Antiangiogenesis Research and the Dynamics of Scientific Fields: Historical and Institutional Perspectives in the Sociology of Science

David J. Hess

Citation: Hess, David J. 2006. "Antiangiogenesis Research and the Dynamics of Scientific Fields: Historical and Institutional Perspectives in the Sociology of Science." In Scott Frickel and Kelly Moore (eds.), *The New Political Sociology of Science: Institutions, Networks, and Power*. U. Wisconsin Press. Pp. 122-147.

In 1958 a Harvard Medical School student named Judah Folkman worked with an MIT engineer to develop an implantable pacemaker. Because the medical school did not seek patents at that time, the two researchers published the results and left the product in the public domain for firms to commercialize (Cooke 2001: 37, Folkman and Watkins 1957). In the intervening years Folkman developed a theory of cancer based on angiogenesis (that is, the idea that tumors required the growth of blood vessels), and he also helped pioneer a new level of university-firm collaboration. By 1998 his work was generating increasing attention among researchers, biotechnology firms, drug companies, and the major media. In contrast, in 1957 a young associate professor at Columbia Presbyterian Medical Center named John Prudden found that bovine cartilage could accelerate the healing of wounds and reduce inflammation in rats (Prudden, Nishikara, and Baker 1957). Over the decades he developed a cartilage-based therapy for cancer, but when he died in 1998, his approach was largely lost to mainstream medicine. The story of the growth of antiangiogenesis drugs, considered in comparison with the parallel story of the stunted development of cartilage research and related natural products, provides an opportunity for the sociology of scientific knowledge to consider theoretical frameworks that examine institutional factors such as changing regulatory policy, commercialization, and social movements.

Theoretical Background

What is at stake in revived attention to institutional factors such as states, markets, and social movements in science and technology studies? In Politics on the Endless Frontier Kleinman suggests that the issue involves the conflict over democratic participation science and

technology policy, which in the U.S. dates back at least to the state funding order that emerged after World War II. Whereas Vannevar Bush, a former vice-president of MIT and the head of the Office of Scientific Research and Development during World War II, advocated a large degree of autonomy for the scientific community, the New Deal Senator Harley Kilgore advocated a funding model that included participation from representatives of farmers, labor unions, and the public. The Bush model eventually triumphed, and the institution of science was cloaked in the policy of "exceptionalism," that is, the view that high levels of autonomy are socially valuable.

The autonomy assumption was defended not only by scientists but also by sociologists and philosophers of science (Daniels 1967, Mulkay 1976, Fuller 2000). The embrace of the autonomy assumption in science studies was evident in various research traditions, including Merton's depictions of science as a self-regulating system and Kuhn's account of paradigm change as governed by epistemic relations internal to the scientific field (Merton 1973, Kuhn 1970). To some degree the subsequent generation of studies in the sociology of scientific knowledge (e.g., Knorr-Cetina and Mulkay 1983)—which emphasized the microsociology of laboratories, discourse, networks, and controversies—also represented a continuation of the autonomy assumption (Hess 2001a: 39-42). Although those studied tended to emphasize the agency of scientists, their networks, and related microsociological units of analysis, they provided glimpses of the causal shaping role of states, firms, and social movements in the making of scientific knowledge. Attention to institutional factors was also evident in other STS traditions, especially the Marxist literature (e.g., Bernal 1969, Hessen 1971) and the interests analyses of the late 1970s (MacKenzie and Barnes 1979), but also Merton's more Weberian work (e.g., Merton 1970, orig. 1932). Likewise, the work of anthropologists and feminists in the 1980s and 1990s drew attention to macrosociological categories of analysis, social problems, culture and power, and interactions with lay groups and social movements (Hess 2001b). In significant ways their work was parallel to renewed attention to structure and external institutions in the sociology of scientific knowledge (e.g., Kleinman 2003).

Drawing on the two strands of the post-laboratory studies literature, this essay contributes to the renewed attention to institutional factors such as states, markets, and social movements by arguing for the value of a more deeply historicized sociology of scientific knowledge. Neither the Mertonian nor the constructivist research traditions emphasized the questions raised in a historical sociology of modernity, yet those questions are often very close

to the surface of the new studies of regulatory politics and expertise, commercialization and privatization, civil society, social movements, public understanding of science, and public participation in science (Misa et al. 2003). The new problem areas often involve reference to contemporary historical change, which is framed under various rubrics (e.g., late capitalism, postmodernity, reflexive modernization, and globalization). My own view is that modernity needs to be conceptualized not as an event but as an ongoing process that has taken on specific forms during the last decades of the twentieth century, but those forms are largely continuous with long-term historical developments since at least the sixteenth century. As a result, early and mid twentieth-century social theories of modernity continue to be of value, even if they are in need of revision.

This essay hypothesizes specific tendencies in the contemporary historical development of science as a field of action. The term is borrowed from Bourdieu (e.g., 2001) but is located in a more historical sociological perspective based on the following four processes.

1. Expansion of scale. In laboratory sciences the cost and scale of research has increased and outpaced the ability of public institutions to fund them. As scale increases, new arrangements with the private sector have become necessary, and ongoing negotiations over central control and local autonomy occur. The Bush/Kilgore debate is merely one example of an ongoing negotiation of the relative autonomy of scientific fields, which continues today in debates over commercialization and the university.

2. Differentiation of institutions. Human and organizational actors in scientific fields increasingly face conflicts of coordination and alignment of roles and organizational goals with those of other fields of action. For example, scientists and universities develop increasingly complex goals as they negotiate their roles in education, research, fundraising, management, policymaking, citizenship, community development, and entrepreneurship. New boundary roles and organizations emerge to negotiate the increased complexity, which in turn generates further differentiation of fields of action (Frickel 2004, Guston 2001, Moore 1996).

3. Universalization of values. The cultures of scientific fields tend to become increasingly universalistic in the sense of developing increasingly formalized methodologies and methods of dispute resolution among competing research networks. In the applied fields, such as clinical medicine, regulatory policies encode the universalism through mandated standards that determine the translation of laboratory findings into clinical applications. The formalization of methods and standards for acceptance of both facts and artifacts creates conflicts over access

to the means of knowledge production and clashes between expert and lay positions on knowledge-making priorities.

4. Denaturalization of the material world. Both research technologies and the technologies/products generated by research tend to become increasingly synthetic or distanced from living entities over time. In scientific fields research innovation is driven in part by the problem of diminishing returns of research efforts to a given method, which results in efforts to find new research methods and technologies (Rescher 1978). Patent law and the commercialization of research also drive an increasing emphasis on invention, innovation, and synthesis. However, technological innovation also generates new hazards, side effects, and risks (Beck 1992), and as a result it drives an ongoing negotiation between new technologies and their societal and environmental implications. The safety and environmental concerns raised by civil society organizations create an ongoing negotiation of innovation oriented toward profits versus societal and environmental amelioration.

