Bioprospecting and Incentives for Biodiversity Conservation: Lessons from the History of Paclitaxel

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1 The Medical Value of Biodiversity

Bioprospecting is the search for active ingredients for pharmaceuticals or other commercially useful compounds among living organisms. It is an important source of medicines. Aspirin was originally produced from willow bark. The antimalarial medicines quinine and quinidine are still produced from cinchona bark. The anti-cancer drugs vincristine and vinblastine were developed from the rosy periwinkle (*Catharanthus roseus*), native to Madagascar, as was ajmalicine, used to treat hypertension. Soejarto and Farnsworth (1989) estimated that roughly a quarter of prescription drugs contained some natural products, derived from plants and animals. The drug Glucobay, used to treat high glucose levels, was originally derived from bacteria found in a Kenyan lake. Developed into a pharmaceutical, it has generated more than $4 billion in sales revenue for Bayer Corporation (Heal, 2020). In addition, natural products are widely used in the developing world as traditional remedies for a host of ailments (Reid, 1995). Even today, most anticancer drugs have been derived from natural sources (Cragg & Pezzuto, 2016).

Besides directly providing raw materials for pharmaceuticals, natural products provide information for pharmaceutical development. Artemisinin, extracted from annual wormwood (*Artemisia annua*), critical to treatment of malaria resistant to other drugs, is produced through semi-synthesis (Croom, 1995). Semi-synthesis isolates large, complex molecules from plants, animals, or bacteria to serve as building blocks to produce a wide range of medicines (Nicolaou et al., 1996). *Artemisia annua* has long been used in traditional Chinese medicine (Croom, 1995). The molecular structures of natural products serve as blueprints or as

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leads in developing compounds. Over the past 40 years, about 30% of all new pharmaceuticals were "natural product mimics." These are compounds produced via total chemical synthesis but whose molecular framework came from a natural product (Newman & Cragg, 2020).

In the course of millions of years of evolution, nature has produced molecules that organic chemists or pharmaceutical companies would never have thought of. These molecules have novel modes of action to combat diseases. Advances in biotechnology and bioinformatics have greatly increased the possibility of using genetic information embodied in the Earth's biodiversity to develop medical breakthroughs. Biologist E.O. Wilson has suggested that the Earth's biodiversity could be thought of as a vast, little-explored library, a "genetic library." This library contains information that has led to, and could lead to, many medical and other scientific breakthroughs. Only a small fraction of known species have been screened for potential medical activity. Moreover, medical screening processes continually improve, so compounds that might not seem promising today might lead to blockbuster drugs in the future.

The wildlands that are home to this biodiversity have an option value as a potential source of genetic materials and information. The tropics are home to most of the world's plant and animal species; tropical forests are especially species-rich (Pimm & Raven, 2000; Wilson, 1988). Based simply on the number of species, tropical rainforests are promising places to explore for new drugs. Mendelsohn and Balick (1995) identified 47 major pharmaceuticals developed from tropical flowering plants. Extrapolating based on past discoveries and estimates of species numbers, they estimated that tropical forests may hold over 300 undiscovered drugs with an economic value of $147 billion. Conducting a similar exercise for marine biodiversity, Erwin et al. (2010) estimated that the world's oceans could lead to the discovery of anticancer drugs worth $563 billion to $5.69 trillion. Bioprospecting has extended from the geysers of Yellowstone National Park (Doremus, 2003) to Antarctica (Haefner, 2003; Stix, 2004; Herber, 2006). In principle, tropical forests (or other undeveloped areas) could become extractive reserves, where medicinal plants (and other products) are harvested renewably.

Yet, the past realized and potential future value of medical discoveries from biodiversity begs some questions. First, if species have such value (actual or potential) for pharmaceutical development, why are their habitats being depleted so quickly? For example, from 2010 to 2020, net forest loss in Africa averaged 3.9 million hectares per year, while for South America, this net loss averaged 2.6 million hectares per year (UN FAO, 2020). Habitat conversion, mainly for subsistence agriculture, commercial crop production, and cattle ranching, is considered the main cause of biodiversity loss (Wilson, 1988; Forster, 1992; Pimm & Raven, 2000; Innes & Frisvold, 2009). Second, why aren't the economic values from natural product pharmaceutical development being marshalled to create incentives to preserve species habitat?

One explanation is a divergence between social values and private incentives. While conserving genetic resources that are potential sources of new medicines

makes sense from a social perspective, private decision-makers often lack incentives to do so. Even though natural products remain important sources of new pharmaceuticals, the pharmaceutical industry has hesitated to make large investments to collect and test genetic materials. While companies have had natural product development units, funding of these has been erratic over time (Rouhi, 2003a, b; Ortholand & Ganesan, 2004). This underinvestment (from a social perspective) stems from the public-good nature of information about the value of genetic resources (Brown & Swierzbinski, 2012; Sedjo, 1992).

A company that collects and screens biological samples would have difficulty excluding rivals from the knowledge that particular samples show promising medical activity. The drug-development application process and clinical trials approval process require companies to disclose information about a compound's origins, mechanism of action, and efficacy. Rival companies have an incentive to free-ride off the search and discovery activities of others. So, an individual company's expected private economic gains from bioprospecting could be considerably smaller than potential social gains.

The historically weaker intellectual property protection for biological innovations, compared with mechanical or chemical innovations, is another disincentive for natural product collection and screening. A new organism discovered in the wild or new compound derived directly from that organism cannot itself be patented. This limits companies' abilities to exclude rivals from access to raw genetic materials once a discovery is made. Because of these private disincentives, the search and screening of biological materials for medical or agricultural applications have been carried out historically by the public sector.

Another problem is that countries where the biodiversity resides have been unable to capture the gains from medical breakthroughs developed from their genetic resources. For example, Eli Lilly earned $100 million per year from the drugs vinblastine and vincristine, derived from Madagascar's rosy periwinkle. Yet, Madagascar, the source of the plant, received no royalties from the sale of these drugs (Day-Rubenstein & Frisvold, 2001). In theory, if the home countries *could* capture some of these gains, they would have greater economic incentives to protect these resources. The global benefits of drug development are not filtering down to the source nations nor to the local inhabitants on the forest frontier, who are often making the proximate habitat conversion decisions. This disconnect between global benefits and local incentives can lead to too little habitat preservation.

2 Legal Changes Affecting Biological Innovation and Resources

In the 1980s and 1990s, various legal changes increased both private incentives for biological innovation and the potential for countries to capture more economic gains from their genetic resources. The US Supreme Court ruled in *Diamond v. Chakrabarty* (447 U.S. 303, 318 (1980)) that organisms bred or genetically

modified for novel traits could be patented. The US Patent and Trademark Office extended *Diamond v. Chakrabarty,* allowing utility patents to be awarded for human-developed traits in plants (Ex parte Hibberd, 227 USPQ 443 (B.P.A.I. 1985)) and animals (Ex parte Allen, 2 USPQ 2d 1425, 1427 (B.P.A.I.1987).

The United Nations Convention on Biological Diversity, which entered into force on December 29, 1993, redefined country sovereignty of genetic resources. Article 15 of the Convention asserts that (a) countries have sovereign rights to their genetic resources (Sect. 1), (b) access to genetic resources shall be subject to prior informed consent of the source country (Sect. 5), and (c) access shall be on mutually agreed terms (Sect. 4). In addition, Article 15 (7) of the Convention states: "Each Contracting Party shall take legislative, administrative or policy measures ... with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources. Such sharing shall be upon mutually agreed terms." (United Nations, 1992).

