketing approval for Taxol from the Food and Drug Administration. In exchange, Bristol will provide Taxol to NCI for clinical studies and will assemble and submit a New Drug Application (NDA) for the anti-cancer agent" (Blume 1991, 1055). *Fortune* magazine stated that "Bristol-Myers' huge financial resources obviously helped" in the CRADA bid and quoted Bruce Chabner, director of cancer treatment at NCI as saying, "In our judgment Bristol-Myers Squibb was clearly the most qualified because of its extensive experience in the development of anticancer drugs and its ability to follow through to final new drug application status" (Bylinsky 1992, 102). BMS went on to win "orphan drug" status for Taxol as an ovarian cancer treatment from the FDA. That gave them a seven-year monopoly on selling Taxol for that purpose once the drug was approved by the FDA (Bylinsky 1992). That approval was granted in December of 1992. That means that no other firm can sell Taxol to treat ovarian cancer until 1999 and Bristol-Myers will also retain exclusive rights to the clinical data until that time.

In order to supply enough Taxol to NCI for its clinical trials and to cancer centers around the country, Bristol-Myers needed a ready supply of the yew bark. The heaviest concentrations of Pacific yew are on lands in Oregon and Washington currently managed by the Department of Agriculture's Forest Service and the Department of the Interior's Bureau of Land Management (BLM). Bristol-Myers signed cooperative agreements with both agencies, giving them exclusive rights to the yew trees on those public lands which contain the greatest number of yew trees in the country (Newman 1992, 20). The collection of yew bark from these government lands is managed by Hauser Chemical

Research, Inc. of Boulder, Colorado, which also processes the bark to extract the Taxol for Bristol-Myers (Blume 1991). According to *Fortune* magazine this amounts to a virtual lock up of the domestic supply of Pacific yew trees (Bylinsky 1992, 100).

As the exclusive commercial producer of Taxol, Bristol-Myers stands to make large profits from its sale. Bristol-Myers has said that it will provide Taxol without charge to patients who are not insured, ineligible for government assistance, or who lack the ability to pay and, of course, under its agreement with NCI it must continue to provide Taxol free to the institute for its clinical trials. For all others, however, the company set the wholesale price at $986 for each cycle of therapy. A cycle consists of one continuous intravenous infusion over twenty-four hours every three weeks. NCI estimates the average number of treatment cycles per patient at four to five (Leary 1992), resulting in an average cost of almost four to five thousand dollars per patient. Before the agreement with Bristol-Myers, NCI was able to manufacture Taxol for about 60 cents per milligram, or $1000 for an entire course of treatment (Nader 1993, 28). However, Bristol-Myers has set Taxol's maximum price at $6000 for a complete treatment (Borman 1993) in spite of the fact that, with large-scale production, their costs should have fallen. These figures are somewhat outdated by the fact that they are based on the earlier recommended dose of 202.5 mgm. Patients in clinical trials are now being given from 210 to more than 300 mgm of Taxol per dose. An average dose of 240 mgm will cost the patient $1,169. If she responds favorably to the treatment and receives a full course of Taxol, up to eight cycles, the total treatment cost would be $9,350 in spite of the fact that the Government was able to produce the same amount of Taxol for $1,152 (Nader 1993, 28). Ronald Nordmann, an analyst with Paine Webber Securities, is

quoted in *The New York Times* as saying that Taxol is the most important drug which Bristol-Myers is developing. He expressed the opinion that the market could reach $350 million by 1995 and that Taxol has the potential to be a billion-dollar drug for the company (Kolata 1992). A *Kiplingers* article in October of 1992 stated that Taxol could be a "gusher" for Bristol-Myers once the supply problems are solved and could become a $500-million -a-year product for the company (Moreau 1992). The *Fortune* article relates that Zola Horovitz, a Bristol-Myers vice president, who runs the company's project to mass-produce Taxol, calls such numbers sheer speculation but adds that Bristol-Myers is not worried about recovering its investment - $100 million so far (Bylinsky 1992, 100).[2]

There is a fair pricing clause in the CRADA, the text of which the *Multinational Monitor* obtained under the Freedom of Information Act. It reads: "NCI has a concern that there be a reasonable relationship between the pricing of Taxol, the public investment in Taxol research and development, and the health and safety needs of the public. Bristol-Myers Squibb acknowledges that concern, and agrees that these factors will be taken into account in establishing a fair market price for Taxol" (Newman 1992, 19). However, NCI has no way of knowing if the price set by Bristol-Myers for Taxol is actually fair because the pricing clause in the CRADA does not give the agency access to corporate cost data (Borman 1993). Nader claims that it is "so weakly worded and lacking in enforcement measures that it may only serve the public-relations interests of the company" (Nader and Love 1993, 28).