The Case Studies: Background

The empirical research presented here develops a comparative analysis of two American research and therapy fields for cancer, one successful the other unsuccessful. The dual case studies provide a good example of why the sociology of scientific knowledge needs to take into account historical changes such as commercialization, new regulations, and civil society participation. For example, the development of the two research programs takes place within a rapidly changing context of commercialization of medical research. The Bayh Dole Act of 1980, which facilitated patenting and licensing for universities, is generally considered the watershed moment in commercialization of university-based research in the U.S., but in the case examined here some of the partnerships predated the act and suggest how commercialization was a much longer-term process. The commercial appeal of patented drugs makes it easier for one pathway of scientific research, drug-based angiogenesis research, to overcome significant opposition from scientific and medical elites, whereas an alternative pathway, cartilage-based research, remained underfunded and enveloped in controversy.

With respect to the regulatory function of states, another watershed moment was the passage in 1962 of the Kefauver-Harris amendments to the Food, Drug, and Cosmetics Act of 1938. The amendments, which were in response to the safety concerns raised by thalidomide, created new standards of efficacy and higher standards of safety for drug approval, but they

significantly increased the cost of bringing a new drug to market. By the late 1990s the research and development cost of bringing a drug to market has been estimated to be as high as $800 million, although some studies indicate that after-tax research costs are only a tenth of that figure (Young and Surrusco 2001). Still, even the lower end of the estimate range represents a significant investment that drives the preferences of capital-bearing private-sector firms to favor the financial security of drug-based patents, in contrast with the uncertainties of the intellectual property rights associated with food-based products. However, the food/drug distinction has also undergone change; under the Dietary Supplement, Health, and Education Act (DSHEA) of 1994, the regulatory system in the U.S. grappled with an emergent category between food and drug—the nutritional supplement or nutraceutical—and granted wide over-the-counter access while restricting manufacturers from making claims about treating disease.

A third area of historical change has been the development of civil society organizations. Behind the appeal of both antiangiogenesis drugs and cartilage-based products is a patient-driven reform movement that has demanded changes in the therapeutic regimes of chemotherapy and radiation therapy. The movement existed before the 1960s, but it coalesced into a mass social movement to protest the suppression of laetrile in the 1970s, and by the mid 1980s it had diversified into a broad-based alternative cancer therapy movement (Hess 2003). Alongside the patients stand many doctors who are frustrated by the high toxicity and low efficacy of the conventional cancer therapies, but there is also a history of opportunists who have developed proprietary products, made excessive health claims, and preyed on the vulnerabilities of cancer patients. As a result, the leaders of the patient advocacy movement are very cautious of leading patients toward products that lack efficacy, and they sometimes put the brakes on over-stated claims, including those associated with shark cartilage.

The changes in regulatory policies, intellectual property regimes, and social movements intersected with many other historical changes that can only be flagged here. For example, the medical profession itself was losing autonomy due to the rise of countervailing powers such as health maintenance organizations and patient advocacy movements. The resulting decline in autonomy helped open the door to the proliferation of complementary and alternative cancer therapies. Likewise, research methods were undergoing shifts that both favored drug development (through the increasing emphasis on clinical trials as the standard of evaluation) and allowed spaces for evidence-based medical claims for the complementary and alternative

therapies (through the development of retrospective methods and databases with historical controls).

The case studies presented here draw on primary and secondary sources, and they are part of a broader research project that has involved over a decade of ethnographic observation, semi-structured interviewing, and archival research in the U.S. and other countries. The case study method is widely used in the STS field, and it is modified here in two ways that are consistent with the theoretical framework. First, the use of closely related but inverted "twin" cases of success and failure is used to facilitate the development of a non-autonomous analysis that includes regulatory, private sector, and social movement factors (see also the similar comparative strategy adopted by Woodhouse, this volume). Second, the historical scope of the cases is long term (that is, decades) rather than short term. The longer temporal perspective facilitates a more deeply historical analysis.

The Making of a Research Field and Industry

"Angiogenesis" is no newcomer to science; the surgeon John Hunter used the term to describe blood vessel growth in 1787, and as early as 1907 researchers had observed tumor vascularization (Angiogenesis Foundation 2003, Goldman 1907). In 1941 a medical researcher reported that tumors implanted into guinea pigs' eyes would grow and develop blood vessels (vascularization), but in cases where vascularization did not occur, the tumors also did not grow (Greene 1941). A few years later cancer researchers published the hypothesis that blood vessels grow toward tumors (Algire and Chalkley 1945). In the 1960s Judah Folkman and colleagues observed the same process in transplanted animal tumors, and the young surgeon went on to play the central role in the development of the research field in the U.S. Because of his central role, this section will focus on the shifting position of his work in the fields of cancer research and, eventually, cancer therapy.

As a surgeon, Folkman entered the field of oncology research as an outsider, but he had credibility within the broader medical field because of his reputation as a stellar medical student, his rapid rise to prominence as a professor of surgery at Harvard Medical School, and his position as chief of surgery at Boston Children's Hospital. However, during the first decades of his work on angiogenesis inhibitors, his position in the medical field was due to his work as a surgeon. His laboratory work was tolerated as a voluntary activity, and his first publications on angiogenesis and cancer were largely ignored, even when in top journals (e.g., Folkman 1971).

Skeptical scientists argued that the growth of blood vessels toward tumors was due to inflammation, and clinicians remained uninterested because applications seemed remote (Cooke 2001: 100). When the renowned Boston oncologist Sidney Farber encouraged the public relations coordinator of the American Cancer Society to feature Folkman in its annual press seminar, the ensuing media attention that he garnered only increased his isolation among cancer researchers (Cooke 2001: 116-119).

During the 1960s and 1970s cancer research in the United States was dominated by a network that had first pursued viral oncology and then shifted to oncogene research (Chubin 1984, Fujimura 1996). A few other researchers were studying the problem of angiogenesis (e.g., Greenblatt and Shubik 1968), but the emergent research field was both small in size and marginal to the emergent molecular frameworks for cancer research. Even into the 1970s the field of angiogenesis research was producing only about three papers per year (Birmingham 2002). One factor that helped shift the position of this marginal research field was the finding that the problem of vascularization in tumors was related to the problem of endothelial cell growth. As a result research on tumor angiogenesis could be connected to another, somewhat larger research field, and Folkman's work became part of a network called the "blood vessel club," which was attempting to isolate endothelial cell growth factors (Cooke 2001: 131). By 1974 Folkman's laboratory and another lab had reported the successful cultivation of endothelial cells in culture (Gimbrone et al. 1973, Jaffe et al. 1973). With the new success behind him, Folkman attempted to get a major grant from the National Cancer Institute, but the reviewers demanded that he first team up with a biochemist (Cooke 2001: 134).

