Introduction

> One of the few organic compounds, which, like benzene and aspirin, is recognizable by name to the average citizen.[1]

> . . . taxol is the first naturally occurring plant-derived drug product to gain FDA approval in more than a quarter of a century.[2]

This book is the history of taxol, the anti-cancer drug, and of the tree, *Taxus brevifolia*, the Pacific yew, from which it derives. Our story begins in the 1960s when Western science 'discovered' the existence of taxol in the yew bark and ends, for our purposes, in the 1990s when corporate capitalism took over the drug and abandoned the tree. Taxol is arguably the most celebrated, talked about and controversial natural product in recent years: celebrated because of its efficacy as an anti-cancer drug and because its discovery has provided powerful support for policies concerned with biodiversity; talked about because in the late 1980s and early 1990s, the American public was bombarded with news reports and special programmes about the molecule and its host; and controversial because during the early 1990s the drug and the tree became embroiled in a number of very sensitive political issues with wide implications for the conduct of public policy.

Taxol is currently available in clinics throughout the world for the treatment of ovarian and breast cancer. It is approved for use against non-small cell lung cancer and Kaposi's sarcoma in the United States; approval in other countries is pending. Clinical trials for other types of cancer continue world-wide; however, from early results, it is expected it will be approved for other uses. It is the best-selling anti-cancer drug ever. World sales reached $1.2 billion in 1998 and are expected to continue growing for the foreseeable future.[3] Taxol is made and sold by Bristol-Myers Squibb, the world's largest supplier of anti-cancer drugs, and the fourth largest pharmaceutical company in the world.[4] Taxol is Bristol-Myers Squibb's second biggest pharmaceutical earner,

accounting for about ten per cent of the company's total pharmaceutical sales.[5] The drug is widely available but at a price basically set by Bristol-Myers Squibb, although the first thirty years of the research and development of taxol was carried out in the public sector, and managed and funded by the United States Government.

As the source of taxol, the Pacific yew, *Taxus brevifolia*, has also had its share of fame. For a while in the early 1990s it became a symbol of the value and precariousness of the old-growth forest in the Pacific Northwest. Although the media portrayed a battle between the defenders of the habitat of the spotted owl, and the oncologists and their patients who needed the tree bark for making taxol, in the Pacific Northwest it was hoped that the harvesting of *Taxus brevifolia* for taxol might provide a new source of revenue for a depressed area, and possibly an example of how to use and preserve a forest habitat. These hopes were dashed when Bristol-Myers Squibb adopted a semi-synthetic method of production that did not use *Taxus brevifolia* or any other American tree.

Much has been written about taxol, but mostly in newspapers, magazines or journals.[6] Less ephemeral accounts, sometimes by participants in the story, have told only part of the tale. Looking back, the story of taxol can be told either as a triumph of science and individual effort or dismissed in a few words as it was by Bruce Ross, who held a highly responsible position at Bristol-Myers Squibb in 1992. In 1998, he was quoted as saying: 'Taxol was developed in the early 1960s and languished for almost 30 years because nobody could make it.'[7]

Ross's dismissive attitude to the work of the National Cancer Institute is representative of Bristol-Myers Squibb's version of the history of taxol. In a published report the company writes: 'It was not until 1971 that both chemical and biological testing enabled the isolation of paclitaxel, initially described as "compound 17", as the molecule responsible for remarkable antitumor effects against murine tumors and leukemias. In this effort, Dr. Wall was helped by his collaborator Dr. Mansukh C. Wani.'[8] In fact Monroe Wall named the bioactive compound from the bark of *Taxus brevifolia* 'taxol' in 1967.[9] Wall and Wani published their account of the structure of taxol in 1971, but had been submitting their accounts of the compound to the National Cancer Institute under the name 'taxol' since 1967. The first published use of the name 'taxol' was in 1969.[10] It was only in 1990 that Bristol-Myers Squibb applied to trademark the name 'taxol', and the name was not registered until 1992. It was then that taxol became Taxol® and the generic name of 'paclitaxel' was approved. Since that time Bristol-Myers Squibb have insisted that the molecule be referred to as paclitaxel and that the drug is called Taxol®, even, as the excerpt from their report shows, when it means rewriting history.