According to Daniel Newman, the Taxol case is particularly noteworthy

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[2]Evidently Wall Street agrees with the general assessment of profits to be made from taxol because, as reported by *The New York Times*, the shares of Bristol-Myers Squibb rose immediately after the FDA approved taxol.

because Bristol-Myers stands to make so much money for so little effort. Bristol-Myers did not discover, develop, or test the drug; the federal government did all these things. NCI has already spent more than $12 million on Taxol research, tests, and clinical trials and plans to spend over $20 million more. The federal government also owns much of the land upon which the Pacific yew grows and Bristol-Myers is paying little or nothing for access to the trees that grow on it (Newman 1992, 17).

There are some possible factors behind, what Newman terms, the "giveaway" of Taxol to Bristol-Myers. One of these is the activities of Dr. Robert Wittes, who in the late 1980's oversaw the clinical trials of Taxol in his position as associate director for cancer therapy evaluation at NCI. He then left NCI to fill a position as Bristol-Myers' senior vice president for cancer research. After less than a year at Bristol-Myers, Wittes returned to NCI in August 1990 as chief of its medicine branch, which conducts in-house research. Wittes declined to answer questions posed by Newman but James Love, director of the Washington, D.C.-based Taxpayer Assets Project (TAP), believes that Wittes helped Bristol-Myers win control of Taxol by assisting them in preparing for the CRADA bid (Newman 1992, 19). Such "revolving door" practices give the appearance of a conflict of interest and seem to be unethical, if not illegal. This type of activity has been outlawed between the government and the military/industrial complex. Similar restrictions ought to apply in this setting.

Another contribution to this potentially very profitable arrangement for Bristol-Myers is a loophole in the federal law. Neither Taxol nor the idea for using Taxol is patentable, since both have been in the public domain for decades. But Bristol-Myers obtained monopoly rights to market Taxol under the Orphan Drug Act, legislation to encourage drug companies to develop and

market treatments for rare diseases which affect small numbers of people. Even though ovarian cancer is the fifth-leading cause of death among women cancer victims and one out of every seventy women will develop this cancer, it qualifies as a rare disease. "Ovarian cancer has an estimated client population of 164,000 - large enough for Bristol-Myers to earn huge profits, but well under the 200,000-patient cutoff in the law" (Newman 1992, 19). The Orphan Drug Act has been amended several times over the years since its enactment. Each amendment has broadened the definition of "orphan disease" until today such conditions as asthma, AIDS, lung cancer, and chronic pain qualify. AZT, human growth hormone, and other very profitable drugs received monopoly marketing rights under the Orphan Drug Act (Nader and Love 1993, 27).

Along with the TAP group mentioned above, some of our legislators have become concerned about the nature of the arrangement between NCI and Bristol-Myers. In July 1991 both federal and corporate officials were questioned by the House Subcommittee on Regulation, Business Opportunities, and Energy headed by Rep. Ron Wyden (D-Ore.). Rep. Wyden believes that the CRADA does not provide adequate protection against price gouging. Committee members also expressed concern about the agreements between Bristol-Myers and the U.S. Forest Service and Bureau of Land Management feeling that they could prevent other companies' attempts to produce Taxol by alternative means (Reynolds 1991). Wyden and TAP are calling for reforms in the Orphan Drug Act but legislative action seems unlikely thus far (Newman 1992). The legislation that the subcommittee has proposed includes: a presetting of a drug's price at the time of the CRADA signing; making available corporate pricing data to the NIH; and allowing firms to recover only investment plus a fixed rate of return. Rep. Wyden said that he is concerned by the pricing of Taxol and other drugs

which have been developed in cooperation with Federal agencies at taxpayer expense. "Up to half of the most valuable cancer and AIDS drugs are developed with substantial taxpayer support. Consumers who have funded drug development through the gift of tax credits and federal lab research should not be bludgeoned by price gouging" (Borman 1993, 8)

Meanwhile cooperation continues between NCI and Bristol-Myers and it appears as though nothing will disrupt it. The CRADA gives Bristol-Myers the right to terminate the agreement with NCI if it decides that developing Taxol will not be financially rewarding. NCI, on the other hand, can only terminate the agreement if it decides that the company "has failed to exercise best efforts" (Newman 1992, 21) in commercializing the drug. NCI is also bound by a clause in the CRADA that prevents it from assisting any other company to develop Taxol as long as Bristol-Myers does not abandon the drug and "public health needs are adequately served" (Newman 1992, 21).