Up to this point the story is largely one that can be told within a perspective limited to the position of a "challenger" research program within a broader research field. However, a new actor now enters the stage. With the grant now approved, Folkman's new partner, a professor of biochemistry named Bert Vallee, argued that they needed to scale up significantly in order to produce the tumor angiogenic factor that Folkman was now able to isolate. Vallee had a consulting arrangement with Monsanto, and as a result he was able to facilitate arrangements that led to a new form of university-medical school partnership (Cooke 2001: 136-148). The Harvard-Monsanto agreement is now a classic case in the history of technology transfer and private sector partnerships. It provided the Folkman and Vallee laboratories with $22 million over twelve years, and it granted them the right to publish their work in return for Monsanto's right to patent products coming out of their laboratories (Culliton 1977). The

agreement necessitated a sea change in Harvard's intellectual property policies and provided a model for emerging policies at other medical schools (Cooke 2001: 145-187). In the world before the Bayh Dole Act, Harvard did not seek patents on health agents, and the university had no patent attorney.

In addition to the historic importance of the Monsanto agreement for the commercialization of biomedical research in the United States, it also moved Folkman's research program a step closer to institutionalization by providing a funding base. However, winning a secure funding base was only part of the picture; Folkman and his colleagues also needed to win acceptance by the scientific community, a process that would take more time. In fact, backlash against the Monsanto agreement was tremendous, both within Harvard and within broader scientific research communities. Folkman found his next NIH grant proposals turned down and his research program dismissed as quixotic. When he took the podium at one conference, he watched as a hundred people walked out of the room, and he heard postdocs tell of how they were advised to avoid his lab (Cooke 2001: 145-187). A skeptical article in *Science* (Culliton 1977) led to a negative external committee review of Folkman's work. On top of this the administrators at Children's Hospital asked him to choose between surgery and research, and in 1981 he reached the key decision to step down as chief of surgery (Cooke 2001: 198).

Notwithstanding the professional setbacks, the laboratory was slowly accumulating a successful track record. In 1976 Robert Langer, a chemical engineer who at the time was a post-doctoral researcher in Folkman's laboratory, processed huge amounts of bovine cartilage, then shark cartilage, and found that he could isolate a substance that inhibited angiogenesis (Langer et al. 1976). In 1979 a microbiologist in the laboratory succeeded in getting a special kind of endothelial cells, those from the capillary, to grow in culture (Folkman et al. 1979). The achievement led to international recognition, and Folkman's lab began training researchers in the technique (Cooke 2001: 194). Subsequently the laboratories of Folkman and Vallee isolated angiogenic growth factors (Shing et al. 1984, Fett et al 1985). As a result, by the mid 1980s research on angiogenesis had become part of the burgeoning field of growth factor research, which was attracting increasing attention from industry. A researcher at Genentech found that a factor they had identified, vascular endothelial growth factor, was identical to the tumor angiogenesis factor of Folkman's laboratory (Leung et al. 1989). Although Monsanto decided to focus on agricultural biotechnology and consequently did not renew its agreement with Harvard, Folkman soon had new support of one million dollars per year from a Japanese

company that wanted to enter the market, Takeda Chemical Industries (Cooke 2001: 209-217). The ability to find support from firms was crucial to keeping a laboratory alive that was challenging some of the dominant assumptions of cancer research and opening up the doors to a therapeutic approach that did not rely on cytotoxic chemotherapy.

With the development of clinical applications, the position of the research field underwent another level of transformation. In 1989 alpha-interferon became the first antiangionesis agent used clinically, and in 1992 Takeda's TNP-470 became the first antiangiogenesis drug to enter into a clinical trial (Folkman 1996: 150). Angiogenesis research spread rapidly to many laboratories, and research on leukemia and angiogenesis became a burgeoning field (Cooke 2001: 236-7). Competition among postdoctoral candidates for a position in the once-spurned laboratory became intense (Cooke 2001: 245) However, even at this point the National Cancer Institute turned down a major grant proposal from Folkman's laboratory, and the major pharmaceutical companies remained interested only in research that would result in rapid clinical applications. Consequently, in 1992 Folkman worked out an arrangement that brought in support from EntreMed, a biotechnology start-up company (Cooke 2001: 248-250). The collaboration led to the development of angiostatin, an angiogenesis inhibitor that blocked metastases in murine models (O'Reilly et al. 1994). By 1996 seven antiangiogenesis drugs were in clinical trials (Folkman 1996: 154). With the transition of the field into drug development, the size of the research field grew to hundreds of papers per year (Cooke 2001: 260).

In May, 1998, the *New York Times* journalist Gina Kolata reported on the excitement in a front-page article that had international repercussions. She quoted Nobel Prize laureate Francis Crick as saying, "Judah is going to cure cancer in two years." Although Crick denied the quote, the controversial story set off a storm of international media attention, and EntreMed's stock prices soared. The article also set the stage for subsequent critical coverage of angiogenesis research when one of the drugs encountered some difficulties in replication attempts (e.g., King 1998). EntreMed also suffered some setbacks, including a lawsuit from Abbot, which had an agreement with Takeda. Meanwhile, other companies initiated clinical trials, and old drugs such as thalidomide were reintroduced for their antiangiogenic properties.

By the first decade of the twenty-first century angiogenesis and antiangiogenesis research had become mainstream. As Folkman noted in an interview in 2002, the field of angiogenesis research was growing at a rate of forty papers per week, that is, over two

thousand papers per year (Birmingham 2002). Previously disconnected diseases such as cancer, cardiovascular disease, arthritis, diabetes, and macular degeneration were now connected through the common thread of angiogenesis. A whole industry of drugs designed to enhance angiogenesis in some cases, such as cardiovascular disease, and to inhibit it in others, such as cancer, had emerged. According to the Angiogenesis Foundation (n.d.), by 1999 there was a "massive wave" of both angiogenic and antiangiogenic drugs undergoing clinical trials for cancer, macular degeneration, diabetic retinopathy, psoriasis, coronary artery disease, peripheral vascular disease, stroke, and wound healing. By 2002 there were three hundred companies worldwide were involved in angiogenesis research, embracing seventy-one agents, 10,000 patients, and $4 billion dollars of research (Angiogenesis Foundation 2002).

