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Cancer chemotherapy, biodiversity, public and private property: the case of the anti-cancer drug Taxol

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Abstract

The drug taxol has been hailed by many in the cancer community as a major breakthrough in the treatment of cancer. It has already been approved in use against ovarian and advanced breast cancer in many countries worldwide. Taxol has also promoted profound debates in the policy arena not, as one might expect, because of the characteristics or purposes of the drug itself, but because of other far-reaching effects. Taxol is a complex compound found in the bark of the Pacific yew tree, primarily in Oregon and Washington in the USA. The bark was first collected in 1962 and cytotoxicity demonstrated in 1964. Yet it was not until 1989 that the first results of clinical trials were reported. In the US taxol was then rushed through the Food and Drug Administration's regulatory procedures, approval being granted for use in refractory ovarian cancer in 1992. The controversies surrounding taxol surfaced in 1989 and grew substantially over the next few years. In this paper we examine two principal controversies concerning taxol, the first of which focused on apparent conflicts between the needs of environmental protection and those of cancer chemotherapy. Although the media portrayed this as a clash of interests between the environment and people with cancer, we argue that it was an attempt to increase lay participation in biomedical decision making and policy formulation. The second controversy was between health policy and the transfer of public scientific property to the corporate sector. The pharmaceutical company Bristol–Myers Squibb was given exclusive rights to provide taxol from Pacific yew trees under a Co-operative Research and Development Agreement signed in 1991. While this was seen to be in the US Government's (as well as the company's) interest, it provoked a public reaction questioning the terms and consequences of the transfer of publicly generated scientific knowledge to the private sector.

Keywords: Taxol; Health policy; Environmental policy; Intellectual property; Pacific yew tree; Co-operative research and development agreements; USA

Introduction

Taxol has been hailed by many in the cancer community as a major breakthrough in the treatment of cancer. In 1991, the year before it received approval from the Food and Drug Administration (hereafter FDA) in the United States in the treatment of refractory ovarian cancer, the Director of the National Cancer Institute (hereafter NCI) referred to taxol as "the most important new drug we have had in cancer in 15 years" (Kolata, 1991). It has already been approved for use against ovarian and advanced breast cancer in many parts of the world; and its potential use against other types of cancer continues to grow.

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Part of taxol's biomedical appeal is that it is an unusual molecule (Kingston et al., 1993; Nicolaou et al., 1994). It is an extremely complex natural product discovered, in the early 1960s, as part of the NCI–United States Department of Agriculture (hereafter USDA) plant screening program, to be present in the bark of the Pacific yew (*Taxus brevifolia*), growing principally in the Pacific Northwest of the United States, in Oregon and Washington. Until quite recently, this tree was the principal source of the molecule.

Taxol's biological activity was first demonstrated in 1979 and, until a year or two ago, was thought to be unique in the natural world (Suffness, 1994; Lindel et al., 1997). The first that the public heard of this new anticancer drug came in 1989, with the announcement of taxol's potential in the treatment of ovarian cancer, an announcement made all the more poignant by the highly publicized death from this disease of the very popular actress Gilda Radner. Very rapidly the concern over Gilda Radner's death was coupled to the concern over the future of the Pacific yew. Over the next two years taxol was seldom out of the public gaze as the drug appeared centre stage in an ever-increasing number of policy controversies. Not only did the drug attract the attention of the media but also, and most significantly, many federal agencies and several senate sub-committees. From a political perspective, the taxol story spoke directly to several major issues in the United States in the early part of this decade: the need to protect biological diversity; the funding of and access to treatment for diseases—such as ovarian and breast cancer—specific to particular groups in society; the manner by which the United States was managing technology transfer between the public and private sector; and the ethics of pharmaceutical pricing. From being just a 'wonder drug', taxol became a reference point for critical contemporary policy issues in the United States, what we have called 'a drug of our time' (Goodman and Walsh, 1997). All this happened before it received approval from the FDA for clinical use. Most of the drugs that have run into controversy have done so after approval for clinical use (Abraham, 1995).

In these few years, taxol had become politicized, embroiled in a number of timely controversies which this paper analyzes. Like the anti-AIDS drug AZT before it, the case of taxol shows, in particular, the extent to which the practices of biomedicine have been prised open through lay participation in the decision-making process; how the public has come to participate directly in the process of policy. As Steven Epstein has recently demonstrated, the AIDS story presents a compelling case of how science is invaded by those on whose behalf it seeks to act and speak (Epstein, 1995, 1996, 1997). The crux of his argument is that lay (AIDS) activists challenged the 'monopolization of credibility of credentialed researchers' by insisting on viewing the clinical trial not as a biomedical black box but as a political, therefore, negotiable process (Epstein, 1995, 1997). By insisting on their rights and claims as patients, these activists insinuated themselves at the centre of contemporary biomedical practice and changed it. Eveleen Richards, in her study of the controversy over vitamin C as an anti-cancer agent, follows a similar line of argument (Richards, 1988, 1991). She too analyzes the process by which non-experts seek active participation in the process of therapeutic (biomedical) assessment and decision-making leading, in this case, to the opening up of alternative cancer therapies (Lerner, 1994; Hess, 1997). Epstein and Richards have thus greatly expanded our insights into the public understanding of and the public participation in science.