This provision formalizes the right of a country to use its property rights over genetic resources to gain a greater share of the benefits from technologies using those resources. It had been a common (though contested) practice for botanists and plant scientists to send biological materials back to their home countries for screening without the knowledge or consent of the country of origin (United Nations, 1992).

Provisions in the Uruguay Round of the General Agreement on Tariffs and Trade (GATT, 1994) also marked a legal shift in treatment of genetic resources. It created minimum standards for intellectual property protection for commercially developed seed and plant varieties. Article 27, 3(b) states, "Members shall provide for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof."

3 Bioprospecting as a Mechanism to Protect Biodiversity?

These institutional changes opened up new opportunities for private firms to capture gains from biological innovations and for developing countries to capture gains from their genetic resources. In the early 1990s, biologists and conservationists began to tout bioprospecting arrangements as a way to simultaneously develop medicines and generate incentives to protect biodiversity (Blum, 1993; Laird, 1993; Eisner, 1989–90; Reid, 1995; Roberts, 1992).

One early and much-studied bioprospecting agreement was between Merck, the multinational pharmaceutical giant, the government of Costa Rica, and a Costa Rican nonprofit private organization, the Instituto Nacional de Biodiversidad (INBio) (Blum, 1993; Simpson & Sedjo, 1994; Day-Rubenstein & Frisvold, 2001; Frisvold & Condon, 1994; Roberts, 1992; Sittenfeld & Rodrigo Gomez, 1993). Under an initial, two-year agreement, Merck would pay INBio $1 million for sample collection, screening, and processing and an additional $100,000 for equipment.

INBio scientists received technical training both in Costa Rica and at Merck facilities. Merck retained first rights to all patent discoveries, while INBio would receive royalty payments for any profitable discoveries. Royalty payments would be shared with the Costa Rican Ministry of Natural Resources to support habitat preservation (Blum, 1993). The agreement, renewed in 1997, provided INBio with an additional $1 million in research funding (Day-Rubenstein & Frisvold, 2001).

Similar agreements soon followed. INBio and the Costa Rican government also signed agreements with Bristol-Myers Squibb and Cornell University to collect and screen insects as possible sources of drugs (Rosenthal, 1997; Day-Rubenstein & Frisvold, 2001). In 1992, the US Agency for International Development (USAID) initiated a program to encourage joint biodiversity research and development between the private sector and developing countries (Cohen, 1992). The US National Cancer Institute (NCI) has entered into bioprospecting agreements with organizations in Madagascar, Tanzania, Zimbabwe, and the Philippines, while the British firm Biotics signed agreements with organizations in Ghana and Malaysia (Simpson & Sedjo, 1992). In 1993, the US National Institutes of Health (NIH), the US National Science Foundation (NSF), and USAID launched the International Cooperative Biodiversity Group (ICBG). Its goals were to promote drug discovery, biomedical research, and biodiversity conservation by supporting research consortia and encouraging royalty payments to developing countries if discoveries were made (Wilentz, 2003).

Bioprospecting entails collecting samples that are screened for activity against a certain disease (such as AIDS or different forms of cancer). One approach is to search through random collections of organisms. Pharmaceutical companies often prefer these random collections because samples can be more diverse (Day-Rubenstein & Frisvold, 2001). Another approach is to use ethnobotanical or ethnomedical information from the indigenous peoples of source countries to narrow the search for promising drug leads (Blum, 1993; Downes, 2000; Laird, 1993; Clapp & Crook, 2002). A number of breakthrough drugs have been based on compounds from plants and other organisms used in traditional medicine. Complicated intellectual property rights issues may arise under this approach concerning how suppliers of traditional knowledge are compensated (Rubin & Fish, 1994). Determining who has a right to compensation for traditional knowledge could also be difficult (Rubin & Fish, 1994; Downes, 2000). For example, it may be difficult to identify which group originally developed the knowledge.

Shaman Pharmaceuticals, founded in 1989, was based on the premise of using traditional knowledge to conduct more focused searches but also more equitable sharing of the returns from any discoveries. Shaman pledged to direct royalty payments to indigenous groups and local forest conservation programs. In 1992, the pharmaceutical giant Eli Lilly entered into an agreement with Shaman, investing $4 million in the company in exchange for the right to investigate any promising anti-fungal compounds that Shaman identified (Clapp & Crook, 2002). The following year, Shaman went public and its initial public offering (IPO) raised $42 million.

4 Economists Weigh In

In the early 1990s, environmentalists and conservation biologists saw hope that bioprospecting contracts between pharmaceutical companies and parties in species-rich developing countries could create economic incentives for habitat preservation. Economists – generally, but not uniformly – were less optimistic. Simpson et al. (1996) argued that, even though biodiversity as a whole is a valuable source of pharmaceutical leads, bioprospecting would not increase the value of individual species much. Their analysis focused on the value of the marginal, or incremental, discoveries. They argued that, if several species produce the same chemical compound, discovery in one species would render the other species (and their habitats) redundant from the point of view of drug development. If a compound were unique to a single species, there would be no redundancy problem, but then the likelihood of actually discovering the compound would be exceedingly small. Developing a model formalizing this reasoning and conducting numerical simulations, they estimated that the marginal value of species habitat would only be about $21 per hectare. Given that habitat conversion could often yield larger per-hectare returns, they argued that bioprospecting contracts were unlikely to generate significant incentives for habitat preservation. To put things in perspective, Silva et al. (2019) have estimated that the opportunity cost of preserving forest in the Amazon (in terms of forgone revenues from crop, livestock, and timber) averaged $979 per hectare.

Beginning with a similar modeling framework, Rausser and Small (2000) obtained quite different results. They found that the marginal value of a species could be quite large – in some cases, more than $9000 per hectare. Rausser and Small (2000) argued that the reason for this large difference stemmed from assumptions about the drug search and screening process. Rausser and Small (2000) assumed bioprospectors could use information to carry out more efficient searches, while Simpson et al. (1996) assumed species were randomly searched. Rausser and Small (2000) argued that using scientific information improved the efficiency of the search process, thus raising the value of incremental searches. The implications of these results were that bioprospecting contracts could indeed create sufficient economic incentives for habitat preservation and that investments in scientific information could enhance the conservation potential of such contracts.

Costello and Ward (2006) later sought to reconcile the differences in the Simpson et al. (1996) and Rausser and Small (2000) results. They estimated the marginal value of land in biodiversity hotspots using parameter values employed in both studies. They compared results under a random search process (as used in Simpson et al. (1996)) and under an optimal search process (as employed in Rausser and Small (2000)). Costello and Ward (2006) found that use of scientific information raised marginal values, but the effect was small. They found the difference in search assumptions accounted for just 4% of the differences in marginal values between the studies. Costello and Ward (2006) found that much more of the difference in model results stemmed from differences from other modeling parameters. They then conducted a sensitivity analysis, using ranges of modeling parameters from

other studies. The results of this exercise supported Simpson et al. (1996) in that the marginal value of land would be low, and likely insufficient to create preservation incentives. Even assuming information-based search (which raises marginal values), the marginal value of the most biodiverse hotspot averaged just $14 per hectare.