It might be tempting to describe the ascendancy of angiogenesis research and therapies by using the concept of a paradigm shift or scientific revolution, or even the framework of the rise of one network to dominance over another network. However, those interpretive frameworks miss some of the complexity of the transition. To date, molecular approaches to basic research and chemotherapeutic approaches to clinical applications remain dominant in the cancer field. Although traditional cancer chemotherapy drugs are now recognized to exhibit antiangiogenic effects at low doses, the clinical trials of antiangiogenic drugs have tended to position the drugs as additions to the traditional cancer chemotherapy armamentarium. A similar process is occurring with monoclonal antibodies, which are being tested for antiangiogenic properties. Rather than viewing antiangiogenic drugs as replacing existing research programs and drug cocktails, it seems more accurate to describe their development as being integrated into a diversifying therapeutic field. Angiogenesis research and drugs have not so much replaced existing frameworks and research programs as grown into them.

Food, Cartilage, and Angiogenesis

In contrast to angiogenesis research, the story of cartilage research for cancer represents a case of what I have called "undone science" (Hess 2001a, Woodhouse et al. 2002). The field of cartilage-based therapies for cancer in the U.S. was developed by John F. Prudden, whose career was in some ways similar to that of Folkman, but with a much less positive outcome. Prudden graduated from Harvard Medical School somewhat earlier than Folkman, in 1945, and then received a doctorate in medical science from Columbia University (Moss 1993).[1] After a stint in the army, he practiced as a surgeon at Columbia Presbyterian Hospital and,

during the late 1960s and early 1970s, was an associate professor of clinical surgery at Columbia. In the 1950s he found that placing pieces of cartilage in wounds accelerated their healing (Prudden et al. 1957). Although he built his reputation for research on the enzyme lysozyme, he remained intrigued by the therapeutic potential of cartilage and soon obtained an investigational new drug permit from the Food and Drug Administration to treat cancer patients with bovine cartilage. He began treating cancer patients with subcutaneous injections of bovine cartilage in 1972, but the chair of the surgery department did not like the research, and Prudden eventually left Columbia to develop affiliations with other hospitals. In 1985 he published a review of 31 patients, which concluded that the drug was so safe that no upper limit of toxicity was reached. Furthermore, in a subset of patients for whom the treatment was applied consistently, all of whom were late-stage patients who had failed conventional therapy, he claimed to have 61% complete responders (Prudden 1985). In an interview in 1993, Prudden claimed that in a subsequent study with renal cell carcinoma, a very lethal form of cancer, the cartilage drug had a 25% complete or partial response rate (Moss 1993). He attributed the failure of cancer researchers and clinicians to follow up on the research as due to their dislike of natural products. He died in 1998, unable at that point to have brought bovine cartilage into the mainstream of cancer treatment.

Prudden's research was eclipsed not only by the growing attention to antiangiogenesis drugs but also by the growing attention to shark cartilage. The leading advocate of shark cartilage, I. William Lane, did not have a medical degree and lacked a university position, but he did have significant credentials relevant to the use of shark cartilage as a nutritional supplement. He received a master's degree in nutrition from Cornell University and a doctorate in agricultural biochemistry and nutrition from Rutgers University, and he had also served as the vice-president of the Marine Resources Division of W.R. Grace and Co. [2] During subsequent consulting work in the 1970s, he became interested in shark fishing. He learned about bovine cartilage from a business associate, met with Prudden in 1981, and tried Prudden's cartilage pills for his back pain. Finding that the pills helped not only his own back pain but also the severe arthritic symptoms suffered by the wife of a colleague, Lane became very interested in the therapeutic abilities of cartilage. A few months later he met with Langer, the chemical engineer who had worked with Folkman, and he became even more convinced of the therapeutic potential of cartilage. At Lane's urging, the Institute Jules Bordet in Brussels conducted toxicity and dose-response studies in rats as well as human arthritis patients. According to Lane the

results were all positive, but they apparently went unpublished, and Lane was unable to interest the National Institutes of Health, whose representatives told Lane that they did not want to research natural products. Thwarted in the U.S., he pursued partnerships with clinicians in Panama, Mexico, Costa Rica, and Cuba. In 1992 Lane published the book Sharks Don't Get Cancer, and in 1993 the CBS newsmagazine 60 Minutes covered the Cuban trial, for which Lane claimed that 40% of the 18 patients showed significant improvement.

By the mid-1990s cartilage products were one of the leading over-the-counter supplements products, and shark cartilage had displaced bovine cartilage. Retail sales for shark cartilage in the U.S. at that time were $50-60 million per year, and Lane estimated in an interview that 25,000 people were using shark cartilage products (Flint and Lerner 1996). Under the DSHEA regulations, cartilage products could be sold in stores as food supplements without requiring a prescription, provided that manufacturers made only structure and function claims (e.g., they promote healthy joints and bones). If manufacturers were to make disease claims (i.e., they can successfully treat cancer), supplements would become classified as drugs and would be required to go through the expensive approval process using clinical trials. In other words, it is not the "naturalness" of the product that determines its legal status but the health claims that are associated with it.

Although the DSHEA regulations created a loophole through which over-the-counter supplements could be made available for off-book therapeutic uses, Lane went the official route and in 1994 obtained an investigational new drug permit from the Food and Drug Administration (Lane and Comac 1996). He described the Food and Drug Administration at that time as cooperative, but by the late 1990s the agency came to believe that shark cartilage products were being used in unapproved ways. In 1999 it filed a lawsuit against Lane Labs USA to limit distribution of products unless they were for approved clinical trials (Angiogenesis Foundation 1999). The Federal Trade Commission also intervened to stop the marketing of shark cartilage products by various firms that were making claims related to cancer treatment (Health Supplement Retailer 2000). In the case of Lane Labs, the settlement reached in 2000 mandated that the company fund a Phase III study of their shark cartilage product (ibid.). In my review of U.S. web sites for cartilage products in late 2003, the claims were carefully restricted to the legally allowable categories of health structure and function.

In addition to the regulatory and evidential problems, during the 1990s advocates of shark and bovine cartilage became caught up in their own controversies, including differences

between the shark and bovine cartilage advocates. One debate involved the mechanism of action: Prudden believed that the therapeutic effect involved activation of the immune system via mucopolysaccharides (carbohydrates), whereas Lane believed that it was via antiangiogenesis factors (proteins). Environmentalists were also raising concerns with overfishing due to the growth of the shark cartilage industry. Although Lane responded that the overfishing problem was more related to Asian demand for shark fins and nonsustainable harvesting practices, both of which were problems that needed government regulation (Lane and Comac 1996: 70-72), there was no parallel problem for bovine cartilage. To my knowledge, the growing concerns about "mad cow disease" have not yet been utilized in the shark/bovine controversy, but they could add yet another chapter to the ongoing conflict.

A more general controversy emerged around the question of absorption of any cartilage product when it is delivered orally or rectally, rather than by injection. Folkman, who injected cartilage rather than administering it orally, claimed that the pharmacologically active substances in cartilage are unlikely to be absorbed by the gut, and that a cancer patient would have to eat hundreds of pounds of cartilage daily to derive a therapeutic benefit (Beardsley 1993). Although an independent review of the issue indicated that gut absorption was possible, it also raised concern about the high doses of cartilage needed and the potential risk of excess calcium from oral cartilage (Flint and Lerner 1996).