The American media portrayed taxol's controversies as conflicts of interest between chemotherapy and biodiversity, between those seeking and wanting a cure for cancer and those seeking to protect an individual plant species. This became the dominant narrative. We maintain, on the contrary, that the story of taxol should be read as an example of the process of lay participation in biomedical practice. By politicizing taxol, environmental activists were able to insist on their participation in formulating policy to protect biological diversity and bringing the drug regulation system (through the FDA) into line with this thinking (Heiken, 1997; Heiken, personal communication). They argued that sustainable management of the yew would not deny cancer patients taxol for treatment, but on the contrary would increase its supply and make it secure. Jerry Rust (environmental candidate in the Democratic Primary in Oregon for the US Senate) suggested that the establishment—government agencies and drug companies—wanted to discredit the Endangered Species Act, and blame the environmentalists (Hartzell, 1991). This part of the taxol story is covered in the first section of the paper.

In the second section, we turn to another major policy conflict that the case of taxol highlighted; namely, the relationship between public research and development and private ownership. Early in 1991, the NCI, the Forest Service, the Bureau of Land Management and Bristol–Myers Squibb entered into a series of Cooperative Research and Development Agreements (CRADAs) to develop taxol commercially. By these various agreements, Bristol–Myers Squibb had exclusive rights to the results of publicly funded taxol research and publicly maintained national physical assets. This combination of rights, unique to taxol, sparked two major enquiries by a congressional subcommittee.

Although these hearings did not receive the media attention that the yew tree received, they were a

further example of a similar phenomenon; namely, the extent to which the public was seeking to participate in biomedical politics. In this case, public affair and consumer activists (joined by their colleagues from the environmental wing) were insisting on their rights to formulate policy regulating agreements between the public and private sector as they affected the provision and price of health care.

Though we are discussing the policy conflicts in succession, by that we are not implying that the two sets of conflicts are unrelated. Both the media and subsequent academic comment have taken this position implicitly (Wolf and Wortman, 1992; Day and Frisvold, 1993). On the contrary, we insist that they are deeply related. Not only did taxol appear as the key object in both policy arenas but, more significantly, enfolded the one into the other, making the issues inseparable. Those who participated in the one set of policy issues also participated in the other, taking their knowledge of and attachment to taxol with them. Arguments in one policy arena flowed over into the other. In this sense, taxol is an interesting case of what some social scientists have called a 'boundary object'; an object residing in different sites of practice but which has the remarkable capacity to produce new collaborations, alliances and interactions (Star and Griesemer, 1989; Keller, 1996; Fujimura, 1992; Löwy, 1992; Marcus, 1995).

If the politics of policy is to be measured by success then it might be argued that the taxol story represents mixed results. The environmental argument achieved a limited victory. The petition to list the Pacific yew as a threatened species failed but the tree did get its own act, the Pacific Yew Act of 1992, containing, for the first time, specific harvest policies, and an environmental impact statement for taxol. Pressing the FDA to authorize an environmental impact statement for each and every drug application which involved harvesting natural products was much less successful, even though, "under the National Environment Policy Act (NEPA–1969), all Federal agencies are required to assess the environmental impacts of their actions..." (Federal Register, 1996; Heiken, 1998). The FDA only complied in the case of products containing taxol. Less successful, too, were the congressional hearings. Though they were wide-ranging and involved many interested parties, they did not lead to any change in policy.

Cancer chemotherapy and environmental protection

By any measure, the 30 years it took for taxol to get from the forest to the clinic was a long time. The story of its progress from the one place to the other is long and complicated and largely unnecessary to the main arguments in this paper (Suffness, 1995). But there is significance in the fact that it took this length of time, for in the intervening period, between 1962 and 1992, much had changed in American society and politics. The rise of an environmental consciousness, the visibility of women and the political successes of the women's movement, the rise of biomedical activism exemplified by ACT UP, and the escalating costs and increasing privatization of health care all contributed to a change in milieu (Rabinow, 1996). In the early 1990s, taxol was a different object from what it had been in the 1970s. Put another way, had taxol received approval for clinical use earlier than it did, then the political turmoil which it generated would probably not have occurred.