Other economic studies considered different aspects of bioprospecting but reached similarly pessimistic conclusions regarding habitat preservation potential. Barbier and Aylward (1996) modeled a situation where a developing country can make investments in biodiversity protection, in increasing information about the pharmaceutical properties and potential of samples, or both. Based on numerical model simulations using royalty rates from the Merck-INBio agreement, they argue that the country can gain the most from contracting via their information-generating investments. Their results suggest that simply preserving habitat by itself will not allow a country to capture pharmaceutical value. Revenues (based on observed royalty rates) are unlikely to create sufficient preservation incentives. Barbier and Aylward (1996) do suggest, though, that bioprospecting contracts could be used to encourage developing countries to invest in taxonomic and other scientific information.

Frisvold and Condon (1994) considered the marginal benefits of habitat preservation versus their marginal opportunity costs. These opportunity costs are forgone returns to clearing habitat. A stated goal of bioprospecting contracts is to allow the source countries to capture a greater share of the benefits of pharmaceutical development. Frisvold and Condon (1994) emphasize, however, that the marginal opportunity costs of not converting habitat are borne by the poor living in frontier areas of tropical forests. Often land clearing is their only source of livelihood. Frisvold and Condon (1994) noted that opportunity costs are increased by inequality of landholding, insecurity of tenure, and government policies that encourage land clearing (Binswanger, 1991). They argued that the marginal opportunity cost curve of habitat preservation can be quite steep in developing countries. So, policies to increase the marginal benefits of preservation, even if successful, would have little impact on the optimal level of preservation. Rather, policies to address underlying problems of landholding inequality and insecurity and poverty on the forest frontier could potentially do more to reduce land clearing.

Barrett and Lybbert (2000) consider bioprospecting incentives for conservation at two levels. First, would such arrangements generate sufficient value for the source country? Second, would those values at the aggregate level trickle down as incentives to the local residents making the proximate land clearing decisions? Having remunerative contracts at an aggregate level is a necessary but not sufficient condition for habitat preservation. As in Frisvold and Condon (1994), they emphasize that asset poverty is a major driver of habitat loss. Barrett and Lybbert (2000) were skeptical of sufficient resources being transferred down from bioprospecting contracts to the local level, noting the lack of actual examples of this occurring in a significant way. They also note that there is an important difference in whether the biodiversity rich area is an extractive reserve, where source material is accessed on a regular basis, or whether drug development is a "single shot" process, where materials are discovered and tested, but then production is conducted ex situ. If it is

the latter case, then once a discovery is made, the source region (and its habitat) is ironically no longer a source for that particular drug. In turn, the value of preserving that area for that particular drug vanishes. They concluded that providing the poor with income-generating opportunities *away* from the land frontier will have more scope for preserving habitat.

5 A Case Study Approach: The History of Paclitaxel

The ex ante economic assessments of the drug discovery process discussed above have been based on numerical simulations, sensitive to (highly uncertain) parameter values and stylized assumptions about the drug search process. The present study takes a different tack: an ex post, historical study of the search for, and discovery and commercialization of, the cancer drug paclitaxel, derived originally from the Pacific yew tree (*Taxus brevifolia*) found in the Pacific Northwest's old growth forests (Croom, 1995). The discovery of paclitaxel resulted from a 20-year program of the National Cancer Institute (NCI) and US Department of Agriculture (USDA) to collect and screen biological resources as potential cancer treatments. In 1989, Bristol-Myers Squibb (BMS) Corporation entered into a Cooperative Research and Development Agreement (CRADA) with NCI to commercialize paclitaxel. Brought to market in 1993 to treat AIDS-induced Kaposi's sarcoma as well as late-stage breast and ovarian cancer, paclitaxel had sales of $9 billion between 1993 and 2002, becoming the world's top-selling cancer drug (US GAO, 2003; Hemphill, 2006).

5.1 Paclitaxel: Discovery and Early Screening

In 1958, the NCI instituted a natural products program to screen plants for anticancer activity. NCI began formal collaboration in 1960 with the USDA, which had plant collection expertise. This formal collaboration continued until 1981. In 1962, USDA botanist Arthur Barclay collected samples from the Pacific yew tree from Gifford Pinchot National Forest in Washington state (Goodman & Walsh, 2001).

The USDA's collection program did not search randomly but prioritized plants where traditional uses and folkloric knowledge of plants existed (Suffness & Wall, 1995). Folkloric knowledge of the activity of European yew species had long existed, but yew was associated more with poison and death than curative properties (Hartzell Jr, 1995). Yew was sacred to Hecate, the ancient Greek goddess of the underworld. In Shakespeare, Hamlet's father is poisoned by Hamlet's uncle using a yew extract, "cursed hebona." In Macbeth, one ingredient in the three witches' cauldron was "slips of yew slivered in the moon's eclipse." In a more contemporary example, Lord Voldemort, Harry Potter's arch-nemesis, used a wand of yew. However, Native Americans of the Pacific Northwest had long used Pacific

yew to treat headaches and bronchitis as well as stomach and lung problems (Croom, 1995).

In early screens, yew extracts were found to kill tumor cells. In 1966, Monroe Wall of the Research Triangle Institute isolated a pure sample of a complex molecule derived from Pacific yew (Goodman & Walsh, 2001). At the 1967 American Chemical Society meetings, Wall first reported on the compound's structure, calling it "taxol" (from *taxus* and alcohol). It was not until 1971 that Wall and colleagues published descriptions of paclitaxel's structure as well as its antileukemic and antitumor properties (Wani et al., 1971). This publication placed the molecule's name "taxol" and structure in the public domain. The name Taxol® subsequently became a registered trademark for the compound produced by Bristol-Myers Squibb (BMS), while paclitaxel is the official International Nonproprietary Name (INN) given to generic formulations of the drug. Most early publications, however, simply called the compound taxol (little "t"). It was also thought at the time that placing the isolated molecule's structure in the public domain could preclude it from being patented.

There were a number of times where it seemed that paclitaxel's medical and commercial prospects had reached a dead end (Goodman & Walsh, 2001). NCI conducted screens on paclitaxel from 1967 to 1982. While it showed activity against different types of tumors, it was essentially insoluble in water or other solutions. Solubility is necessary in order to administer chemotherapy drugs intravenously. Other compounds being screened at the time seemed as promising as paclitaxel in terms of activity against tumors but were also soluble (Stephenson, 2002). At that point, it looked like paclitaxel would be dropped from further consideration.

Two things put paclitaxel back on track. First, in 1979, researchers published findings showing that paclitaxel had a unique and novel mode of action for stopping tumor growth (Schiff et al., 1979). Next, scientists discovered paclitaxel could be dissolved in a castor oil-derived compound (Stephenson, 2002). This new formulation proved active in tumor screens conducted in 1980. In 1983, NCI filed an Investigational New Drug Application for paclitaxel with the Food and Drug Administration (FDA). Phase I clinical trials – used to determine a drug's safety and dosage – began the following year (Goodman & Walsh, 2001).

In these trials, some patients had hypersensitivity reactions, which included anaphylactic shock and two deaths. As a result, some phase I trials were halted (Suffness & Wall, 1995). It again looked like paclitaxel would be dropped from further consideration, until it was found that hypersensitivity reactions could be controlled. This could be done by excluding patients with greater underlying risk factors, premedicating patients, and slowing the rate of drug infusion.