Cartilage research was additionally weakened as the leaders of the CAM (complementary and alternative medicine) cancer therapy movement shifted from optimism to more cautious or even critical statements. Initial reports by leaders of the CAM cancer therapy movement, such as Ralph Moss (1991, 1993) and Ross Pelton (Pelton and Overholser 1994), as well as other CAM leaders (e.g., Williams 1993) were optimistic, but by the late 1990s the leaders were more skeptical. A key study led by Michael Lerner, head of the patient support organization Commonweal and a moderate voice in the CAM cancer therapy movement, concluded that the therapy remained unproven (Flint and Lerner 1996). Patrick McGrady, Jr., the founder of a patient-oriented cancer information-providing service called CanHelp, told me in the late 1990s that he was very skeptical of both bovine and shark cartilage products (Hess 1999: 35). Likewise, Ross Pelton, who in 1994 published a major book on CAM cancer therapies that had given shark cartilage relatively positive coverage, told me half a decade later that he preferred fermented soy products, which also had antiangiogenic properties (Hess 1999: 151). Robert Houston, a journalist who had been a consultant to 60 Minutes for the Cuban story and

was widely recognized as a pre-eminent scholar of CAM cancer therapies, confirmed that Lane's analysis of the Belgian data was essentially correct, but remained unconvinced that shark cartilage was dramatically effective in humans (Hess 1999: 141). Ralph Moss, in many ways the "dean" of the CAM cancer therapy movement in the U.S., subsequently added a comment to his 1991 article stating that the "jury is still out" (Moss 1991) and, in 1997, described himself as speaking in "measured tones" about the product (Moss 1998).[3] In summary, although there are clinicians in the U.S., Mexico, and other countries who continue to use cartilage products and claim to see some benefit at the bedside, by the late 1990s several of the patient advocacy leaders in the U.S. were cautious about the claims for therapeutic efficacy, even though they continued to support the need for increased public funding for evaluation of natural products with antiangiogenic effects.

The lack of support from CAM-oriented patient advocacy leaders may appear counter-intuitive. One might expect from them an uncritical embrace of all alternative cancer therapies. However, the patient advocacy leaders today are generally well-educated and quite sophisticated both methodologically and politically. Several hold doctorates in the social sciences and humanities, so they understand how to do research and how to interrogate both its methodology and politics. They understand that overhyped claims can come from CAM clinicians or innovators as easily as from oncologists and pharmaceutical companies. They are particularly critical of some CAM advocates who assume that products are safe and efficacious because they are natural. Instead, they tend to keep their eye on the bottom line of decreasing toxic side effects and increasing efficacy, notwithstanding the "naturalness" of the product. If a new class of drugs is proving to have few side effects and potentially high efficacy, such as the antiangiogeneis drugs at the current stage of their historical development, the CAM advocates could end up preferring the nontoxic drugs to a natural product that is bogged down in a variety of yet unresolved controversies. Furthermore, the patient advocacy leaders tend to warn patients not to chase after a single therapy (whether it is an experimental drug or a new food supplement), just as newcomers to investing may select one favorite stock. Instead, the patient advocacy leaders tend to support diversified, individualized therapeutic portfolios of surgical, nutritional, immunological, and mind-body protocols that are offered under the guidance of qualified clinicians. Although the advocates disagree on many specific issues, including the value of some or any concomitant chemotherapy and radiation therapy, they generally agree that

more funding is needed to evaluate CAM cancer therapies and they are skeptical of magic bullets.

In the past it took mass mobilization from the patient advocacy groups to pressure the federal government to fund clinical trials of controversial substances such as laetrile. By the mid 1990s an integration process was well underway (Hess 2003), and some federal funding was available for cartilage-based research. By 2003 the National Center for Complementary and Alternative Medicine (2003) listed two cartilage trials that it had funded, and the National Cancer Institute had also funded two clinical trials for genistein, a bioflavonoid found in soy that has antiangiogenic properties (National Cancer Institute 2003b). Likewise, other food components that may have antiangiogenic properties were being explored, such as thiol compounds (found in garlic) and vitamin A analogs (Boik 1996: 29-30). Notwithstanding the availability of limited government funding as well as funding from supplements companies and clinicians from their own income streams, research on cartilage was progressing at a snail's pace in comparison with that on antiangiogenesis drugs. According to the National Cancer Institute listing (2003a), between the 1970s and 2003 there were eight clinical trials and one case series of cartilage products, three of which were for a bovine product, four for a shark product, and two for a purified cartilage-based drug called Neovastat. None of the listed trials was at a Phase III level. Why?

Leaders of the CAM movement have frequently noted that food-based or other "natural" products become the orphans of clinical research because private sector firms are unwilling to invest the capital in a product that cannot be patented. Because patentability is a precondition for the heavy private-sector investment that is needed to bring most drugs to market, there is an indirect relationship between "naturalness" or proximity of a supplement to food and animal products and the status of the product as a drug. It is true that the distinction is increasingly murky because of the various ways in which intellectual property rights are becoming associated with food and food supplements. For example, the emerging "nutraceutical" industry can acquire intellectual property rights in food substances through trademarks, just as it is can patent processes used to derive a purified form of the food product. Furthermore, it is possible to develop patents for therapeutic use of natural products. Indeed, in 1991 Lane obtained a patent on the use of cartilage as an angiogenesis inhibitor at a dose of twenty grams, and Prudden held a more general patent on the therapeutic use of any type of cartilage for cancer (Flint and Lerner 1996). However, just as trademarks or process patents are

relatively weak forms of intellectual property, so the patent rights that Prudden and Lane held were weak because they covered mechanism or use rather than the substance itself. The Lane patent was particularly vulnerable because it was limited to a specific dosage (Flint and Lerner 1996). As a result, investment in developing drug status for a food-derived product can run the risks of creating free-riders who can subsequently enter the market with similar products and benefit from a market leader's investment costs. Unless the public sector steps in to pick up the tab, the research field is condemned to developing products at a very slow pace, or it must market its products as supplements that lack disease-curing legal status and run the risk of regulatory intervention when off-book uses become too prominent. To keep pace with the angiogenesis industry, the public investment natural products with purported antiangiogenic properties would need to be on the order of hundreds of millions, if not billions, of dollars.

Conclusion

By the first decade of the twenty-first century, antiangiogenesis drugs were attracting increasing excitement among mainstream researchers and clinicians, as well as patients and some patient advocates, whereas cartilage-based research remained enveloped in various circles of controversy. Arguably, the situation was not optimal from the point of view of cancer patients. In other words, investing more public resources in food-based angiogenesis products, such as cartilage or genistein, might have been a wise use of public funds. If successful, food-based drugs would be less expensive and more readily available, particularly to segments of the world's population that are off the medical grid of health insurance and pharmaceutical products. If not, then the thousands of users of those products would have good critical information that might steer them away from inefficacious products.