When this kind of misrepresentation is perpetrated it is essential that a properly documented account of what actually happened is published. Fortunately not only are many of the protagonists of the taxol story alive, but many kept documents, letters and memos, as well as publications, and have been generous in sharing them with us. We have been able to use material from the National Cancer Institute and the United States Department of Agriculture, as well as congressional hearings, newspaper reports, unpublished papers, papers in journals, and articles in magazines. The breadth and depth of these sources, the way in which they reinforce and interact with one another, offers the best hope of presenting as complete and coherent a version of the taxol story as possible.

How to organize such a large amount of material, oral and verbal, published and unpublished, and to make it as comprehensible and fascinating as it deserves to be, is a problem. Taxol is an entity with multiple identities, a natural product, an anti-cancer drug, a complex organic molecule, a biomedical research tool, an agent of political leverage, an object of hope and a bone of contention. Perhaps a biography of taxol would be the answer. Igor Kopytoff writes:[11] '. . . an eventful biography of a thing becomes the story of the various singularizations of it, of classifications and reclassifications in an uncertain world of categories whose importance shifts with every minor change in context. As with persons the drama here lies in the uncertainties of valuation and of identity.'

This is suggestive, and the method has been very successfully used by art historians in recounting the histories of art objects, but the model of personal biography does not quite accommodate taxol's peculiar state of coexistence with its source *Taxus brevifolia*, or its ability to appear in different roles in different milieus at the same time.[12] A more useful approach would be to combine biography with the approach of actor–network theory, in which the distinction between objects and humans is not given, but made and remade, and which offers the research and narrative strategy of following the object wherever it leads, thus allowing a relationally based biography to be constructed.[13] Instead of settling on one trajectory in time, or dissecting the object and its situation into different categories or compartments, one can, as Bruno Latour suggests, simply follow the 'fragile thread' of the object's associations through the various networks of which it is part.[14] 'The only task of the analyst is to follow the transformations that the actors convened in the stories are undergoing.'[15]

A major advantage of actor–network theory is its capacity to encompass transformation and change. As Michel Callon says 'the actor network should not . . . be confused with a network linking in

some predictable fashion elements that are perfectly well defined and stable, for the entities it is composed of, whether natural or social, could at any moment redefine their identity and mutual relationships in some new way and bring new elements into the network. An actor network is simultaneously an actor whose activity is networking heterogeneous elements and a network that is able to redefine and transform what it is made of.'[16] An actor, in this theory, can, of course, be a thing; humans are not privileged. Although, as Callon says 'by themselves, things don't act. Indeed, ... there are no things "by themselves." ... instead, there are relations, relations which (sometimes) make things.'[17]

All the interests of the other actors, people and things, techniques, instruments, etc. are inscribed on the object. The object becomes an archive, a text of all the actors and events that have gone before, but it is in no way static.[18] The elements are constantly regrouping and forming new objects and new networks. This recognition of the inherent instability and contingency of the actors and their networks is a central tenet of the theory.[19] Other notions specific to the theory are those of 'enrolment', 'translation', and 'obligatory points of passage'. 'Enrolment' is the process whereby one actor attempts to enlist other actors for some purpose involving imposition rather than mere invitation. The enroller is active in constructing the network, assuming the role of spokesperson, and assigning roles to the other actors; this activity is termed 'translation'. Crucial to the idea of 'translation' is the creation of 'obligatory points of passage', i.e. 'unavoidable conduits through which they (the actors) must pass in order to articulate both their identity and their raison d'être'.[20]

We have found these ideas of great value both in researching and writing about such a complex and diverse body of material. Actor–network theory is implicit throughout the text, and occasionally explicit. Welcome to the taxol/*Taxus brevifolia* network of which we are all now part.