5.2 Supply Chain Problems

While paclitaxel faced challenges in terms of its efficacy and safety, it also faced challenges of supply chain constraints. First, Pacific yews used to produce the drug were not considered an economically important tree. They were occasionally used to make fence posts, canoe paddles, or tool handles (Preston Jr., 1948; Hosie, 1969). The species was characterized as having "little or no commercial importance" (Tirmenstein, 1990). They grew in the understory of Douglas firs. But they were commonly burned on slash piles as "trash" trees after Douglas fir clear-cutting operations. Because they were thought to be commercially unimportant, little was known about their total number or geographic distribution. It was thought that most yews were on public lands administered by the Bureau of Land Management and the US Forest Service (Croom, 1995). Because the yews were on federal lands, federal laws regulating and limiting timber harvesting, such as the National Environmental Policy Act (NEPA) and the Endangered Species Act (ESA), would affect supply. More regulatory hurdles would have to be cleared than if the trees were on private lands.

The mathematics of getting sufficient supplies of paclitaxel from Pacific yew bark was daunting (Croom, 1995). About 5900–7200 kg of dry yew bark were required to produce 1 kg of paclitaxel, while only about 1.5–2.25 kg of bark could be harvested per tree. Further, stripping the trees of bark killed them. While paclitaxel could be produced from other, more renewable parts of the tree, such as needles, the yield from such sources was minuscule compared to the yields from the bark. Researchers looked to more common ornamental varieties of yew. But these, such as Japanese yew (*Taxus cuspidata*) or European yew (*Taxus baccata*), produced far lower amounts of the paclitaxel molecule. Further, there was evidence that compounds derived from these varieties posed greater risks to patients' hearts than formulations from the Pacific yew (Suffness & Wall, 1995). Another supply issue was that Pacific yews are extremely slow growing. It was found that it could take 25 years for trees to reach 1 inch in diameter and 100 years to reach 6 inches diameter (Bolsinger & Jaramillo, 1990). So, Pacific yew bark supplies were not quickly or easily renewable.

As supply chain challenges became more apparent, so did paclitaxel's promise as a cancer treatment. Phase II clinical trials, to establish drug efficacy, were approved in 1985 and began for treatment of melanoma and renal cancer, but paclitaxel showed the most promise in treating ovarian cancer (McGuire et al., 1989; Goodman & Walsh, 2001). In these trials, women who failed to respond positively to previous chemotherapy treatments responded to paclitaxel. Ovarian cancer patients needed about 2 grams of paclitaxel per treatment (Croom, 1995). At the time, about 12,000 women in the United States died from ovarian cancer per year (Schilder & Ozols, 1992). So, treating late-stage ovarian cancer could require up to 24 kg of paclitaxel annually. This could require stripping the bark from (and killing) 60,000–115,000 Pacific yew trees per year. Despite the promising results, some clinical trials were put on hold because of insufficient paclitaxel supplies. Contractors hired by the NCI

to harvest yew bark had difficulty delivering the needed quantities of bark on time to produce all the paclitaxel needed (Goodman & Walsh, 2001).

In response to supply chain problems, the NCI started to look for alternatives and approached Weyerhaeuser, the timber giant, about propagating Pacific yew seedlings on a massive scale. (Goodman & Walsh, 2001). Producing paclitaxel via total syntheses, which would bypass the need for yew bark, became possibly the number one target of synthetic organic chemists (Denis et al., 1988). Although the NCI funded some of this research, their scientists were skeptical about the success of a total synthesis approach. Only about 4% of natural product pharmaceuticals were produced commercially using total synthesis (Soejarto & Farnsworth, 1989).

In 1988, a French research team used needles of the European yew tree to build the main part of the paclitaxel molecule. They then used synthetic methods to create and attach the rest of the molecule (Denis et al., 1988). This semi-synthesis approach relied on needles, which could be harvested more sustainably because it did not require killing trees. Moreover, European yews were more abundant. This method, though, produced much lower amounts of paclitaxel than methods relying on Pacific yew bark and was not pursued by the NCI. In 1989, a Florida State University research team patented a method of producing paclitaxel through semi-synthesis with twice the yield of the French process (Stephenson, 2002). The paclitaxel molecule itself could not be patented because it had been in the public domain. Novel methods for producing it, however, *could* be patented. The next year, Florida State University signed a licensing agreement with Bristol-Myers Squibb for commercial development and use of this semi-synthesis process (Stephenson, 2002).

5.3 The NCI: Bristol-Myers Squibb CRADA

Although the NCI led a program for 30 years to screen natural products for cancer treatments, they lacked the formal authority or technical capacity to produce and market drugs they found promising. The NCI was a research agency, lacking extract-processing and pharmaceutical production facilities. Yet, under the Federal Food Drug and Cosmetic Act, a party petitioning the FDA for a new drug application (NDA) was required to provide FDA "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing, of such drug (21 U.S.C. § 355(b)(1)(D) (2000))." The NCI had no experience in or capacity for forestry, which would be needed to secure adequate supplies of raw materials for commercial-scale paclitaxel production.

In 1980, Congress passed two laws that sought to encourage commercialization of technologies developed through federal funding. One was the Stevenson-Wydler Technology Innovation Act of 1980 (Pub. L. No. 96–480, 94 Stat. 2311), which focused on inventions owned by the federal government. The other was the Bayh-Dole Act (Pub. L. No. 96–517, § 6(a), 94 Stat. 3015 (1980), which addressed inventions developed under federal contracts, grants, and cooperative research and

development agreements (CRADAs). The Federal Technology Transfer Act (Pub. L. No. 99–502, 100 Stat. 1785 (1986)) later amended Stevenson-Wydler to set guidelines to encourage commercialization of new technologies through licensing to private firms. It also authorized federal agencies to enter into CRADAs with private firms, universities, and other non-federal entities. In 1989, the NCI announced a call for bids to firms to enter into a CRADA to commercially develop paclitaxel (54 Fed. Reg. 31,733 (August 1, 1989)).

In all, only four companies actually placed bids: Rhone-Poulenc (now Aventis), a France-based pharmaceutical and chemical multinational; two small biotechnology firms; and Bristol-Myers Squibb (BMS). Of these, BMS had the most experience with marketing drugs in the United States generally and developing cancer drugs in particular. BMS had already been discussing large-scale production of paclitaxel with Weyerhaeuser. National Institutes of Health (NIH) reviewers determined BMS was the strongest of the four applicants.

In 1991, the NCI and BMS signed a CRADA with the goal of obtaining FDA approval to commercialize paclitaxel. Although paclitaxel could not be patented, CRADA provisions effectively gave BMS exclusivity to profit from the drug's development. Under the agreement:

- Officials from the NCI and BMS would jointly review clinical trials and share research findings.
- The NCI would provide its own clinical trial data to BMS, exclusively.
- The NCI would "urge" outside researchers it funded at universities and hospitals to cooperate with BMS (as a major funder of cancer research, the NCI's "urging" could hold significant sway over researchers).
- The NCI would work exclusively with BMS to obtain FDA approval for paclitaxel and to develop it into a marketable product.
- BMS would provide paclitaxel to the NCI for clinical trials and other research, collect clinical trial data, and fund additional studies (Day & Frisvold, 1993).