NCI defends the kind of exclusive agreement guaranteed by the CRADA on the basis that they are needed to bring promising drugs to market quickly and that pharmaceutical companies are not willing to expend the considerable resources necessary for such development without such exclusive rights (Newman 1992). If this is the case, why is it that other firms are willing to spend millions of dollars to compete with Taxol? Rhone-Poulenc Barr, one of the original competitors for the Taxol CRADA, is testing Taxotere, a synthesized product obtained from the European yew tree, to treat cancers of the ovary, breast, and lung (Nader 1993). This strongly indicates that a monopoly was not necessary to bring Taxol to market and that the drug would have been developed without those assurances of exclusivity and without the considerable tax-supported assistance given to Bristol-Myers. However, since Bristol-Myers

still retains the rights to the clinical data as well as to the yew trees on public land, competition for Taxol will surely be considerably reduced, at least for the next few years. I find it most interesting that an industry report for 1990 which compared the top sixty-four drug companies internationally judged Bristol-Myers Squibb the best performer based on profitability. Their sales had increased 18.4 percent and their profits 28.7 percent over the past year (Chem Insight's 1991). As a company they were hardly impoverished and could no doubt have afforded to develop Taxol without so much government assistance.

CHAPTER 3

THE PRODUCTION OF TAXOL

Ecological Impact

Approximately 12,000 women die every year from ovarian cancer. This number represents women for whom other treatment options have presumably failed and for whom Taxol might represent a last hope. Each course of treatment for an ovarian cancer patient requires about 300 milligrams of Taxol, with a minimum of four courses (1.2 grams) of treatment and up to ten courses (three grams) when the patient responds positively to the treatment. Assuming an average of two grams per patient the NCI estimates the short-term annual need for just 12,000 ovarian cancer patients at twenty-four kilograms of Taxol (Daly 1992, 80).

The Forest Service has estimated that there are 130 million Pacific yews on federal lands in Oregon and Washington, though only 30 million of them may be harvestable. However those numbers are by no means certain because only now with the worth of the tree established, have efforts been organized to inventory their actual prevalence. These numbers sound more than adequate but some simple mathematical calculations begin to reveal the extent of the problem (Daly 1992).

Using current production methods, it requires up to thirty pounds of western yew bark to yield a gram of Taxol. According to NCI calculations, a mature tree will yield about twenty pounds of bark, although some feel that this

is too generous a figure. Using those numbers, 12,000 women with ovarian cancer would require about 720,000 pounds of bark from about 36,000 trees or three trees per patient (Daly 1992). Other authors estimate as many as six trees per patient (Shugert 1991, Amato 1992).

Compounding the supply problem is the fact that Taxol is showing favorable results in trials on breast cancer (Holmes et al. 1991). The NCI now estimates that, with one out of every nine women in the U.S. expected to contract breast cancer, the need for Taxol may be 250 to 300 kilograms per year in the next few years. That translates into over 7.5 million pounds of bark or over 400,000 trees per year. Considering the fact that it takes a Pacific yew at least ten to fifteen years to grow one inch in diameter, it becomes clear that the trees as well as the habitat which they support are in danger (Daly 1992,80).

Hauser Chemical Research, Inc. of Boulder, Colorado is the sole supplier of Taxol to Bristol-Myers. According to Hauser, it was selected by Bristol-Myers because of its past "success at extracting medically valuable compounds from natural substances" (Hauser). Hauser Northwest, a subsidiary of Hauser Chemical Research, collects the yew bark in the spring and summer when it is easily peeled, dries it, and then sends it to Boulder where the Taxol is extracted and purified. In other seasons, Hauser purchases yew logs collected at existing harvest locations, or contracts with loggers and timberland owners to prelog areas scheduled for future timber harvest. Hauser claims that its collectors must not only have permits but must adhere to strictly enforced environmental regulations. The company says that since the yew is a hardy tree which sprouts naturally from roots deep underground. special care is taken to leave enough material above ground to stimulate sprouting (Hauser). In 1991, Hauser Northwest collected 1,600,000 pounds of yew bark. Of that amount, 852,000

pounds came from federal lands and the rest from private lands (Jans 1992, 31).