The National Cancer Institute and National Center for Complementary and Alternative Medicine have funded some relevant research, but advocates in the CAM community, and some of their supporters in Congress, have argued that funding is tiny in comparison with total health-related research expenditures and disproportionately small when contrasted with the large number of patients who are using such products or who could benefit from them. As a result, the current confluence of private and public sector resources in favor of drug-based research creates a situation of a rapidly changing world of drug-based research and a very slowly developing world of research for food-based therapies. Whereas in many ways a consensus shift occurred during the 1990s around the value of angiogenesis research and antiangiogenesis

drugs, it may take decades for a similar shift to occur around the therapeutic value of food-based interventions such as cartilage and soy products.

Understanding the current situation, where two research fields and associated therapies have developed radically different levels of credibility and research funding, requires a sociology of knowledge that is attendant to industrial priorities, regulatory policies, and social movement politics. However, the argument here goes beyond the problem of bringing markets, states, and social movements back into the study of scientific change. The point is also to raise the historical sociological question of the ways in which scientific and technological fields are themselves undergoing change. In returning to the four processes outlined at the start, a few elaborations are now possible.

Clearly, the issue of the increasing scale of institutional structures is evident. In my earlier historical research on another nondominant but nonetheless biological approach to cancer research (the networks of researchers who studied bacterial etiologies and the clinicians who employed bacterial vaccines, Hess 1997), the costs of doing animal-based research and developing vaccines were relatively small during the middle decades of the twentieth century. The costs could be internalized by clinicians or microbiologists on a part-time basis, somewhat akin to Folkman's work at the earliest stages of his career. In contrast, as the antiangiogenesis research program developed, it soon grew into a complex series of related problem areas that required collaboration with biochemists, molecular biologists, and microbiologists. Purification of the antiangiogenesis factors was prohibitively expensive, and the need to scale up drove the collaboration with Monsanto. Furthermore, the translation of such research into a legally approved drug has become extremely expensive in comparison with the relatively open and unregulated clinical testing environment of prior decades, when the first bacterial vaccines and sera were being tested. During the earlier period, a potential scientific or therapeutic "revolutionary" in the biomedical field only needed a low-tech laboratory, some mice, a vaccine or serum, and a clinical setting for small-scale testing. The costs and size of network that were needed to develop a therapeutic product and bring it into a clinical setting were smaller. The research and therapy programs related to cartilage have lacked the level of capital infusion found in drug development, and as a result they have had to rely on self-capitalization from sales of cartilage-based supplements products or meager government funding resources. Whereas the strategy of self-capitalization might have worked fifty years earlier, before the tighter regulatory environment engendered by the Kefauver-Harris amendments, by the late

twentieth century the strategy created a mismatch between the funding and the scale of the projects needed for success in a competitive world of cancer drugs.

A second major historical change has involved the ongoing differentiation of institutions and roles. A scientist such as Folkman juggled conflicts among his roles as medical school instructor, manager of a laboratory, research scientist, clinician, public spokesperson, fundraiser, and party to contracts with private sector firms. At some points the roles spilled over in uncomfortable ways, such as in the "backfire" (Jansen and Martin 2003) that occurred in the wake of his media attention or private sector contracts. At one point he even hired a public relations person to handle his relations with the press (Cooke 2001). The increasingly complex set of roles that scientists must juggle accompanies a parallel growth of new organizations that have emerged in the interstices of previously separated organizational fields: the medical school technology transfer office (between the university and private sector), the supporting foundation (among researchers, clinicians, patients, and donors), and the biotechnology start-up company (among researchers, investors, and the pharmaceutical industry). The level of role conflict and negotiation, coupled with the formalization of requirements for role specificity, create the conditions for actual or apparent conflicts of interest and subsequent crises of credibility. However, the crises of credibility have been greater for Lane than for Folkman. Rather than attempt to reduce the difference to a psychology of personal integrity, a sociological perspective would point to how a scientist needs conviction to stay with a research program and battle for its success, but an entrepreneur with equal conviction can run into legal constraints on issues such as health claims rules. The battle for the acceptance of a research program that is linked to a new therapy hinges on maintaining the separation of roles between researcher and entrepreneur, but the processes of commercialization make it increasingly difficult for the roles to remain separate, particularly for small-scale defenders of natural products.

A third change is in the culture of biomedical research and its clinical applications. On the research side, there is an increasing concern with mechanism, with understanding causal pathways at the molecular level of growth factors and gene expression. The black-boxing of therapeutic agents that occurs in foods, herbs, cartilage, and other naturally occurring products is anathema to a research culture that is focused on mechanisms. Although the reason why there is so much focus on mechanism is beyond the scope of the study, the hypothesis that drug-based research priorities drive such a concern would be worthy of study. As a result, there

is ongoing resistance from establishment research communities to the empiricism of food-based research when it is accompanied by weakly understood mechanisms (see also the article by Woodhouse in this volume on various types of scientific momentum). On the clinical side, there is an increasing formalization of the hurdles required for clinical approval. While in theory the three phases of clinical trials required for drug approval in the U.S. constitute a level playing field, in practice it is a pseudo-universalism similar to the American criminal justice system. As I have sometimes heard in CAM-oriented cancer conferences, the idea that the randomized clinical trial represents the "gold standard" of research is well-named because those who have the gold set the standards. The older model of clinicians who tinker with therapies, introduce them to patients, and present case study series, has been rejected, at least in the U.S. and other wealthy countries (less so in Mexico, which is home to many of the rejected American cancer therapies).

Regarding the technological and natural world, the cancer therapy field is characterized by increasing recognition of the failure of conventional therapies and the emergence of movement for less toxic cancer therapies. Ralph Moss (1992) even made "toxicity" the central issue in a survey of CAM cancer therapies. Concern with the negative side effects of radiation therapy and chemotherapy, and with their inability to cause remission or prevent recurrence at desirable levels, has spurred a general movement among cancer patients and some clinicians to reject those therapies or, at the minimum, to seek nutritional interventions that mitigate the toxicities of conventional therapies (Hess 1999). Yet this "greening" of cancer therapy is accompanied by a denaturalization process; in other words, the older generation of high-dose chemotherapy with its undesirable side effects is being replaced not so much by natural products and nutritional interventions as by a new, less toxic wave of biological therapies, such as antiangiogenesis drugs. Even when traditional chemotherapy continues to be used, often its mode of delivery has been modified to reduce toxicity, such as by emphasizing low-doses and slow infusion over a long period of time instead of short-term blasts followed by a recovery period. In fact, antiangiogenesis research suggests that chemotherapy used in this manner may have antiangiogenic properties.