The original draft of the CRADA included a clause about "a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public" (US GAO, 2003). This draft also stated that supporting evidence might be required to justify paclitaxel's price. However, BMS insisted that this "reasonable price clause" be dropped, and it was deleted from the final CRADA draft signed in 1991 (US GAO, 2003).

Also in 1991, the NIH, USDA, and the Department of Interior signed a memorandum of understanding concerning the harvest of Pacific yew for paclitaxel production on Forest Service (USDA) and Bureau of Land Management (BLM, Department of the Interior) lands (Goodman & Walsh, 2001).

The memorandum granted BMS exclusive access to yew bark on these federal lands. It also designated Hauser Chemical Research (which had contracted with BMS) as the sole recognized supplier of Pacific yew bark and processor of bark into paclitaxel (Day & Frisvold, 1993). While BMS did not hold a patent on the paclitaxel molecule, it did have exclusive access to the medical data needed to obtain

FDA approval. Through the memorandum and its contract with Hauser, BMS had exclusive access to Pacific yew bark on federal lands.

5.4 Pacific Yew Harvesting Controversies

The BLM and Forest Service received criticism for this exclusive access arrangement and for not charging BMS more for harvesting yew bark on federal lands (Newman, 1992; Nader & Love, 1993). Some also complained that giving Hauser and BMS essentially monopoly control over yew bark harvesting led to wasteful practices. Bark harvesters would strip the lower, easy-to-reach parts of trees but leave the remaining bark unharvested. Some critics argued that more bark per tree would be harvested if more competition were allowed (Egan, 1992).

The merits of these arguments are dubious, however. It is not clear how a policy increasing harvesting costs would have improved overall welfare or that of cancer patients in particular. By not charging for the harvesting of yew bark, the federal agencies may have avoided a double marginalization problem (Lerner, 1934). If one firm in the supply chain faces a downward sloping demand curve and marks up the product's price above its marginal cost, the series of mark-ups leads to a higher retail final price and lower combined profit for the supply chain than if the firms were vertically integrated. By merging the harvesting and production in a vertical chain without markups, industry profits would be higher (as critics noted). But final prices and costs to consumers (i.e., cancer patients) would also be lower.

The argument that a more "competitive" harvesting regime would have improved harvesting efficiency is also dubious. The problem was more one of incentives for individual harvesters. Bark harvesters were paid on a piece rate, in terms of pounds of bark. This created an economic incentive for harvesters to strip what they could from each tree quickly and move on to the next one. It is not at all clear that letting more harvesters into the forest would have improved this situation. Rather, it is more likely that this would have set off a "rush" for easy-to-reach bark, actually making the problem of waste worse.

Before large-scale yew bark harvesting began, the Pacific Northwest was already in the midst of intense controversies over the effects of timber harvesting on endangered species in old-growth forests. In 1989, the Fish and Wildlife Service (FWS) listed the Northern Spotted Owl as an endangered species; timber sales on BLM and Forest Service land deemed critical owl habitat were halted (Goodman & Walsh, 2001). Falling timber sales led to intense debate over "jobs vs. owls."

Debates over the Endangered Species Act (ESA) soon became framed as owls vs. timber sales vs. cancer patients (Weiss, 1991). Some environmental groups argued that the discovery of paclitaxel from a little valued "trash tree" in old growth forests vindicated the ESA's protections. Pacific yew populations, which would have been destroyed during Douglas fir harvests, were more abundant because they shared habitat with the owl (Goodman & Walsh, 2001). In 1990, environmental groups and cancer researchers petitioned the FWS to list the Pacific yew as a threatened

species under the ESA, to preserve the yew as a source of paclitaxel (EDF, 1990). They argued that forest clear-cutting destroyed Pacific yew habitat and sought to limit timber harvests more broadly. The following year, FWS found against listing the Pacific yew as threatened because of insufficient scientific information about logging's impact on the long-term viability of the species (USFWS, 1991). The FWS decision was based in part on Forest Service estimates – based on satellite photography – that there were 130 million Pacific yew trees on federal land. The Forest Service, however, later revised their estimate downward, to just 20 million Pacific yews on federal lands (Day & Frisvold, 1993). FWS based their estimates of Pacific yew depletion on incidental destruction of yews during logging of other trees. FWS argued that yew bark harvest itself would only affect mature trees needed for cancer treatment and not threaten smaller, younger ones.

In December 1991, the Environmental Defense Fund and the Wilderness Society petitioned the USDA and the Department of the Interior to require that Pacific yew bark be harvested prior to the logging of other timber where the yews grew (EDF, 1990). They cited a Forest Service internal memo stating 60–75% of bark was wasted if it was not harvested before logging. The BLM required no yew harvesting prior to clear-cutting, while the Forest Service urged, but did not require, the harvest of yew trees prior to clear-cutting. The Oregon Natural Resources Council tried to block timber sales until the Forest Service and BLM issued guidelines for harvesting yew trees and completed yew inventories and long-term management plans (Cockle, 1991; Monje, 1992; Tims, 1991).

Federal agencies placed some restrictions on yew bark harvesting near spotted owl nesting areas. They also encouraged bark harvesting in areas that were approved for clear-cutting or that had already been clear cut. In the latter case, bark could be harvested from slash piles. As a result of these harvesting restrictions, new stories and editorials appeared framing the debate in terms of owls vs. cancer patients (McGuire, 1991; Safire, 1991; Tisdale, 1991). Environmental groups countered that it was not the harvest of yew bark they opposed, but that bark was not being harvested either sustainably or efficiently (Wood, 1992; Ross, 1992).

In 1992, Forest Service crews still burned Pacific yew bark when disposing of clear-cutting residue (Egan, 1992). A 1992 GAO report on constraints on obtaining yew bark supplies concluded that yew bark was often not harvested, either prior to clear cutting or taken from slash piles on federal lands (GAO, 1992). The report did not mention protections for spotted owl nesting areas as a constraint on harvesting. At hearings of the House Subcommittee on Regulation, Business Opportunities, and Energy, Forest Service and BLM officials testified that yew harvesting would be required before commercial logging on federal land (Day & Frisvold, 1993).

In 1992, the Congress passed the Pacific Yew Act (Pub. L. No. 102–335, 106 Stat. 859 (1992), requiring that an inventory of yews be taken and providing for guidelines to prevent the wasting of Pacific yew bark. Guidelines were eventually developed in *An Interim Guide to the Conservation and Management of Pacific Yew* (Daoust, 1992) and in draft and final environmental impact reports (USFS, 1993a, b). It had been known a decade earlier that large-scale Pacific yew harvesting was likely to take place. Yet, it required an act of Congress before formal guidelines

were implemented. Yew "poaching" had become a problem itself (Barnard, 1992; Monje, 1991; Nalder, 1991; "Yew Bark Theft Reported", 1991; "Two Oregon Men Get Probation for Stealing Bark from Yews", 1992). The Forest Service estimated about 300,000 pounds of wet bark were stolen, equivalent to about half as many pounds of dry bark (USFS, 1993a, b; Croom, 1995). Some poached yew bark ended up as supplies to BMS, while other supplies were believed to be shipped overseas. Yew bark harvesting also shifted from federal lands to private lands that had fewer regulatory restrictions. While all legally harvested yew bark came from public lands in 1990, by 1993 this had fallen to 21% (Croom, 1995).