Others claim that the yew collecting process is not as carefully controlled as Hauser makes it sound. Harvesters, who must have a permit from the Forest Service, are paid $2.25 per pound of bark. Because that is good money in an area which has been hard hit economically, there have been abuses. Some have been arrested for harvesting without a permit. Federal agents engineered a sting operation which netted a major yew-bark poacher and the Secretary of Agriculture has offered up to $10,000 to anyone who helps convict yew bandits (Begley 1991). Kevin Freeman, a criminal investigator for the Bureau of Land Management, which manages 2,236,100 acres of timberland in Oregon, says poaching has become a significant problem on BLM lands and Kent Tresidder, a timber management and appraisal agent and yew coordinator for the BLM, relates recent estimates that there is more bark stolen than is sold legally from BLM forests (Daly 1992, 82).

Not only is bark poaching a problem, but frequently the bark is harvested irresponsibly. Wendell Wood of the Oregon Natural Resources Council claims that bark collectors often strip bark that is easily accessible leaving the rest behind. He claims that they have no incentive to take bark off the top of the tree. Hauser says it monitors and penalizes its harvesters for wasted bark and the Forest Service and BLM say that they have learned from abuses during past harvest seasons and will more closely supervise bark collectors in the future. Even when bark is not wasted, large scale bark collecting endangers the future of the species because stripping the trees kills them (Newman 1992).

Needless to say these issues have aroused the concern of environmental groups. Medical demand could be the salvation of the yew, according to the Environmental Defense Fund (EDF) and eight other ecological groups that are

petitioning to have the Pacific yew given protected status. They claim that in the past loggers, considering the yew as trash lumber, were bulldozing and burning the yew as they cleared the valuable Douglas firs from the old growth forests of Washington and Oregon. Bruce Manheim of the EDF says, "the tree would be managed instead of bulldozed" (Joyce 1990, 20) and feels that protecting the yews could also help to stem the felling of old growth trees around them (Joyce 1990). The timber industry, segments of which routinely clear cut large areas of land to maximize profits, is already embattled over the issue of preserving spotted owl habitat, and objects strongly to designating the yew as endangered. Some Forest Service personnel agree with lumber interests that the tree is abundant enough not to require federal protection but acknowledge that the collection of yew bark can not continue indefinitely (Murray 1991). Bristol-Myers announced in 1992 that it would decrease its reliance on yew bark for Taxol production in coming years as other sources are perfected. The company predicted that its need for bark should cease completely within five years. However, Bristol-Myers also announced in 1991 that it planned to deliver sixteen kilograms of Taxol to NCI in 1992. That represented a twelve fold increase over the production of the previous year (Borman 1992). In 1993, by all reports, Bristol-Myers sharply curtailed its harvesting of yew bark. It is not clear whether this is due to ecological concern or to the fact that Bristol-Myers has large stockpiles of bark from previous harvests, as some have claimed (Borman 1992). The drug firm is now pursuing other sources for Taxol. However the fact remains that the ecology of the northwest has sustained a negative impact due to that harvest that was, at least in part, both irreparable and unnecessary.

The Ornamental Yew Alternative

There are eight species of yew in the genus *Taxus* ranging all over the world and in a variety of climates. Usually, like *Taxus brevifolia* the pacific yew, they thrive in the moist, dark, forest understory. Yew trees are not as numerous as they once were, especially in the more developed areas of the world, but their cultivars, varieties produced by selective breeding, are plentiful in the form of ornamental yews used as shrubbery in landscaping. They are easily cultivated, transplant well, and can survive the cold weather of northern temperature zones. Most importantly they withstand repeated pruning (Hartzell 1991, 64) which makes them a wonderfully renewable source of Taxol.

At The Research Institute of Pharmaceutical Sciences of the University of Mississippi it was discovered that Taxol is present in the needles and twigs of certain types of ornamental yews at comparble concentrations to that of the Pacific yew bark (Shugert 1991). In fact, one cultivar, *Taxus media Hicksii*, has a yield almost twice that of the bark (Daly 1992, 84). If that source could be tapped the result would be not only an increase in the availability of Taxol but a decrease in the impact on the environment of the Northwest. Dr. Edward Croom of the Institute contacted Zelenka Nursery, Inc. in Grand Haven, Michigan. As the world's largest grower of ornamental yews, Zelenka had an immediate and almost endless supply of yew clippings due to the nursery's regular pruning process. With a thousand acres of ornamental yews, the nursery produces tons of yew cuttings from the millions of yews it prunes and sells each year (Shugert 1992, May 26). A voluntary alliance was formed to provide scientific and technical support for the Taxol project. The members of the Alliance for Production of Taxol (Alliance) are Zelenka Nursery, along with

several other nurseries nationwide, the Research Institute of Pharmaceutical Sciences at the University of Mississippi and the Ohio Agriculture Research and Development Center (OARDC), Ohio State University. The University of Mississippi supplies the analytical data, OARDC supplies some assistance with agricultural procedures and machinery, with Zelenka and the other plant nurseries providing the dried yew clippings (Shugert 1991).