The event which sparked the political conflicts happened in December 1990 when the NCI put out a tender for an unprecedented amount of yew bark, to be supplied in 1991, to make the taxol for women taking part in clinical trials. Stripping the bark from the yew killed the tree. The 750,000 pounds was 12 times as much bark as the NCI was collecting in previous years (Wolf and Wortman, 1992). How many trees this represented could only be estimated: figures ranged anywhere from 30,000 to 250,000 (Forest Service, 1992; Hartzell, 1991; Wolf and Wortman, 1992). By contrast, over the entire period from 1974 to 1989, the NCI had extracted bark from approx. 7500 trees (Snader, 1990). Much, of course, had changed over the intervening years. Until 1984, all of the taxol supply went for investigative research, primarily to cell biologists. After 1984, when taxol entered phase I clinical trials, taxol was distributed to hospitals as well as to laboratories. The supplies the NCI asked for increased gradually, and then more rapidly after 1989 when the early clinical results began to be published. The news of the NCI's tender was met by an outcry of concern for the yew tree.

As Deborah Stone points out, policy agendas are formed when 'situations come to be seen as caused by human actions and amenable to human intervention' (Stone, 1989). "Political actors" she goes on to say, "*deliberately portray* them [conditions, difficulties, or issues] in ways calculated to gain support for their side". That portrayal, as Stone argues, depends crucially on composing causal stories that attribute blame to other actors and, in consequence, call forth government action. The stories, in their turn, depend on facts and arguments.

The first major clash of policy exposed by taxol was between health policy, articulated by the 'war on cancer', and environmental policy to protect endangered and threatened species. A central story in this clash of policies was that of the yew tree. The yew did not have much of a story before Arthur Barclay, a USDA botanist working on the NCI plant screening program,

stripped some bark from the tree in August 1962. Botanical investigations of the yew dated from the nineteenth century and had not been updated (Hartzell, 1991; Bolsinger and Jaramillo, 1990; Mitchell, 1992). The kind of information that had been amassed for Douglas fir, red cedar and spruce—distribution, numbers, habitat, ecology, etc.—was simply non-existent for the Pacific yew. Logging companies, the Forest Service and the Bureau of Land Management, the stewards of the national forest system, considered the yew as trash. It was destroyed in clear-cuts of old-growth forests and then burned on slash piles (Hartzell, 1991). It had no economic value and attracted no serious scholarly attention. USDA botanists and their contacts in the Pacific Northwest, who collected samples of bark during the 1960s, were able to add a few more facts to the meagre list. These were: the yew is a slow-growing and long-lived tree randomly and quite sparsely distributed in old growth forests among Douglas fir, cedar and other trees that were at the time (and still are) economically valuable to the logging, timber and paper-making companies; only the bark from mature trees at least 5″ or more in diameter have significant amounts of taxol; only mature trees will produce seed and therefore contribute to the perpetuation of the species; even under optimum conditions (stripping the bark at the best time of the year, drying the sample under ideal conditions etc.) there is not much taxol in the bark; and finally, stripping the bark of the yew kills the tree (Spjut, 1996).

No one had a clear idea of how much taxol was present in the bark, because the quantity depended on the circumstances in which the dried bark was procured and on the methods used to extract the taxol from it. Monroe Wall and Mansukh Wani, chemists at the Research Triangle Institute who first isolated and named taxol, reported in 1971 that they achieved a yield of 0.02% (1 g of taxol obtained from 5 kg of dried bark) under experimental conditions (Wani et al., 1971). Nor did anyone know the average amount of bark obtainable per tree. The NCI received supplies of bark through a series of intermediaries. No records of the collection were kept, other than the weight of dried bark delivered to the NCI. The yew tree was no more than the source of the molecule.

Between Barclay's first collection in 1962, and the selection of taxol as a development candidate in 1977, about 2000 pounds of dried bark had been collected, representing the destruction of about 400 trees, from which just under 0.1 kg of taxol was obtained (an average yield of 0.01%) (Croom, 1995). Even though taxol had been chosen as a development candidate and, since 1984, was being assigned in clinical trials, the demand for yew bark was still small—between 1977 and 1987, only 6500 pounds of bark was collected (Croom, 1995; Arbuck and Blaylock, 1995).