Notes

1 Nicolaou, Dai and Guy, 'Chemistry and biology', p. 15.
2 Kinghorn and Balandrin, 'Preface', p. xi.
3 'Bristol-Myers Squibb reports record fourth quarter and annual sales (1998)', http://www.prnewswire.com/cgi-bin, 20 January 1999.
4 Barker, 'Merck', p. 39. This ranking is based on prescription sales.
5 Calculated from 'Bristol-Myers Squibb reports record fourth quarter and annual sales (1998)' http://www.prnewswire.com/cgi-bin, 20 January 1999.
6 The newspaper coverage of taxol in the early 1990s was enormous. In 1991 and 1992, for example, *The Oregonian*, Oregon's major newspaper and published in Portland, ran a 'taxol' story more than once a week on average.

Between 1990 and 1995, according to the medical database MEDLINE, about 250 biomedical articles appeared annually on the subject of taxol. Many of these accounts provided a short background to taxol's history, focusing primarily on the biological, clinical and chemical work since the 1980s. The first accounts to concentrate on the history of taxol before the 1980s were by Persinos, 'Taxol' and 'The Pacific yew and cancer'. The first review of taxol by participants in its development at the National Cancer Institute and the Research Triangle Institute began to appear from 1993. See: Suffness and Wall, 'Discovery and development'; Wall and Wani, 'Paclitaxel'; Suffness, 'Taxol'; Suffness, 'Overview'; and Cragg, 'Paclitaxel'. Joyce, *Earthly Goods*, pp. 235–248 and Fellers, 'The medicine market' are two recent general treatments that discuss taxol. See also Parks, 'Taxol' for a wide-ranging discussion of taxol based on published materials.

7 Quoted in Fellers, 'The medicine market', p. 24. Ross, according to this article, was Bristol-Myers Squibb's chief negotiator in a meeting with the National Cancer Institute in July 1992 concerned with setting a price for taxol.

8 Bristol-Myers Squibb, 'The development of Taxol® (paclitaxel)', March 1997.

9 A full account of Wall's work with taxol in the 1960s can be found in Chapter 2.

10 Perdue and Hartwell, 'The search for plant sources'.

11 Kopytoff, 'The cultural biography', p. 90.

12 In 1995, the Association of Art Historians had 'Objects, histories and interpretations' as the theme of their annual conference, in London. A whole session was devoted to the life histories of artefacts. Debbora Battaglia argued this point in her paper, 'Do objects have individual histories: a critical examination from postcolonial New Guinea'. We have shown, in other places, that the biography of an object is written by the network dynamics of which the object is a participant. See: Goodman, 'Plants, cells and bodies'; Walsh, 'Industrial R&D', pp. 323–334; and Goodman and Walsh, 'Attaching to things'. Contingency, or non-essentialism, is central to Kopytoff's ideas about the biography of objects. This seems to have been overlooked in a recent attempt to apply Kopytoff's ideas to the case of pharmaceuticals. Instead of contingency the reader is offered a programmatic biography, following life cycles within prescribed stages and teleological in character – see Van der Geest, White and Hardon, 'The anthropology of pharmaceuticals'.

13 Following 'actors' was proposed by Bruno Latour as a research methodology in Latour, *Science in Action*. The literature on actor–network theory is vast, growing and changing. Aside from the writings of Michel Callon, Bruno Latour and John Law, those most frequently associated with this analytical tool, there are a number of good studies using it, and a number of good overviews. On case studies, two of the best are also early examples of this kind of analysis: Callon, 'The state' and Callon, 'Some elements'. Other notable case studies are: Singleton and Michael, 'Actor–networks and ambivalence' and Prout, 'Actor–network theory'. Both cover the literature well. As for overviews, one of the best is also one of the most recent. Though written primarily for an audience of geographers, the coverage of actor–network theory is excellent. See Murdoch, 'Inhuman/nonhuman/human'. Another useful overview and critique can be found in a special issue devoted to the topic 'Humans and others: the concept of "agency" and its attribution,' *American Behavioral Scientist* **37** (1994), 731–856. In 1997, the Centre for Social Theory and Technology at Keele University, UK, hosted a

workshop entitled 'Actor Network Theory and After'. The internet site for the workshop which contains several of the plenary papers and links to bibliographical information is at http://www.keele.ac.uk/depts/stt/stt/ant. Some of the papers have been published in Law and Hassard, *Actor Network Theory*. See also Law, 'Notes on the theory'.