In 1989 application was first made to NCI for a grant of $500,000 for the research and development of Taxol from yew clippings. In 1991, almost two and one-half years later, the Alliance was granted approximately $320,000 for that purpose. Under a cooperative agreement with NCI and the USDA, Zelenka and the Alliance agreed to harvest, scientifically sample, dry and ship enough cuttings, 40,000 pounds dried, to produce two and one-half kilograms of Taxol. According to NCI that would be enough to treat approximately 1,250 patients. Zelenka supplied 100,000 pounds of yew clippings which were dried on site in a corn dryer, yielding the required 40,000 pounds, the last of which was shipped to NCI in May 1992. Through this cooperative agreement, for the first time, Taxol was made from commercially grown yews on a production basis (Shugert 1992, May 26).

Along with the clippings from pruning, many needles can be obtained when unsold yews are removed from fields on a rotating basis. Each field is allowed to lie fallow for two years after turkey manure and commercial fertilizer are rotatilled into the soil. These plants are dried and the needles removed (using, strangely enough, a chicken plucker). In this case 100,000 trees would produce 100,000 pounds of dry yield (Shugert 1992, May 26).

Other research projects connected with the production of Taxol from yew cuttings have been initiated or are planned for the future. Ralph Shugert, staff

horticulturalist at Zelenka Nursery, is working with Dr. Robert Schutzki of the horticulture department at Michigan State University to test the effect of variable amounts of nitrogen in the soil on the Taxol production of ornamental yews. On a nearby Zelenka owned farm, plants are being grown with variable amounts and types of fertilizer or none at all to test that variable in the potential yield of Taxol. Data from this study should be available by late 1994. Dr. Croom believes that the yews may produce more Taxol at specific times of the year so Zelenka is sending cuttings every month for analysis. Shugert also hopes to survey other growers to determine their pruning times and other growing practices. From the results of this survey a sampling protocol will be developed and eventually clippings from prunings done at variable times and grown under variable conditions will be able to be compared as to their content of Taxol. Zelenka Nursery is also cooperating with the University of Wisconsin where in vitro research will attempt to discover where and how Taxol is produced in the plant (Shugert 1993, Feb.8).

During the course of the involvement of the Alliance in producing Taxol from yew clippings, Bristol-Myers was well informed about their efforts. They, in fact, visited Zelenka Nursery on more than one occasion to view the operation there. Persons from the Alliance were also presenters at Taxol conferences held in Oregon in the summer of 1992 at which both Bristol-Myers and NCI were well represented (Shugert 1992, Oct.2). In spite of this knowledge, Bristol-Myers continued to harvest large amounts of yew bark for their Taxol production. Although that harvesting apparently decreased considerably in 1993, that may be partly due to the large amount of bark stockpiled in 1992 (Borman 1992). Early in the decade, Bristol-Myers contracted with Weyerhauser, a large lumbering concern in the northwest, to plant hundreds of acres of yew seedlings

(Junod 1992). Shugert estimates that these will be ready for harvest three to four years from planting, either for the entire plant or various of its parts. Since Bristol-Myers obviously intends to use yew plants as a source for Taxol, one wonders why they did not pursue this source earlier and lessen their dependence on the yew bark, the harvest of which has been expensive financially and environmentally. Also, if NCI had proceeded more quickly on the grant request from the Alliance, the process for extracting Taxol and other taxanes from yew needles in large enough amounts for drug production might have progressed much more quickly, again lessening the expenses noted above. As it is, Bristol-Myers and other drug companies find themselves in the uncomfortable position of trying to play catch up to the French in production of useful analogs of Taxol. It is interesting that, in a recent article in the *Journal of Natural Products*, Dr. Schepartz and others are decrying the Taxol supply crisis and outlining new NCI policies intended to avoid that problem in the future (Cragg et al. 1993).