In 1987, largely because of a sharp rise in the number of requests for Phase II taxol trials, it became clear that a crisis was looming in the yew bark supply (Arbuck and Blaylock, 1995). The NCI became aware that its rather haphazard and indirect system for collecting bark in Oregon would have to be put on a more secure footing. It put out a tender for 60,000 pounds of bark to be supplied that year and the same again in 1988. Compared with 6500 pounds in the previous 10 years and 2000 pounds in the 15 years before that, 60,000 pounds of yew bark per year was two orders of magnitude greater. That tender turned out to be a disaster, and after a series of fraught negotiations the new contract went to a Portland businessman with logging experience who hurriedly organised a company, Yew Wood Industries, to concentrate on bark collection. The director of the Natural Products Branch of the NCI, for the first time, went on a reconnaissance trip to Oregon and Washington state in 1988. The Johns Hopkins University Oncology Group reported next year that taxol produced a very high response rate in women with ovarian cancer that had been unresponsive to other chemotherapeutic agents (McGuire et al., 1989).

Questions now began to be raised about the yew tree and all those missing facts that, before 1987, were of no concern to anyone, suddenly became crucial. Moreover, in Oregon, people were beginning to speak on behalf of the yew alluding to its mystery and dark secrets as an understory tree (Hartzell and Rust, 1983; Hartzell, 1991). The director of the NCI Natural Products Branch came back from his trip with the realisation that the collection of bark would no longer be as straightforward as it had been in the past. These were not the monkey-wrenchers and the eco-warriors of the forest campaigns of the early 1980s (Dietrich, 1992). They were people with influence, friends in high places, substantial political abilities, experience dealing with federal agencies and access to the courts. On 19 September 1990 the Environmental Defense Fund (hereafter EDF), a Washington-based environmental action organization, struck the first blow with a petition to Manuel Lujan, the Secretary of the United States Department of the Interior, to list the Pacific yew (*Taxus brevifolia*) as a "threatened species" under the Endangered Species Act of 1973. The petition argued that the yew needed protection because its numbers were falling rapidly. Continuing forestry practices, principally clear-cutting, were liquidating the tree, both directly in the process of harvesting commercial species such as Douglas fir, spruce and cedar, and indirectly by destroying its habitat (Environmental Defense Fund, 1990).

The petition spoke about the need to protect the yew because it was a depleted species and because of the importance of preserving biological diversity. In

this respect, it followed most other petitions under the Endangered Species Act, which, since its passage, provided the legal basis for protecting non-human life without reference to its instrumental value (Proctor, 1995). There was, however, more to the arguments than the simple depletion of a scarce resource. The Pacific yew was the unique source of taxol, an extremely valuable and highly promising anti-cancer agent. In the words of the authors of the petition, "addition of that species to the federal list would be the only way to ensure its continued existence and a sustainable source of the important anti-cancer compound taxol" (Petition, p. 11).

The plight of the Pacific yew was brought to the attention of the EDF by Elliot Norse, then Chief Scientist at the Wilderness Society, who had just published *Ancient Forests of the Pacific Northwest*, a book that eloquently pleaded for the preservation of a unique ecosystem while advocating and popularizing new forestry practices (Norse, 1990). Norse signed the petition, as did representatives of a host of national and regional environmental groups, including The Wilderness Society, the National Audubon Society, the National Wildlife Federation and the Oregon Natural Resources Council. To defend the argument about taxol, the EDF enlisted the support of two prominent scientists involved in the development of taxol: Dr William McGuire, then of the Johns Hopkins Oncology Center, who in 1989 reported taxol's effectiveness in the treatment of refractory ovarian cancer; and Professor Susan Horwitz, of the Albert Einstein College of Medicine, who, in 1979, first described the novel biological properties of taxol (Schiff et al., 1979). The American Cancer Society, one of the country's most powerful mission organizations, were also convinced of the need to do something about the Pacific yew (Rettig, 1977). They, too, petitioned the Department of the Interior.

There were several important aspects of the petition to list the Pacific yew as a threatened species. The timing of the action was one of these. For most of the 1980s, and especially in the final years, the Pacific Northwest had been a hot political topic. Long a backwater in American politics in comparison to the more populous, richer and politically vocal Northeast, the Pacific Northwest now appeared as the leading news item on television, radio and in newspapers (Brown, 1995; Raphael, 1994). The nation's attention became focused on the 'battle for North America's last great forest' symbolized and politicized by the northern spotted owl (Ervin, 1989; Caufield, 1990). After a decade or more of 'one of the biggest resource controversies in the nation', the northern spotted owl was listed, after several successful court injunctions against logging activities, on 23 July 1990, as a threatened species. Nearly 7 million acres of ancient forests became designated as critical owl habitat (Dietrich, 1992, p. 85; Proctor, 1995, p. 279).

Because of the withdrawal of this substantial tract of land from logging, the petition sent a strong signal to the Forest Service and, indirectly, to the American public, that the American people could no longer trust the Forest Service to act in their best interests. It was widely felt that the Forest Service had, for too long and with dire consequences, simply served up the nation's great and ancient forests to the timber companies (Foster, 1991; Booth, 1992; Proctor, 1992). Now the people had acted through other agencies of the state and the courts to reclaim what was theirs (Dietrich, 1992).