14 Latour, *We Have Never*, pp. 2–3. Latour's thoughts on following actors also appears in anthropology as 'multi-sited ethnography' – see Marcus, 'Ethnography'.

15 Latour, *The Pasteurization*, p. 10.

16 Callon, 'Society in the making', p. 93.

17 Callon and Law, 'Agency', p. 485. See also Michael, 'Narrative space'. On identity, see Michael, *Constructing Identities*, pp. 79–104.

18 For similar ideas, see Latour, 'Do scientific objects' who writes: '... the meaning of the word *substance* changes profoundly and becomes the gradual attribution of stable properties attached by an institution to a name lastingly linked to a practice, the whole circulating in a standardized network,' – p. 85. See also Strathern, 'What is intellectual property after?' and Law, *Organizing Modernity*. Marilyn Strathern, referring to John Law's concept of relational materiality, has given the following interpretation of objects. 'If people were not divided into different kinds of experts then we would not have an expert description of the substance divided up like that. Moreover because experts get themselves into permanent positions of competence, as the authority on this or that aspect, they presuppose that there is no substance which could not be divided up thus. Any organic substance can have a biochemical analysis done on it. Whether anyone wishes to will depend on other interests, but properties attributed to the thing will summon forth their own experts, and thus justify the divisions between people. Things come to seem heterogeneous this way ... the thing itself will identify what people have to be mobilised.' – pp. 172–173.

19 An appeal to take account of and incorporate contingency in historical studies of science (and technology) is not new. See, for example, Shapin, 'History of science'; MacKenzie, 'Marx and the machine'; Noble, 'Social choice'; and David, 'Clio'. For environmental history, see also: Taylor, 'Making salmon'; Dann and Mitman, 'Essay review'; and McEvoy, *The Fisherman's Problem*. Donna Haraway has also made a plea for contingency over essentialism in cultural studies of science – see Haraway, 'Universal donors'. On contingency from a philosophical perspective see Ben-Menahem, 'Historical contingency' and Rorty, *Contingency, Irony, and Solidarity*. For contingency in the writing of natural history, see Gould, *Wonderful Life*, pp. 284–285.

20 Singleton and Michael, 'Actor–networks and ambivalence', pp. 229–230.

Part I

Agents

1

Cancer Chemotherapy: Plant Knowledge and Practice

In 1960, the National Cancer Institute (hereafter NCI) and the United States Department of Agriculture (hereafter USDA) began an inter-agency programme to procure and screen plant products as potential anti-cancer agents. It was an ambitious programme that would consume vast amounts of labour and laboratory time. The programme lasted just over twenty years and, although a huge number of plants were screened, no plant product reached the clinic during the period of the programme's existence. Though samples of the Pacific yew, *Taxus brevifolia*, were procured in 1962, taxol, the tree's promising compound, had not yet reached clinical trials by the time that the programme was wound up.

To follow and understand taxol's path through the American cancer research and biomedical community, it is necessary to explore, in some detail, two principal contexts: the history and development of cancer chemotherapy and its target; and the structure and strategy of the NCI–USDA plant screening programme.

Cancer Chemotherapy and the Malignant Cell

The years from roughly 1945 to 1970 were formative in the history of cancer chemotherapy in two principal senses.[1] First, chemotherapy came to achieve status as a therapeutic regimen for the cure or at least the palliation of cancer, towering over surgery and radiotherapy, during this period.[2] Secondly, chemotherapy became a research regimen in biomedicine that mirrored, incorporated and modified models of large-scale cooperative ventures in other scientific endeavours.

The medical literature abounds with reviews of the historical development of cancer chemotherapy. The general consensus of the literature is that 'modern' cancer chemotherapy emerged from research in gas warfare by the Americans and British during World War II.[3] The landmark papers on nitrogen mustards contributed to a heightened

interest and belief in chemical agents rather than radiotherapy and surgery as the techniques of choice in cancer treatment:[4] attacking the 'biochemical soil' in which cancers arose, as a leading advocate of chemotherapy put it.[5] Wartime programmes devoted to the large-scale production of penicillin and antimalarial drugs built on the success of the sulpha drugs of the late 1930s in convincing many people that disease could be eradicated by chemical means.[6]