Meanwhile foreign drug firms have shown a marked interest in the yew clippings and roots which Zelenka Nursery is able to provide. Drug firms from both Italy and India have sent representatives to the nursery and Zelenka is now supplying, Indena, a natural products company in Milan, Italy with dried root material. The extract from these roots is in turn being purchased by Bristol-Myers and reportedly being used by them as a precursor, or foundational material, from which they seek to develop an analog of Taxol (Shugert 1993, April 23). No doubt Bristol-Myers was, at least in part, inspired to this effort by the fact that Rhone-Poulenc Rorer, the French pharmaceutical firm and former competitor for the original NCI bid, has developed an analog of Taxol, Taxitere, which, Dr. Schutzki reports, it is finding to be less toxic and therefore more effective since larger doses can be given with fewer side effects (Schutzki 1993).

This international juggle appears to be a very convoluted route to drug development and it certainly seems logical to assume that it will add considerably to the final cost of the drug which results. I know that Shugert of Zelenka Nursery wishes that Indena had a processing plant in this country because of the difficulties and expense involved in shipping the dried yew root material to them (Shugert 1993, April 23).

CHAPTER 4

THE FUTURE OF TAXOL AND TAXOL-LIKE DRUGS

The future of Taxol and its analogs appears to be headed in four basic directions: finding more effective ways to produce and utilize the present form of Taxol; growing Taxol and related compounds in cell cultures; producing Taxol and related compounds through semi-synthesis; and creating Taxol and related compounds through total synthesis.

Attempts are being made to more efficiently produce and utilize Taxol. Botanists and chemists from around the world are studying species and cultivated varieties of the yew to see which hold the most Taxol and in what way they might be manipulated to increase their yield (Nicholson 1992). For instance, a variety of the yew tree found in the Himalayas has larger amounts of Taxol in their needles. There are other advantages to these trees. They are very plentiful and the people who would collect the needles would not demand North American wages to do so. This would also help to preserve the dwindling Himalayan forests since cutting the trees for fuel would mean a loss of income (Yewsful 1992). Various forms of cultivation of yews are also being tried and the Forest Service has been exploring the propagation of yews from branch-tip cuttings (Blume 1991). Attempts to increase the effectiveness and especially the length of response with Taxol include; trials of Taxol as a first-line drug alone or in combination with another agent, the use of Taxol with radiation therapy, and intraperitoneal instillation of the drug.

Efforts are underway to "grow" Taxol or a related compound using cell

culture. This is a fermentation process that stimulates cells of the yew to produce Taxol in a tank of nutrients, similar to the way yeast makes alcohol. It is hoped that this process might also result in the production of other useful taxanes. These might serve as precursors for Taxol. Many believe that this partial synthesis of taxanes will be cheaper and easier than trying to make Taxol itself (Erickson 1991). Recently, scientists in Montana discovered a yew tree fungus that when grown in a liquid medium produced Taxol and other taxanes. Again the amounts yielded were very small and methods to boost the output of this process are being studied (Stierle, Strobel, and Stierle 1993).

Semisynthesis has produced the most positive results thus far in the search for alternate means to produce Taxol and its analogs. In 1988, French scientists succeeded in making a semisynthetic Taxol from a precursor, baccatin III, found in the needles of the English yew. The drug, Taxotere, started phase I trials in 1990. This drug has an advantage to Taxol in that it is more soluble in water and therefore easier to administer (Daly 1992). Testing continues in various countries and French, Dutch, and Canadian researchers are reporting very promising activity against breast cancer. In 1992, NCI signed an agreement with the French drug firm to help test Taxotere (Borman 1992). Robert Holton, an organic chemist from Florida State University, has proceeded along similar lines and has obtained a patent for the process which involves adding a synthesized tail of atoms to the baccatin III. Holton says that the compound in the English yew is much more concentrated than Taxol is in the Pacific yew bark (Hanson 1992). Bristol-Myers has licensed this process and is trying to scale it up (Borman 1992). The world's largest supplier of baccatin III, also called 10-DAB III is Indena, a natural products firm located in Milan, Italy. (This, incidentally, is the same firm to which Zelenka Nursery has been sending yew

roots for processing). Indena recently discovered a new taxane, a baccatin compound with an additional hydroxyl group, in an extract from yew needles. The presence of the hydroxyl group gives the compound higher water solubility. Analogs developed from the new taxane are more water soluble than either Taxol or Taxotere which potentially could make them easier to administer. Similar work with the new compound is being done in this country and is showing great promise (Borman 1993).