The theoretical frameworks developed in this essay and others in this volume urge research on science, technology, and society to pay more attention not only to factors such as commercialization, regulatory policy, and civil society participation, but also, as I would argue, to the patterns of historical change that characterize the recent development of science and

technology. The new theoretical frameworks promise to provide social scientists and historians with a helpful lens for understanding change in science, technology, and society, and they may also be helpful for reform movements in science, industry, and society that are strategizing efforts for political and technological change.

Acknowledgements

I wish to thank Joerg Albrecht, Arthur Daemmrich, Scott Frickel, Daniel Kleinman, and Kelly Moore for helpful comments on an earlier draft, as well as comments from faculty and students at the University of Pennsylvania, University of Sydney, and various conferences.

Footnotes

1 The biographical information in the remainder of the paragraph is based on an interview between Ralph Moss and John Prudden in 1993 (Moss 1993).

2 The biographical material in this paragraph is based on Lane and Comac (1993).

3 However, after the approval of Avastin in 2004, Moss was also critical of the costs, low efficacy, and side effects of the Avastin-chemotherapy protocol, and he continued to support the need for more funding for evaluation of low-cost natural products that have antiangiogenic effects (Moss 2004).

References

Algire, Glen, and Harold Chalkley. 1945. "Vascular Reactions of Normal and Malignant Tissues in Vivo. I. Vascular Reactions of Mice to Wounds and to Normal and Neoplastic Transplants." Journal of the National Cancer Institute 6(1): 73-85.

Angiogenesis Foundation. n.d. "Historical Highlights of the Angiogenesis Field." <www.angio.org/researcher/library/highlight.html>, accessed 10/23/03.

_____. 1999. "FDA Demands Halt to Sale of Lane Lab's BeneFin Citing Unproven Claims." <www.angio.org/newsandviews/archive1999/dec_17_1999.html>, accessed 10/22/03.

_____. 2002. "Angiogenesis State of the Art Highlighted at Florida Summit." Boston: Angiogenesis Foundation. <www.angio.org/newsandviews/archive2002/June02.html>, accessed 10/22/03.

_____. 2003. "Historical Highlights of the Angiogenesis Field." <http://www.angio.org/researcher/library/library.html>, accessed 10/28/03.

Beardsley, Tim. 1993. "Sharks Do Get Cancer." Scientific American October: 24-25.

Beck, Ullrich. 1992. The Risk Society. Newbury Park, Ca.: Sage.

Bernal, John. 1969. Science in History. Cambridge, Ma.: MIT Press.

Birmingham, Karen. 2002. "Judah Folkman." Nature Medicine 8(10): 1052.

Boik, John. 1996. Cancer and Natural Medicine. Princeton, Minnesota: Oregon Medical Press.

Bourdieu, Pierre. 2001. Science de la science et réflexivité. Paris: Raisons d'agir..

Chubin, Daryl. 1984. "Research Mission and the Public: Over-Selling and Buying on the U.S. War on Cancer." Pp. 109-129 Citizen Participation in Science Policy, ed. James Petersen. Amherst, Mass.: University of Amherst Press.

Cooke, Robert. 2001. Dr. Folkman's War. New York: Rome.

Culliton, Barbara. 1977. "Harvard and Monsanto: The $23 Million Alliance." Science 195: 759-763.

Daniels, George. 1976. "The Pure-Science Ideal and Democratic Culture." Science 156: 1699-1705.

Fett, James, D.J. Strydom, R.R. Lobb, E.M. Alderman, J.L. Bethune, J.F. Riordan, and B.L. Vallee. 1985. "Isolation and Characterization of Angiogenin, an Angiogenic Protein from Human Carcinoma Cells." Biochemistry 24(20): 5480-86.

Flint, Vivekan, and Michael Lerner. 1996. Does Cartilage Cure Cancer? Bolinas, Ca.: Commonweal. <www.commonweal.org>, accessed 8/15/04.

Folkman, Judah. 1971. "Tumor Angiogenesis: Therapeutic Implications." New England Journal of Medicine 285: 1182-1186.

_____. 1996. "Fighting Cancer by Attacking its Blood Supply." Scientific American 275 (3): 150-154.

Folkman, Judah, Christian Haudenschild, and Bruce Zetter. 1979. "Long-Term Cultivation of Capillary Endothelial Cells." Proceedings of the National Academy of Sciences 76(10): 5217-5221.

Folkman, Judah, and Elton Watkins. 1957. "An Artificial Conduction System for the Management of Experimental Complete Heart Block." Surgical Forum 8: 331-334.

Frickel, Scott. 2004. "Just Science? Organizing Scientist Activism in the U.S. Environmental Justice Movement." Science as Culture 13(4): 459-469.

Fujimura, Joan. 1996. Crafting Science. Cambridge, Ma.: Harvard University Press.

Fuller, Steve. 2000. Thomas Kuhn: A Philosophical History for Our Times. Chicago: University of Chicago Press.

Gimbrone, Michael, Ramzi S. Cotran, Christian Haudenscschild, and Judah Folkman. 1973. "Growth and Ultrastructure of Human Vascular Endothelial and Smooth-Muscle Cells in Culture." Journal of Cell Biology 59 (2): A109.

Goldman, E. 1907. "The Growth of Malignant Disease in Man and the Lower Animals with Special Reference to the Vascular System." Lancet 2: 1236-1240.

Greenblatt, Melvin, and Philippe Shubik. 1968. "Tumor Angiogenesis." Journal of the National Cancer Institute 41: 111-116.

Greene, Harry S.N. 1941. "Heterologous Transplantation of Mammalian Tumors. I The Transfer of Rabbit Tumors to Alien Species. II The Transfer of Human Tumors to Alien Species." Journal of Experimental Medicine 73(4): 461-486.

Guston, David. 2001. "Boundary Organizations in Environmental Policy and Science: An Introduction." Science, Technology, and Human Values, 26(4): 399-408.

Health Supplement Retailer. 2000. "FTC: Firms Can No Longer Make Shark Cartilage/Cancer Claims." September: Government Watch Column <www.hrsmagazine.com/articles/091govwa.html>, accessed 10/22/3.

Hess, David. 1997. Can Bacteria Cause Cancer? New York: NYU Press.

_____. 1999. Evaluating Alternative Cancer Therapies. New Brunswick, N.J.: Rutgers University Press.

_____. 2001a. Alternative Pathways in Globalization. Niskayuna, NY: Letters and Sciences Publishing. <home.earthlink.net/~davidhesshomepage>.

_____. 2001b. "Ethnography and the Development of STS." Pp. 234-245 in Handbook of Ethnography, ed. Paul Atkinson, Amanda Coffey, Sara Delmont, John Lofland, and Lyn Lofland. Thousand Oaks, Ca.: Sage.