The Pacific yew petition threatened to take the matter of the Forest Service's ethics and practices even further (Wolf and Wortman, 1992). Significantly, the EDF drew support from many of those groups who were involved in the spotted owl controversy. Through the many years of campaigning for the ancient forests of the Pacific Northwest, these environmental groups and groupings had learned many valuable lessons about how to achieve political ends by using the law, the media and science (Dietrich, 1992; Yaffee, 1994). The EDF was "committed to the idea of scientists and lawyers working together on environmental problems, advocating solutions that...are scientifically sound and economically feasible" (Bean, 1977). What it lacked in local knowledge, it could get from these groups (Bean, 1997).

This coalition of interests, knowledge and practices was vital for the petition to have any chance of success. But what gave the petition a sharp edge was the enlistment of two prominent members of the biomedical community and the American Cancer Society, thereby giving authority to the combination of an instrumental and an ethical argument about biodiversity (Booth, 1992). The petition went to unusual lengths to enfold biomedical progress with species protection. "It must be emphasized", the petition maintained, "that federal listing of the Pacific yew as a threatened species would not prevent utilization of the species for the development of taxol" (EDF, 1990).

Cancer chemotherapy and biodiversity as policy issues were, at the time of the petition's signing, an unlikely combination. Their combination was historically and geographically contingent. While cancer chemotherapy had been a policy issue since the 1950s, biodiversity was a newcomer and did not enter the public arena until the 1980s. Geographically, because taxol came from a plant growing in the United States, in the backyard, so to speak, of what was, by the end of the 1980s, one of the most environmentally political places on earth. The authors of the EDF petition positively combined the promise of cancer chemotherapy and the necessity of biodiversity. To do this they

appealed to a body of scientific knowledge underwritten by the enrolment of cancer researchers and environmental groups.

All to no avail. The Fish and Wildlife Service of the Department of the Interior rejected the petition on 7 January 1991 on the grounds that "insufficient scientific information exists to determine whether regulatory protection under the Act may be justified" (Federal Register, 1991). The available evidence (virtually the same as used in the petition and incomplete as it was) did, however, allow the Service also to conclude that listing the Pacific yew was not warranted. The rejection document revealed that, according to the Forest Service, there were 130,000,000 yew trees on nearly 1.8 million acres of National Forest lands in Oregon and Washington: this 'estimate' was based on 'stand information together with satellite imagery' (Federal Register, 1991). The EDF had not put a figure to the stock of Pacific yews; theirs was an argument about depletion, not absolute numbers.

Interestingly, within 6 months of the rejection of the petition, the Forest Service revised their estimates of the number of Pacific yew on their lands in Oregon and Washington down to 23 million trees (Mannheim, 1992; Overbay, 1991). Others, who also claimed to speak for the yew and for whom the rarity of the tree was politically significant, referred to even lower numbers (Hartzell, 1991). Each actor appealed to the authority of science in support of their number. We should not be surprised by the wide range of estimates of the yew count. For many years, sociology of science has argued that scientific facts are shaped and mediated by a host of social factors as much as they are by observation and 'objective logic' (Kuhn, 1962; Pinch and Bijker, 1987; Porter, 1994). Similar 'numbers games' riddled the debate in the late 1970s about listing another threatened species, the black-footed ferret (Clark and Westrum, 1987). There, as in the example of the Forest Service, the scientific data on which wildlife management decisions were based were crucially dependent upon the dominant ideas and preconceptions of the organization making the decisions (Clark and Westrum, 1987; Mohai, 1995).

The attempt by the EDF to construct a seamless web between the needs of cancer chemotherapy and sustainable yew harvests was not how others saw the issue. When he heard of the petition, the owner of Yew Tree Industries wrote a letter to a senior official in the NCI which sums up the impression it made on him and, by implication, those whose livelihood depended on this new activity:

> "I wonder if the American Cancer Society knows that if the Environmental Defence Fund gets their Endangered Species through, no one, not even us, will be able to cut Yew logs. I hope someone makes the American Cancer Society aware of this, as they should be the last ones to support such a proposal, much less fund it."