Achieving total chemical synthesis appears to be the most difficult means to increasing the supply of Taxol or its analogs. While it has been done on a small scale, developing a method to produce larger amounts economically is very difficult. It should be noted that vinblastine and vincristine, important anticancer drugs that were discovered thirty years ago, are still isolated from the original plant source, the periwinkle *Catharanthus roseus* (Cragg and Snader 1991). A major problem lies in the complexity of Taxol's molecule. Charles Swindell, an organic chemist at Bryn Mawr describes its structure. "Taxol has a very unusual network of carbon atoms. Three connecting rings make up its basic skeleton, but they don't lie flat; rather they twist and fold like a crumpled pretzel. What's more, the carbon rings are festooned with additional strings of atoms that are somehow essential to Taxol's anticancer activity. But chemists aren't sure how to pin these tailpieces onto the ring structure" (Hanson 1992, 55). Dr. Paul Wender and his colleagues in the chemistry department of Stanford University have been the most visibly involved in this effort. Wender and his group have developed a five step process that synthesizes the three ring core using as starting material pinene, an extract from pine trees that is the major constituent of turpentine. The Stanford chemists are continuing to work on completing the synthesis (Wheeler 1992). More recently, a group of

California scientists have developed new forms of Taxol called protaxols. These prodrugs were designed to increase their solubility in water and allow for Taxol release under physiological conditions. Human plasma is the catalyst that triggers that release. These drugs must be thoroughly tested yet but they also appear to hold much promise (Nicolaou et al. 1993).

Early detection should be, I feel, the major thrust of research in the area of ovarian cancer. But until an effective and practical screening method can be found, chemotherapy that is successful in the treatment of recurring disease remains a high priority and perhaps the only hope for as many as 12,000 women every year. It may be that much of this research will become redundant in coming decades with the rapid advances in molecular biology, but until that time, scientists will continue to search for that miracle treatment for ovarian cancer that will be not just palliative but curative.

CONCLUSION

Natural products have been in the past, and will continue to be in the future, an important source for new pharmaceuticals. The natural products search conducted by the National Cancer Institute was broad and random in nature. It was not based on information regarding previous use of particular plants by any indigenous peoples or as recorded in folklore. To my knowledge Taxol is the only important drug to have resulted from this search. The search could have been narrowed considerably and rendered much less expensive by consulting data on the medicinal uses of North American plants. Taxol would still have resulted, as the yew bark and needles in which it was discovered have a history of such use.

The bark of the Pacific yew tree continued to be collected in large quantities, often with poor harvesting techniques which resulted in a negative impact on the ecology of areas within forests of the Northwest. This practice continued in spite of research showing that Taxol was present in equal or greater amounts in the needles and roots of many ornamental yews. This renewable resource is readily available from plant nurseries around the country. In fact, an Alliance was formed to develop this source but found little market for its product in the U.S. If the NCI and Bristol-Myers had pursued the ornamental yew source earlier, they not only would have lessened the environmental impact but would now be in a position to compete effectively with foreign drug firms in the production of Taxol and other taxanes from yew needles.

Bristol-Myers signed an agreement with the National Cancer Institute, based on the provisions of the Orphan Drug Act, to be the sole provider of Taxol commercially in this country. There is some evidence that they had an unfair advantage in obtaining this agreement through the hiring practices of both organizations. There was no provision in the agreement for the government to maintain any control over the price charged by Bristol-Myers for Taxol or the amount of profit garnered by the company through its sale, even though the research conducted by NCI in discovering, developing, and testing Taxol was tax supported. These practices engendered criticism by both consumer advocates and government representatives and resulted in a very high market price for Taxol, which was many times greater than production cost.

EPILOGUE

The story of the discovery and development of Taxol raises a number of issues having to do not only with the pharmaceutical industry, but with health care in general. I'd like to discuss those issues, not in order of importance, but as they occurred in the unfolding story of the evolution of Taxol. Then I will make some suggestions for consideration as we look to the future. We're going through a period of great transition in health care with little certainty about what direction it will take. Therefore this is an opportune to look at some lessons which could be learned from the Taxol story and reassess future goals.