The bulk of experimental and clinical research on chemotherapeutic agents from roughly 1945 to 1960 focused on two kinds of chemicals and two mechanisms of action: alkylating agents that combine chemically with cellular constituents, and antimetabolites that compete with the substrate of an enzyme system for engagement in metabolism.[7] Steroid hormones and antibiotics were also examined for chemotherapeutic potential. Cortisone, for example, was studied for its ability to regress tumours long before its more famous effects on arthritis were observed.[8] Among antibiotics, the only one to be used clinically was actinomycin D.[9]

Cancer chemotherapy was not then the core activity it would become. Research glided between experimental (laboratory) activities, predominantly biological work on animal tumours, and clinical trials on humans.[10] Until the 1940s, experimental cancer chemotherapy was carried out by many different investigators in many different disciplinary specialties – biology, physiology, pharmacology and botany, and in many different sites – pathology laboratories, hospitals, universities, and private biological research institutes.[11] One of the most important of the latter type was the Rockefeller Institute which, for many decades, had been actively engaged in experimental cancer research. James Murphy, who was with the Institute from 1911 to his death in 1950, summed up the achievements of cancer research during his period of activity.[12] According to Murphy, the chief insights included: (i) that tumours could be transplanted, a fact that demonstrated that malignancy was centred in the cells; (ii) that genetic factors influenced cancer but that they varied within the population; (iii) that there were certain agents called carcinogens that induced tumours; and (iv) that in the change from normality to malignancy, the cell was altered and that proliferation became automatic and therefore no longer dependent on the causative agent.[13]

With the ending of World War II, the diffracted nature of experimental and clinical cancer chemotherapy gave way to a more standardized practice. As architects of early post-war American chemotherapy, Cornelius Packard 'Dusty' Rhoads and the Sloan–Kettering Institute were instrumental in this change. Rhoads began his professional career in haematology at the Rockefeller Institute in 1928,[14] and in 1933 was

put in charge of the clinical haematology service where he remained until 1940 when he was made director of the Memorial Hospital for Cancer and Allied Diseases.[15] Within a very short time of the date of this appointment, Rhoads became the Chief of the Medical Division of the Chemical Warfare Service of the United States Army. Rhoads assembled under him an impressive array of medical scientists. Many of them joined him after the war at the Sloan–Kettering Institute and those that did not found their way into other cancer research centres in the United States.[16]

It was during his time as Chief of the Division that experiments were conducted with nitrogen mustards, investigating their pharmacology, toxicology and mechanism of action: according to one commentator, nitrogen mustards became 'a model for the study of antitumor drugs'.[17] Once the war ended and the ban on public statements about this research was lifted, it was Rhoads who made the knowledge public to the American Medical Association.[18] At the close of the war, the work on nitrogen mustards came under the direction of the Committee on Growth of the National Research Council who, in turn assigned the work to three institutions, one of which was the Memorial Hospital.[19]

The Sloan–Kettering Institute was founded in 1945 and rapidly became the largest private cancer research institute in the United States. In tracing the first few years of its history, the historian Robert Bud reminds us that the institute was founded on industrial principles of organization and practice.[20] Not only were its founders and many of the trustees industrialists – Alfred P. Sloan and Charles F. Kettering of General Motors, Frank Howard of Standard Oil – but it also expressly adopted a programme of research modelled on the industrial laboratories of such companies as Bell, DuPont, General Motors, etc.[21] The press release announcing the founding of the institute contended that its task was to 'concentrate on the organization of industrial techniques for cancer research'.[22]

Precisely what was meant by the 'organization of industrial techniques' would only become apparent as the system of research evolved over the years. What was emphatically clear, however, was that the centrepiece of the entire organization was the cell. Rhoads had a deep conviction of the truth of the central tenet of chemotherapy, namely that there were chemical agents that could selectively destroy or control the cancer cell, in contrast to the prevailing focus on surgery and radiotherapy. This was founded on his own experience with nitrogen mustards and laid the foundation of what he called 'an empiric attack on cancer'.[23] The laboratories at the institute began to construct an organization and programme to fulfil the promise. The structure of the organization followed on from the strategy of testing as many