In 1991, researchers at the M.D. Anderson Cancer Center published clinical trial results showing that metastatic breast cancer patients responded well to paclitaxel (Holmes et al., 1991). About 40,000 women in the United States die of breast cancer each year, and over 250,000 new cases are diagnosed per year (CDC, 2021). These promising medical findings were expected to place even more pressure on Pacific yew populations to supply paclitaxel. The Forest Service estimated that it could take the bark of 2 to 3 million yew trees to supply potential ovarian and breast cancer patients over the succeeding five years (Croom, 1995).

5.5 Searching for Substitutes

Given the supply chain problems of Pacific yew bark harvest and the growing demand for paclitaxel, the NCI and BMS actively pursued substitute sources to produce paclitaxel (Day & Frisvold, 1993). They explored the potential of other yew species growing throughout the world. USDA scientists had developed methods for using plant tissue culture to produce paclitaxel, and the USDA held a patent on the process. In 1991, a research consortium comprised of USDA's Agricultural Research Service, Colorado State University, Cornell University, Hauser Chemical Company, and the biotechnology firm Phyton Catalytic received a $1.27 million grant from the NCI to pursue plant tissue culture production (Day & Frisvold, 1993). Weyerhaeuser, funded by BMS to begin nursery production of yews, scaled up from 500,000 to 10 million rooted cuttings from 1991 to 1993 (Croom, 1995). The Alliance for Taxol, comprised of researchers from the USDA, the University of Mississippi, Ohio State University, and private nurseries, attempted to find ways to produce paclitaxel from the leaves of common, ornamental varieties of yew (Croom, 1995).

A breakthrough came in 1992 when the Florida State research team developed an even more efficient method to semi-synthesize paclitaxel (Stephenson, 2002). This method used needles from Asian yew or European yew trees to cost-effectively produce paclitaxel on a commercial scale. Florida State researchers patented this process, licensing it to BMS. In 1993, BMS announced it would phase out harvesting Pacific yew bark from federal lands and instead begin producing paclitaxel via this new semi-synthesis method (Goodman & Walsh, 2001).

5.6 Paclitaxel Trademark and Pricing Controversies

The FDA approved paclitaxel for treatment of ovarian cancer at the end of 1992. BMS successfully obtained a registered trademark for its new product, Taxol®, in the United States and several other countries. As noted above, Monroe Wall of the Research Triangle Institute had isolated the molecule in the late 1960s, calling it taxol. Indeed, the name taxol was in the public domain and in common usage for 20 years. A quick scan of citations in this chapter or a Google Scholar search shows that little "t" taxol was how the molecule was most commonly described. Despite various complaints, BMS still maintains the trademarked name, with the generic name assigned as paclitaxel (Goodman & Walsh, 2001). BMS began marketing paclitaxel as a branded product in 1993. While there was no patent on the paclitaxel molecule itself, BMS was given patent-like protection through its exclusive access to and control over medical data required to obtain FDA approval, in addition to the exclusive rights to harvest Pacific yew bark on federal lands.

The FDA's approval of BMS's New Drug Application to market paclitaxel for the treatment of ovarian cancer triggered a provision in federal law granting BMS five years of marketing exclusivity under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act (U.S.C. § 355(b)-(c)(3)(D)(ii) (2000)). Hatch-Waxman prohibits introduction of generic forms of a new pharmaceutical for five years. Thus, BMS was granted exclusive rights to market paclitaxel as a branded product without direct competition. BMS initially proposed a price of $700 per treatment cycle, with patients expected to average four cycles (Day & Frisvold, 1993). This price was comparable to that of other ovarian cancer treatments at the time. Paclitaxel sales rose from $162 million in 1993 to more than $1.5 billion annually by 2000. This, at the time, made paclitaxel the highest selling anticancer drug in the world (US GAO, 2003).

The price Bristol charged for paclitaxel proved controversial, especially given that significant federal funds were spent in natural product search, screening, testing, and development of the final product. Paclitaxel pricing was the subject of congressional hearings (Reynolds, 1991). Pharmaceutical R&D is a high-risk, high-payoff enterprise. The industry claims only one of 10,000 compounds analyzed ever proves useful and that 30% of new medicines recoup their average cost. Pharmaceutical industry rates of return are nevertheless quite high. From 1981 to 1990, the annual rate of return for pharmaceutical companies in the Fortune 500 was more than 25%, while it was less than 16% for Fortune 500 companies overall (Day & Frisvold, 1993).

In House Subcommittee hearings, two means were identified to control paclitaxel's price. One would have been to provide for arbitration of price disputes directly in the CRADA between the NCI and BMS. As noted earlier, language limiting price and requiring information on production costs had been deleted from the CRADA. However, simply including such language in the CRADA might have been insufficient; it would have given the NCI, a medical research agency, the task of monitoring and regulating market competition, and the agency did not have the

staff or expertise for such a job. Further, there is a moral hazard problem, as some NCI staff had moved on to work at BMS. Another strategy was for federal agencies to collaborate with more than one company to increase competition. The NCI also entered into a CRADA with Rhone-Poulenc to develop docetaxel (branded as Taxotere®). Based on the earlier semi-synthesis work of French scientists, docetaxel, whose molecular structure was similar to but distinct from paclitaxel's, could be produced using needles of the European yew tree.

Oregon's Senator Ron Wyden requested that the US General Accounting Office (GAO) evaluate the CRADA between the NIH and BMS (US GAO, 2003). The GAO reported that the US National Institutes of Health (NIH) spent $183 million on paclitaxel R&D from 1977 to 1997. BMS claimed to have spent $1 billion on R&D to commercialize paclitaxel. Still, their gross sales revenues from Taxol® sales exceeded $9 billion from 1993 to 2002. The NIH received royalties at a rate of 0.5% from a licensing agreement with BMS, receiving $35 million through 2002. In contrast, Florida State University negotiated a royalty rate of 4.2% in their agreement with BMS. Florida State received substantially more than the NIH, receiving royalties of $28 million in 1996 alone, and more than $200 million through 2000.

Not only did the federal government pay for critical parts of paclitaxel's development, it also was a major source of final drug purchases, via Medicare payments. These totaled more than $687 million from 1994 to 1999 (Hemphill, 2006). Medicare pays cancer drug suppliers based on a manufacturer average wholesale price, which can greatly exceed the actual price that manufacturers charge. The GAO estimated that Medicare was charged 6.6 times the price that other federal programs were charged for paclitaxel (US GAO, 2003; Hemphill, 2006).

In 1997, other pharmaceutical companies applied to the FDA to sell paclitaxel as a generic drug. BMS sued in a federal district court (Bristol-Myers Squibb Co. v. IVAX Corp., 77 F. Supp. 2d 606, 609 (D.N.J. 2000); Bristol-Myers Squibb Co. v. Ben Venue Labs., 90 F. Supp. 2d 522, 524 (D.N.J. 2000)), alleging violations of its patents on methods to administer paclitaxel; it was granted an additional 2.5 years of marketing exclusivity while the case was being reviewed. In 2002, 29 states filed suit against BMS in federal district court, charging it colluded with other firms to delay entry of generics (see, e.g., Ohio et al. v. Bristol-Myers Squibb, Co., No.1:02-cv-01080 (EGS) (D.D.C. Nov. 19, 2003), specifically concerning Taxol®). Generic paclitaxel finally entered the market in 2002, cutting BMS' sales revenues in half from its high in 2000 (US GAO, 2003).