The media had created their own story. Theirs was one of confrontation between those speaking for the yew and those speaking for women with ovarian cancer. In an article in the *Wall Street Journal* on 9 April 1991, Bruce Chabner of the NCI was quoted as saying: "This is the ultimate confrontation between medicine and the environment.... It's the Spotted Owl versus people. I love the spotted owl, but I love people more." The *Wall Street Journal* cited the case of Mary Davidge, 68 year-old member of the Sierra Club and of a logging family, who had ovarian cancer. "I want to be treated," she said. "I don't want to see the forest destroyed, either." The story was picked up by *The New York Times* with the headline "Save a life, kill a tree". From there it was syndicated across the country. This story of confrontation, repeated as news stories throughout the United States, generated public concern, interest in taxol, and demand for the drug from people with cancer, but also the conviction that it would be necessary to campaign actively for supplies. It became the dominant theme in narratives of taxol, not just in the popular media, but also in many scientific publications (e.g. Nicolaou et al., 1994).

While the petition to list the yew as a threatened species failed, conservationists did have some successes. The speakers for the yew won some recognition for the yew's special—if not threatened—status when Congress passed the Pacific Yew Act on 7 August 1992. This Act required Federal lands containing the yew to be managed sustainably in ensuring a sufficient supply of taxol. An Environmental Impact Statement was published in September 1993 after a 9 month public consultation period. These events, and particularly the Pacific Yew Act, reinforced the claim, made by those who spoke on its behalf, that the tree was a gateway to taxol or, to use another phrase, an obligatory passage point (Callon, 1986). That is, those who spoke for the yew were able to take the political position that taxol had to be discussed with direct reference to the yew. While these activists were far removed from the cancer research community, by their actions, they were able to insinuate themselves into biomedical practice.

Cancer chemotherapy, public and private property

By the end of 1990 the NCI estimated that they would need about 130 kg of taxol to cover the entire programme of clinical trials in the USA and other parts of the world, for which they would require about 1,500,000 pounds of dried bark. But the NCI is a government agency and not a manufacturing company.

Indeed, government intervention in the affairs of industry is, in theory, completely against the philosophy of US industrial policy, despite the high levels of government defence procurement and of government finance of research and development in the life sciences relevant to drug discovery (Arnold and Guy, 1986). The NCI had to procure enough taxol for the clinical trials that were ongoing and planned, and had to make provision for the transfer of both the responsibilities (and the problems) involved to an organisation with more direct experience of making and selling drugs, a more skilled and extensive public relations department and (for these activities) more money: in short, a pharmaceutical firm. The NCI was particularly concerned about money. In 1988 they calculated that $750,000 was needed for processing bark into the drug and another $1.2 million for harvesting and isolating additional material for use two years on (National Cancer Institute, 1988).

Back in 1958, in the early days of the mass screening program, before Arthur Barclay had collected his samples of yew bark to send to the NCI, the Federal Government was already concerned that industry was not sufficiently involved in the "growing national effort to develop anti-cancer drugs" (National Cancer Institute, 1958c). It was decided that to enlist the support of industry, changes in the government's policy on intellectual property would have to be made to allow firms to patent and sell drugs developed under government contract (National Cancer Institute, 1958a,b). By the 1980s, the Government's policy towards co-operation with industry had evolved considerably. Rebecca Eisenberg's survey of the evolution of policy in this area describes 1980 as marking 'a sea change in US Government policy toward intellectual property': the main focus of attention had become the development of new strategies for the commercialisation of defence and other federal technologies (Eisenberg, 1996). The Stevenson-Wydler Technology Innovation Act and the Bayh-Dole University and Small Business Patent Procedures Act became law in 1980 (the latter amended in 1983), and the Federal Transfer of Technology Act was passed in 1986.

Co-operative Research and Development Agreements (CRADAs), defined as comprehensive legal agreements for the sharing of personnel, equipment, funding and intellectual property rights in joint government-industry research, were first authorised in 1986 as the chief mechanism by which government and federal laboratories would work together to transfer technology from public to private sector (Berman, 1995). Over 2200 CRADAs were signed in the first eight years. A tender was announced in the Federal Register in August 1989, for a pharmaceutical company to take over and "develop taxol to a marketable status to meet the needs of the public and with the best terms for the Government."

Very few pharmaceutical companies in the US or elsewhere were particularly interested in cancer chemotherapy, mainly because the research and development costs were enormous; and because the return in terms of successful drugs was particularly small, even by the standards of the drug industry, which expects to synthesise tens of thousands of new compounds for every marketable new drug they find. In addition, cancer chemotherapy accounts for only a small part of the global drugs market—in 1988, 2.7%, compared to over 17% for cardiovascular drugs (Scrip Yearbook, 1990; DiMasi et al., 1994). These, in fact, were the very reasons that the state had taken over the direction of cancer research in the first place, including even the search for new drugs. A further problem was that taxol, occurring as it does naturally, could not be patented and was, at any rate, no longer novel, having been reported in the literature since 1971: only the processes for extracting and purifying it could be patented. Drug companies were not prepared to invest in the necessary research, development, clinical trials and FDA registration to commercialise a drug without some degree of market exclusivity. Other drugs resulting from the mass screening of natural products were likely to pose the same problem.