_____. 2003. "CAM Cancer Therapies in Twentieth-Century North America: Examining Continuities and Change." Pp. 231-243 in The Politics of Healing, ed. Robert Johnston. New York: Routledge.

Hessen, Boris. 1971. The Social and Economic Roots of Newton's Principia. New York: Howard Fertig.

Jaffe Eric, Ralph Nachman, Carl Becker, and C. Richard Minick. 1973. "Culture of Human Endothelial Cells Derived from Uumbilical Veins." Journal of Clinical Investigation 52: 2745–2756.

Jansen, Sue Curry, and Brian Martin. 2003. "Making Censorship Backfire." Counterpoise 7(3): 5-15. <http://www.uow.edu.au/arts/sts/bmartin/pubs/03cp.html>, accessed 12/3/03.

King, Ralph. 1998. "Laboratory Hitch: Novel Cancer Approach from Noted Scientist Hits Stumbling Block." Wall Street Journal Nov. 12: A1.

Kleinman, Daniel Lee. 1995. Politics on the Endless Frontier. Durhan, N.C., and London: Duke University Press.

_____. 2003. Impure Cultures. Madison, Wisc.: University of Wisconsin Press.

Knorr-Cetina, Karin, and Michael Mulkay. 1983. Science Observed. Beverly Hills: Sage.

Kolata, Gina. 1998. "Hope in the Lab: A Special Report." New York Times May 3, 1:1.

Kuhn, Thomas. 1970. The Structure of Scientific Revolutions. Second edition. Chicago: Unviersity of Chicago Press.

Lane, I. William, and Linda Comac. 1992. Sharks Don't Get Cancer. Garden City Park, N.Y.: Avery.

_____. 1996. Sharks Still Don't Get Cancer. Garden City Park, N.Y.: Avery.

Langer, Robert, Henry Brem, Kenneth Falterman, Michael Klein, and Judah Folkman. 1976. "Isolation of a Cartilage Factor that Inhibits Tumor Neovascularization." Science 193: 70-72.

Leung, D.W., G. Cachianes, W.J. Kuang, D.V. Goeddel, and N. Ferrara. 1989. "Vascular Endothelial Growth-Factor is a Secreted Angiogenic Mitogen." Science 246(4935): 1306-1309.

MacKenzie, Donald, and Barry Barnes. 1979. "Scientific Judgment: The Biometry-Mendelism Controversy." Pp. 191-210 in Natural Order, ed. Barry Barnes and Steve Shapin. Beverly Hills: Sage.

Merton, Robert. 1970. Science, Technology, and Society in Seventeenth-Century England. New York: Howard Fertig.

_____. 1973. The Sociology of Science. Chicago: Unviersity of Chicago Press.

Misa, Thomas, Philip Brey, and Andrew Feenberg (eds.) 2003. Modernity and Technology. Cambridge, Ma.: MIT Press.

Moore, Kelly. 1996. "Organizing Integrity: American Science and the Creation of Public Interest Science Organizations, 1955-1975." American Journal of Sociology 101: 1592-1627.

Moss, Ralph. 1991. "Sharks May Take a Bite out of Cancer." Cancer Chronicles #10: n.p. <www.ralphmoss.com/html/shark.shtml>, accessed Nov. 18, 2003.

_____. 1992. Cancer Therapy. Brooklyn, N.Y.: Equinox Press.

_____. 1993. "A Potent Normalization." Cancer Chronicles #16: n.p. <www.ralphmoss.com.html/bovine.shtml>, accessed October 21, 2003.

_____. 1998. "Visit to Toronto." Cancer Chronicles Winter 1997-1998: n.p. < http://www.ralphmoss.com/html/toronto1.shtml>, accessed 11/26/3.

_____. 2004. "FDA Approves Avastin." Townsend Letters for Doctors and Patients May: 30-31.

Mulkay, Michael. 1976. "Norms and Ideology in Science." Social Science Information 15(4/5): 637-656.

National Center for Complementary and Alternative Medicine. 2003. "Shark Cartilage Trials." <http://www.nccam.nih.gov/clinicaltrials/sharkcartilage.htm/>, accessed 11/26/03.

National Cancer Institute. 2003a. "Cartilage (Bovine and Shark) (PDQ®)." Last modified 7/9/3. http://www.cancer.gov/cancerinfo/pdq/cam/cartilage, accessed 11/26/03.

_____. 2003b. "Phase II Randomized Study of Genistein in Patients with Localized Prostate Cancer Treated with Radical Prostectomy; Phase II Randomized Study of Soy Isoflavone in Patients with Breast Cancer." Cancer.gov <http://cancer.gov/search/clinical_trials/results_clinicaltrialsadvanced.aspx?protocolsearchid=412785>, accessed 10/22/03.

O'Reilly, Michael, Lars Holmgren, Yuen Shing, Catherine Chen, Rosalind Rosenthal, Marsha Moses, William Lane, Yihai Cao, E. Helene Sage, and Judah Folkman. 1994. "Angiostatin: A Novel Angiogenesis Inhibitor that Mediates the Suppression of Metastases by a Lewis Lung-Carcinoma." Cell 79(2): 315-328.

Pelton, Ross, and Lee Overholser. 1994. Alternatives in Cancer Therapy. New York: Simon and Schuster.

Prudden, John. 1985. "The Treatment of Human Cancer with Agents Prepared from Bovine Cartilage." Journal of Biological Response Modifiers 4 (6): 551-584.

Prudden, John, Gentaro Nishikara, and Lester Baker. 1957. "The Acceleration of Wound Healing with Cartilage-1." Surgery, Gynecology, and Obstetrics 105: 283-286.

Rescher, Nicholas. 1978. Scientific Progress. Pittsburgh, Pa.: University of Pittsburgh Press.

Shing, Y., J. Folkman, R. Sullivan, C. Butterfield, J. Murray, and M. Klagsbrun. 1984. "Heparin Affinity: Purification of a Tumor-Derived Capillary Endothelial Growth Factor." Science 223 (4642): 1296-1299

Williams, David. 1993. The Amazing New Anti-Cancer Secret That's About to Take the World by Storm. Ingram, Tx.: Mountain Home Publishing.

Woodhouse, Edward, David Hess, Steve Breyman, and Brian Martin. 2002. "Science Studies and Activism: Possibilities and Problems for Reconstructivist Agendas." Social Studies of Science 32(2): 297-319

Young, Robert, and Michael Surrusco. 2001. "Rx R&D Myths: The Case Against the Drug Industry's R&D 'Scare Card.'" Washington, D.C.: Public Citizen. <http://www.citizen.org/documents/ACFDC.PDF>, accessed 10/23/03.