Under Hatch-Waxman, a pharmaceutical company can get exclusivity protections for a brand-name product for five years but must also provide the FDA with information on patents related to that product (CRS, 2016). The FDA then lists these related patents in a publication called the "Orange Book." A company that wants to market a generic version of the brand-name drug must certify to the FDA that production of the generic version either will not infringe on patents in the Orange Book or that those patents are invalid. The potential generic producer also must notify the patent holder, who has 45 days from the notification to file a

patent infringement suit. Under Hatch-Waxman, if the patent holder files a patent infringement suit within these 45 days, the FDA *automatically* postpones approval to market the generic drug for 2.5 years (30 months). The FDA does not consider whether the infringement suit has merit. In fact, the FDA does not review the patents that companies submit for listing in the Orange Book to determine whether they are valid. This delayed generic entry costs consumers millions of dollars.

In 2003, the Federal Trade Commission released a consent order settling charges that BMS unlawfully delayed competition from generic paclitaxel and two of its other major drugs (U.S. FTC, 2003, 2004a, b). The FTC ruled that BMS abused the 30-month stay under Hatch-Waxman by making wrongful patent listings related to Taxol® and two other drugs in the Orange Book.

5.7 Yew Harvest Under Open Access

Once commercially viable methods to produce paclitaxel from other yew species were developed, production increasingly relied on Himalayan yew (*Taxus wallichiana*), European yew (*Taxus baccata*) (which also grows in parts of Africa, northern Iran, and Southwest Asia), and other Asian yew species. Yew harvesting for paclitaxel production in China and South Asia was not carried out following the strict harvesting guidelines required on US federal lands. Rather, it was done under an essentially open access regime. Rikhari et al. (1998) reported "[e]xcessive harvesting of *T. baccata* from the forests all along the Indian Himalaya for Taxol." From 1996 to 2001, illegal extraction of yew leaves averaged 6000 tons annually (CITES, 2005).

In 1995, the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) Secretariat listed Himalayan yew as an Appendix II species (CITES, 2021). CITES regards Appendix I species as threatened with extinction, while Appendix II species are those subject to significant trade-related depletion. Under CITES, exporters of Appendix II species or designated products from those species must obtain export permits from their home governments. Importers are not required to have import permits, but importing countries are required to inspect shipments for proper export permits. Himalayan yew became a listed species, but chemical extracts of yew (used for paclitaxel production), the major part of yew-related trade, were exempt (CITES, 2004).

Trade in yew and its derivatives from other Asian yews continued to increase. China became a major paclitaxel exporter but faced its own supply and illegal harvesting problems. Medical demand for Chinese yew species reduced their populations, especially in northwest Yunnan Province, where about 5000–10,000 tons of bark and 2000 tons of leaves were harvested (Schippmann, 2001). As a result, *Taxus* species have been locally eliminated from a number of Chinese counties (CITES, 2001). Yew species have been listed as endangered in the China Plant Red Data Book: Rare and Endangered Plants. Part of harvesting included felling yew trees. China banned domestic, wild harvest of yews for paclitaxel

production in 2003 (Mulliken & Crofton, 2008). Prior to the ban on wild collection, more than 80% of the *Taxus* resources of Yunnan province were destroyed. Chinese paclitaxel production increasingly relies on yew imported from Myanmar.

Yew harvesting for paclitaxel had required permits in China, but illegal harvesting persisted. At the CITES 13th Conference of Parties in 2004, China and the United States jointly proposed that chemical extracts of yew species be included in Appendix II and that the number of Asian yew species listed be expanded. This proposal was accepted by other parties to the Convention. In 2004, the World Wildlife Fund listed Himalayan yew in their "top ten" species threatened from illegal trade (WWF, 2004). Currently, *Taxus chinensis*, *Taxus cuspidata*, *Taxus fauna*, *Taxus sumatrana*, and *Taxus wallichiana* are listed as CITES Appendix II species (CITES, 2021).

The International Union for Conservation of Nature (IUCN) has maintained a Red List of Threatened Species since 1964. Species are categorized as least concern, near threatened, vulnerable, endangered, critically endangered, extinct in the wild, and extinct, based on the severity of the extinction threat. These assessments are based on population reduction rate, geographic range, population size, population restrictions, and probability of extinction. *Taxus baccata* (common yew) and *Taxus cuspidate* are listed as of least concern, with increasing and stable populations, respectively. Eight other species are estimated to be in population decline. Of these, Florida yew (*Taxus floridana*) is critically endangered, four are endangered, one is vulnerable, one is near threatened, and one is of least concern (IUCN, 2021). Of these, the four in the Western Hemisphere are most threatened by habitat conversion and logging. For four Asian species (*Taxus mairei*, *Taxus chinensis*, *Taxus wallichiana*, and *Taxus contorta)*, harvesting for medicinal purposes is a major threat (IUCN, 2021). For *Taxus wallichiana*, harvesting for paclitaxel production contributed to reported population loss of more than 50% in China and more than 90% in India and Nepal. For *Taxus contorta*, overharvesting for paclitaxel production has reduced populations up to 90% in northwest India and western Nepal (Mulliken & Crofton, 2008).

6 Economic and Policy Implications

Paclitaxel's development sparked controversies over pharmaceutical pricing and forest management as well as protection of and trade in endangered species. We use the case study to draw some policy lessons.

6.1 Economics of Bioprospecting: Some Reevaluation

First, the search, discovery, and commercialization process for paclitaxel differed fundamentally from how it had been modeled in some of the more influential

economics literature on bioprospecting. A key assumption of some of these studies was that discovery of a valuable compound in one species would render similar species producing the same compound redundant, and hence of no marginal value for the purpose of developing that particular drug (Simpson et al., 1996; Rausser & Small, 2000; Costello & Ward, 2006). However, sources of compounds have a vector of attributes. In the case of paclitaxel, this included solubility, toxicity, other side effects on patients, compound yield from raw materials, accessibility of source species, and the renewability of source species. Species do not fit the simplified "hit" or "miss" dichotomy. Because it proved to be so logistically difficult to harvest Pacific yew bark in endangered species habitat in Pacific Northwest old growth forests, attention turned to producing paclitaxel (or similar drugs) from other yew species. Paclitaxel's discovery and development showed that a discovery that a compound from one species has commercial potential can increase the value of a similar species. This calls the entire redundancy premise into question.

Polasky and Solow (1995) provided a more realistic specification. Contrary to the models assuming redundancy, they noted that species sharing a valuable trait may not be perfect substitutes. Search will not necessarily end with the discovery of the first species with the trait (the one-hit assumption). They presented an illustrative example from a "multiple-hit" model with imperfect substitution, where the value of the marginal species can be three times higher than under a single-hit specification. They also argue that discovery of a beneficial trait can induce *greater* search efforts among similar species. This is because similar species will have a higher conditional probability of sharing that beneficial trait. This is indeed what happened in the case of Pacific yew. Rather than terminating interest in other yew species as cancer treatments, the discovery spurred extensive screening and research into other yew species. Some of these other species are the main sources of paclitaxel today. In similar fashion, the drug diosgenin, used in oral contraceptives, was first discovered in the Mexican *Dioscorea* species. A main source now comes from *Dioscorea deltoidea*, native to South Asia.