The discovery of Taxol was, if not a miracle, at least unusual given the randomness of the search and the great number of samples obtained. It is no wonder that there were not more effective drugs developed as a result of that search. The wonder is that the yew bark made it out of the warehouse at all and that it is not still in storage with thousands of other specimens that have yet to be tested. I would like to see future plant specimens gathered with purpose, and only after research into their history of medicinal use. I would also like to see that search confined to this country or at least to North America. I think that it is fair to assume that we have not begun to test all the natural products which have been used medicinally in this country and, until we have, I would like to see our search focused here. That would greatly lessen the cost of the natural product search, and therefore the resultant drugs, and not necessarily its effectiveness, as the story of Taxol illustrates. It would also allow other countries to research and develop their own natural resources. Perhaps the hope of

finding that "miracle" substance, and thus monetary gain, would slow the ravages on the world's forests, particularly in the developing nations.

In consideration of the world's forests, we should first look to our own rather dismal record. I have read that to look down from a plane on some timber areas in the Northwest is to view devastation unequaled in the rain forests of Brazil. The habit of clear cutting and slash and burn lumbering techniques to maximize profits is, I believe, inexcusable, unnecessary, and short sighted. There are lumbering firms, although admittedly in the minority, who use methods that guarantee sustainable resources and still manage to make a profit. Before the discovery of Taxol in Pacific yew bark, large areas of these trees were burned as trash timber after the removal of the profitable Douglas firs, and I suppose, now that we are not so dependent on the yew bark for the production of Taxol, that practice may begin again. In areas that must be clear cut, would there not be some better use for the yew trees than to burn them? In centuries past, yew wood was highly prized in the making of longbows and I have read that the Japanese still favor it for some products. There certainly must be better uses for these slashed trees than simply to burn them. Hopefully, the story of Taxol has taught us one lesson at least. We must husband our resources, not only as habitat for wildlife, but because one never knows what valuable medicine for mankind may be lurking behind some tree or underneath some leaf.

The process that developed and produced Taxol as an accepted pharmaceutical has its own lessons to teach. I believe that when public money pays for pharmaceutical research, as it did in this case, the public should demand more accountability on the part of the government agency that administers those funds and also on the part of the beneficiary of that research. The agency doing the research, in this case NCI, should have written agree-

ments with recipients that include some mechanisms of control. There should be clear rules as to limits on profits and access by the government to the firm's cost data in order to assure compliance with those rules. This is particularly true when, as in this case, the government carries out the clinical trials, the most expensive part of the drug development process. I propose that there also be changes in the Orphan Drug Act to return it to its original purpose of encouraging the formulation of treatments for truly rare diseases. Those proposals made by Representative Wyden and his subcommittee would go a long way toward meeting this goal if enacted. There should also be guidelines at the National Institutes of Health to prevent hiring practices that give the appearance of conflict of interest violations. The "revolving door" practices that occurred with Wittes, NCI, and Bristol-Myers should be outlawed as they have been between the government and the military/industrial complex.

There were practices in the marketing of Taxol that may have less to do with deliberate misleading on the part of Bristol-Myers than with a lack of restraint on the part of the media. There was a great deal of publicity about Taxol in the popular press as well as in the scientific journals. The discovery of a potentially life saving drug in the bark of a tree and the environmental debate that elicited, captured the public imagination. In addition this drug showed promise against a known killer disease against which we have little ammunition. The articles all mentioned the significant responses experienced by some women with advanced ovarian cancer. Very few articles, especially in the popular press, mentioned that those responses were only temporary and Taxol was not a cure. As a result many women's hopes were falsely raised and a clamor to get into the clinical trials ensued. There does not seem to have been any visible effort on the part of Bristol-Myers to dispel these false hopes. I would

like to see more frankness in reporting this type of news and perhaps even some degree of secrecy regarding drugs still in the testing process to prevent this raising of false hopes. Women with ovarian cancer face enough battles without having to contend with this as well.

I read the reports of ongoing research on Taxol and its analogs with mixed feelings. I recognize the fact that although Taxol is no cure for cancer, as it is now used, it may yield significantly better results, perhaps even a cure, when given as a first line drug, or in combination with other drugs or treatments. Or it may be that some part of the ongoing research may reveal some startling new and more successful compound. At the same time, I know that there has been a continuing and intensive search for effective treatments for cancer for decades and the progress which has been made has not been significant enough to justify the huge sums of money which has been invested in this research. I believe that the real hope for the future lies in prevention and effective screening techniques. I would like to see included in our new "health care system," if such a thing exists, a law mandating that a significant percentage of every pharmaceutical company's research and development budget must be spent on these efforts. This may be made more palatable by the fact that, as health care becomes increasingly more managed, third party payers will be more willing to reimburse for this type of intervention that has been proven more cost effective. Insurers are likely to become less and less willing to pay for the type of treatment which Taxol represents; a last hope, a few more months of life.

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