The NCI drew up a list of 23 interested parties to whom they sent the CRADA notice and further information. Another 22 asked for and were sent the same details. By the deadline for applications, 15 September 1989, only four companies had shown genuine interest. Two of them were biotechnology firms and two were pharmaceutical multinationals. By the end of November, the selection committee at NCI had shortlisted the two pharmaceutical companies and by December 1989 the competition was over. Bristol–Myers Squibb was chosen as the CRADA partner. The first the public (or even Congress) knew of this agreement was in January 1991, when the documents were signed by the parties concerned. The National Cancer Institute signed taxol over to Bristol–Myers Squibb. As discussed earlier in the paper, this announcement coincided with the Fish and Wildlife Service declaration that the yew tree was not a threatened species, a combination of events that was not lost either on the media or on environmental campaigners.

The CRADA gave Bristol–Myers Squibb exclusive rights to develop taxol for the commercial market; exclusive rights to all clinical data generated by the NCI from trials it had or would undertake (not just those against ovarian cancer) which the firm would be able to use in applying for FDA approval for new uses of taxol; and under separate agreements with the Bureau of Land Management and the Forest Service,

the right of first refusal on all yew products (needles as well as bark) on Federal lands. In return the firm agreed to supply the NCI with the necessary taxol for further clinical testing and to finance and develop the methods necessary to get the drug to the patient. It would be the firm's responsibility to put together the clinical data to present a case to the FDA, and the NCI's responsibility to oversee and monitor the clinical trials. Bristol–Myers Squibb also obtained orphan drug status for taxol, under the Federal Orphan Drug Act, which allows firms up to 7 years exclusive marketing rights over a drug that has not been patented, and is a mechanism for giving a monopoly to firms over government funded inventions. The US Federal Government, in other words, gave Bristol–Myers Squibb a monopoly over taxol, a monopoly over the use of yew trees on public land, and exclusive rights to a huge array of knowledge generated as a result of the investment of public funds and which had previously been publicly owned. The NCI believed that giving exclusive rights to taxol in this way—there being no patent on the compound itself—was the only way of providing the necessary incentives for commercialisation of taxol to get it to patients, and to prevent foreign interests from benefiting from US funded R&D. Taxol thus passed from the public to the private domain.

But not without a protest. When the formal agreement was signed in January 1991, the CRADA provoked a congressional hearing, held in July and chaired by the Democratic representative from Oregon, questioning the grant of a monopoly to one firm over the yews on public lands and the intellectual property previously in public hands. Chairman Ron Wyden opened the hearing by stating that the CRADA did not protect the public interest; did not assure a reasonable level of commercial fair play; did not assure responsible management of a limited natural resource; and did not stimulate the transition to an alternative supply (Committee on Small Business, 1991). Consumer Groups, such as the Center for Responsive Law established by Ralph Nader, argued that the public was paying twice for taxol: once as taxpayers and once as consumers. They argued that drugs developed with Federal funding were priced considerably higher than those developed without. They also provided figures for the mark-up on taxol, reminding their audience that the company had not invented taxol, carried out clinical trials, nor taken any of the risks usually used to justify such high prices and profits. These figures were as follows: in 1992, the chemical firm Hauser supplied Bristol–Myers Squibb with taxol in bulk for $0.25/mg. The wholesale price of taxol was $4.87/mg in 1993 ($6 in 1997) and the price to the patient was $9/mg in 1995 (a course of treatment typically requiring over 200 mg) (Love, 1997). Sales of taxol in 1992 were $50 million; in 1994 they were $345 million; and in 1995 they were $580 million. In 1995 taxol accounted for one third of Bristol–Myers Squibb's anti-cancer drug sales of $1.6 billion. Bristol–Myers Squibb has the world's largest anti-cancer drug sales, marketing 11 of the 34 drugs which received significant NCI funding 1955–1993, but it has never discovered a cancer drug by itself (Love, 1997).

The drama of taxol had acquired a new script, with parts not only for environmentalists, oncologists and others (as before), but now for policy makers, consumer groups and lobbyists concerned about the conduct of private enterprise and its relationship to public property rights. The response to concern about private monopolies in drugs for cancer and AIDS developed by Federal agencies was a congressional hearing on the pricing of drugs in 1993 and the introduction of the Sanders Bill on Drug Pricing in September 1996. It also gave rise to concern among economists about the economic justification of a variety of intellectual property rights available from patents, CRADAs, and other forms of monopoly rights (Merges and Nelson, 1994; Mazzoleni and Nelson, 1998).