The fact that a potentially valuable compound found in one species may also be present in a number of similar species presents challenges for source countries wishing to monetize their genetic resources. The idea that bioprospecting contracts could provide developing countries with significant financial rewards is based on the premise that the source location is a relatively exclusive source of the biological material. The possibility of multiple alternative source locations means that individual countries will have substantially less bargaining power with pharmaceutical companies. The presence of even an inferior substitute could serve to cap the price a country demanded for source materials or the market price a pharmaceutical company could charge for a finished product. Afghanistan, Bhutan, China, India, Indonesia, Malaysia, Myanmar, Nepal, Pakistan, the Philippines, and Vietnam have all been suppliers of Himalayan yew for paclitaxel production. None had entered into lucrative bioprospecting agreements. Payments to first-line harvesters in South Asia have also been quite low (Mulliken & Crofton, 2008).

The commercialization of paclitaxel corresponded to what Barrett and Lybbert (2000) characterized as a "single shot" process, where materials are discovered

and tested, but then production is conducted ex situ. From the outset of the NCI-BMS CRADA, there were far-reaching efforts to find alternatives to Pacific yew. These included plantation cultivation, tissue culture, and ultimately semi-synthesis. Efforts continue to pursue options relying on tree plantations, plant tissue culture, and synthetic biology (Malik et al., 2011; Expósito et al., 2009; Liu et al., 2016). By 1994, the Pacific Northwest was no longer an important source of supply for paclitaxel. Pacific yew harvesting was only a small and temporary source of jobs and income in the region. The main beneficiaries of paclitaxel's discovery and development were cancer patients throughout the United States and the world, not rural communities in the Pacific Northwest.

Natural products remain a major source of drug discovery, either directly or as "blueprints" or "designs" for novel chemical structures. In a survey by NCI scientists, of the 1394 small-molecule approved drugs worldwide from 1981 to September 2019, 6.1% were natural products or natural product botanicals, 27.5% were derived from a natural product (often relying on semi-synthesis), and 30.5% were "natural product mimics" produced via total synthesis but whose molecular framework came from a natural product (Newman & Cragg, 2020). The importance of drugs "based on" but not necessarily made from natural products suggests that genetic materials are serving more as sources of information than as raw materials in production. Contrary to the hopes of conservationists, the experience with paclitaxel and trends in drug development suggest that bioprospecting contracts are not likely to create strong incentives for in situ conservation and sustainable harvesting, which presumes continued harvesting of resources from their source.

Barbier and Aylward (1996) suggested that, while bioprospecting would be unlikely to encourage investments in habitat preservation, it could encourage investments in taxonomic and other scientific information. The experience of paclitaxel appears consistent with this argument, as its discovery touched off different research into the ecology and chemical properties of Pacific yew as well as other yew species. There were large gaps in basic information about the Pacific yew prior to paclitaxel's discovery. Barbier and Aylward's (1996) conclusions appear consistent with ICBG (International Cooperative Biodiversity Group) projects that have funded such taxonomic information collection but have yet to yield significant royalty payments to finance large-scale conservation effort (Rosenthal, 1997; Day-Rubenstein & Frisvold, 2001). More recent work also suggests that bioprospecting can build scientific capacity in source countries (Miller et al., 2005; Medaglia, 2019; Leal et al., 2020). But, again, there is little indication of this translating into much direct funding for habitat protection.

6.2 Health Agencies Making Economic Policy Decisions

A curious aspect of paclitaxel development was the fact that health agencies – namely, the NCI and FDA – were put in charge of key aspects of what are essentially economic policies: royalty payments to the government, product price, firm entry,

and patent length decision. The NCI negotiated the terms of the CRADA and ultimately omitted the "reasonable price" clause from the agreement. Regarding the royalty percentage negotiated with BMS, Florida State University appeared to extract a much better financial deal than NCI did. Of course, the NCI's primary objective was getting paclitaxel tested, approved, and available to cancer patients quickly. For the cancer patients themselves, that may also be more important than whether BMS was able to extract overly favorable terms in the CRADA. The Hatch-Waxman Act, by allowing an automatic delay in the entry of generics and placing the FDA in charge of listing patents, again placed a health agency in charge of what is essentially antitrust policy. Once the drug was developed, stalling the availability of generics only made treatments for cancer patients less available and more expensive. The consent order on BMS – and the events that led up to it – raise questions about the appropriateness of having FDA assess (or simply assume) the validity of patent claims.

6.3 Substituting One Extinction Threat for Another

One critical lesson we can draw from the experience of paclitaxel is that a bioprospecting discovery can replace one biodiversity threat with another. Species face two main extinction threats (Swanson, 1994). The first is the result of habitat conversion. This occurs if species are not valued (or are undervalued) and their habitats are converted to another economic use, such as crop or livestock production (Innes & Frisvold, 2009). The second threat is overexploitation, where the species has economic value but its use or extraction is managed in an open-access regime. Bioprospecting can exchange one extinction threat (habitat conversion because a species is not valued) for another (overexploitation because the resource is valued in an open-access regime).

Advocates of bioprospecting have argued that forests can be managed as extractive reserves, where genetic resources can be sustainably harvested for pharmaceutical development. Yet, the experience of paclitaxel development in the United States illustrates how difficult this can be. The United States, a developed country with great scientific capacity, environmental protection mechanisms, centralized resource management agencies, and congressional oversight, had difficulty developing harvesting plans. Indeed, harvesting guidelines required an act of Congress (the Pacific Yew Act). Even then, there were nontrivial cases of poaching.

Creating market demand for species without clearly defining rules for their extraction and use can lead to overharvesting rather than conservation. Indeed, overexploitation of plants and animals to meet the demand for ingredients in traditional medicines poses a significant threat to many species (Schippmann, 2001; Byard, 2016; Cunningham et al., 2019; Kumar et al., 2020; Alves et al., 2021; Gusain et al., 2021; CITES, 2021; IUCN, 2021). In response to demands for paclitaxel production, Asian yew species have been harvested rapidly in areas with

less well-defined resource use regimes. A number of yew species are designated as threatened due to such overexploitation (CITES, 2021; IUCN, 2021).

6.4 Using Lotteries to Fund Conservation

From the outset, the issue has not been whether tropical forests and other wild areas can provide enormous benefits via medical discoveries. The example of paclitaxel and other historical discoveries demonstrates that the answer is yes. The question, rather, is whether bioprospecting contracts can provide significant financial incentives to encourage habitat conservation. Here, the lessons of paclitaxel development cast doubt on bioprospecting as a vehicle to finance conservation. From 1960 to 1981, the NCI-USDA program screened more than 130,000 plant and animal extracts (Stephenson, 2002). Of all the compounds screened and dozens that looked promising initially, only paclitaxel (admittedly, a blockbuster drug) moved to the stage of testing on humans (Stephenson, 2002). It took over 30 years from the time the Pacific yew bark was first collected to the time the FDA approved paclitaxel. One blockbuster drug over 30 years from 130,000 screenings has a reward structure very much like a lottery. As such, bioprospecting is akin to purchasing a lottery ticket to fund public investments. Even if returns to bioprospecting could be monetized by source countries, this is a too occasional and uncertain source of revenue for sustained conservation needs. Potential medical values are just one of many reasons biodiversity is worth preserving (Heal, 2020). Yet, the promise of bioprospecting as an effective means to finance this preservation remains unfulfilled.

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