When it became apparent that the demand for taxol was going to be at least ten times as great as had been anticipated, Bristol–Myers Squibb was under pressure. On 19 June 1991 the company had announced that it wanted open access to yew bark until 1998 (Hartzell, 1991), even though it was investigating extracting taxol with other methods and from other sources. That is, negotiations were either taking place or were complete with various firms involved with growing (other species of) *taxus*, with biotechnology (cell culture), and with making taxol using licences to patents on semi-synthetic routes developed in the public sector from an intermediate obtainable in abundance and renewably from the other yew species (above) grown in nurseries and plantations. Many in the state of Oregon welcomed the company's statement as support of the sustainable harvest of yews and therefore of timber companies and logging jobs. Others, however, argued that Bristol–Myers Squibb was taking the easy way out, extracting taxol from the bark because the method was well established and because it avoided making the investment in the time and effort required to extract taxol from renewable parts of the yew, such as the needles, and other sources. The Food and Drug Administration, besides, had not yet approved semi-synthetic taxol.

Bristol–Myers Squibb faced a potentially enormous, and by many accounts, unobtainable demand for yew bark and at the same time were feeling defensive, having been the focus of two Congressional Hearings in 1991 and 1993 and a great deal of media coverage and campaigning by environmental and consumer pressure groups. In 1993 they swiftly changed direction, ending

their contract with their bulk supplier of taxol; winding down their operations in the Pacific Northwest, especially in Oregon; and shifting operations to a bulk supplier of natural products in Milan, Italy. The company turned from bark to renewable parts of yew (clippings, twigs, needles) and, most significantly of all, from the Pacific yew to the European and Himalayan yew, from an extractive process to a semi-synthetic one (Cragg et al., 1993). In one sweep, the Bristol–Myers Squibb brought to an end the long running taxol play. To emphasise taxol's new status as private property, Bristol–Myers Squibb were able to trademark it in 70 countries world-wide in late 1994, transforming it from taxol to Taxol™ (or Taxol®), despite the fact that name taxol has been in use since 1967. (Wall and Wani, it will be recalled, published the name of taxol for the compound in 1971.) Bristol–Myers Squibb had turned themselves into an obligatory passage point, so that anyone wanting taxol for clinical trials, for non-clinical research or for treatment had to get it from them, and anyone wanting to commercialise taxol outside the USA, or taxol analogues inside the USA, would have to take the company into account. Taxol was no longer a public object. It, Taxol®, was now corporate property.

Conclusion

In this paper we have examined controversies focused on taxol in policies concerning cancer chemotherapy, environmental protection and the transfer of publicly-funded biomedical research to the private sector. There have been several stories about taxol. It has been the subject of widespread publicity in the popular press, especially in the United States, as potentially the most successful anti-cancer drug for many years, offering hope of a cure to many patients previously without hope, who had late stage or difficult to treat cancers. On a political level, the success of taxol has lent authority to the oft-repeated claim that the vast resources applied to finding chemical agents, and especially natural products, with anti-cancer activity will pay off (Rowinsky and Donehower, 1995; Donehower, 1996; Kinghorn and Balandrin, 1993). Taxol was an important publicity point for the National Cancer Institute in particular, and for the biomedical cancer research and clinical community in general. It has become, as a group of chemists have recently commented, 'one of the few organic compounds, which, like benzene and aspirin, is recognizable by name to the average citizen' (Nicolaou et al., 1994).

Other stories about taxol have not concentrated on praise. Many of the accounts of taxol in the media, and even in the scientific literature, have presented it as the focus of zero-sum clashes between health policy (the 'war against cancer' and the needs of patients) and environmental policy (the need to preserve biodiversity and save the yew from extinction). Taxol has been used politically to push particular policy agendas. While not denying the popular image of taxol as being controversial, we argue that the confrontations we discuss should be understood as manifestations of increasing lay participation, as experts, in biomedical politics.

Similarly the granting of the taxol CRADA to Bristol–Myers Squibb, and the trademarking of taxol by the firm, raised many issues about the ownership of scientific knowledge and practice, and the price that society pays for the transfer of property rights from the public to the private sector. These had been mooted in the earlier case of AZT but the political nature of taxol drew in many wider issues. These controversies, too, reflected the way in which the public was becoming involved, as experts, in policy arenas from which they had previously been excluded. The environmental issues were brought to bear on those of technology transfer in novel ways. Environmentalists sat next to consumer and policy affair activists to challenge agreements that had become a 'normal' part of biomedical politics in the United States. They argued that there was a conflict between the interests of the public and private sector, and that it was not in the public's interest to give a monopoly over public property (the yews) or publicly funded intellectual property to a private firm.

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