The Problem of Undone Science:

Values, Interests, and the Selection of Research Programs

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Citizens who seek information about environmental, health, and other technoscientific problems often find that the crucial research has never been done or that it amounts to a small trickle. At the same time, there is a torrent of research into problem areas that industrial interests deem worthy and important. Upon examining the state of scientific knowledge on a topic at any given time, it is often the case that the more one looks the less one sees. A good model of science in society needs to pay less attention to how science is done and more attention to what science is left undone. This essay will develop a model of scientific change, illustrate it with case studies of rejected research programs in the chronic disease field, and examine the ways in which the model can be applied to policy.

Conceptual Framework

The problem of establishing a standard for evaluating scientific research as falling within or outside the "public interest" is made difficult by ambiguities in the concept of the public. Often, claims of public interest will conceal sectional interests (Giddens 1995) such as genders, classes, occupations, industries, institutions, and ethnic groups, or even the personal interests of individuals and their networks. Furthermore, the concept of the public is relative: in one context it may be a local community, in another a national interest, and in another a broader global interest (such as in global warming or global epidemics). Consequently, a public interest in one context (a community interest over various competing sections within the community) might be a sectional interest in another context (a series of competing community interests versus a broader regional or national interest).

The problem of defining a public interest for a specific problem (such as a chronic disease) is further complicated by the politics of ventriloquism. When a state, nonprofit organization, or other social unit that is delegated to speak for one level of the public defines a public interest, such as a safe and efficacious therapy for cancer, sectional interests and personal interests will tend to align with the declared public interest or against it. For example, the pharmaceutical industry will oppose therapies emerging from the supplements industry, and biomedicine will tend to oppose holistic or naturopathic providers. Thus, although "the public interest" tends to be defined in a way that allows the alignment of sectional interests, the definitional process itself tends to include some sectional interests while excluding others. It is therefore possible to develop a critical analysis of an existing alignment of public and sectional interests, and to propose alternatives that might better serve a public interest on a specified topic, by reexamining the history of alignments and

exclusions.

As is well-recognized in science studies, sectional and personal interests operate via a variety of mechanisms in science, including agenda setting for research funding; the endowment of programs, prizes, and positions; consulting arrangements; intellectual suppression (Martin 1997); and university-industry partnerships. Through the diverse mechanisms, the general contours of problem areas are shaped by major industrial complexes such as the military-industrial, medical-pharmaceutical, and agribusiness-food. Furthermore, research fields that have excluded nondominant social groups have in some cases selected problem areas, such as race and intelligence studies, and research programs, such as demonstrating hierarchies of racial intelligence differences, that have legitimated their social privileges (Harding 1993). In some cases, the biases are not evident until the excluded groups are admitted to the playing fields of science and challenge the implicit ethnic/gender interests that are embedded in dominant research programs (Haraway 1989, Harding 1993). At a more micro level, individuals, scientific networks, disciplines, and affiliated professions have an interest in self-preservation, and they tend to select research programs that preserve their interest in the status quo. Together, the various types of sectional and personal interests will attempt to advance their interests by coalition-building activities with other interests (as in actor-network theory), by aligning themselves with articulations of public interest, or by attempting to define the public interest in an advantageous way.

More abstractly, an actor's interest in an event is the event's impact on the actor's stake in the distribution of resources, both material and nonmaterial (Bourdieu 1991, Giddens 1995). Because power involves the capacity to mobilize resources for an interest, the conflicts of interests that occur around events can be construed also as conflicts of power. The access to and control over resources affects the ability of an actor (either individual or collective) or societal section to

reproduce and survive, and therefore events have an impact on the selection of social units. Selection in this sense mediates both the general process of social change (as in the evolutionary theory sense of "selection") and the everyday processes that involve social intention and choice (such as the "selection" of a candidate for a position, or the selection of a research proposal for funding).

Although one may analyze selection processes at a number of different levels, the problem of undone science discussed here will focus attention on the selection of problem areas, the research programs in which they are embedded, and the policy issue of which problem areas deserve greater or less public funding. The term "research program" will be used here in a somewhat expanded sense than that of Lakatos (1978), who focused narrowly on only one of the research program's constituent units, the theoretical framework. Here, a research program refers to five basic "research units": a body of solved problems and exemplars organized as an archive or canon, the techniques and methods used to produce new knowledge and adjudicate conflicting claims, the theories and models used to conceptualize and explain knowledge, the problem areas or research front where current research is in progress, and research on affiliated technologies or therapies. A research program may be restricted to a single scientist (usually marginalized), or it may be shared by hundreds of scientists. A research field embraces a group of sometimes competing, sometimes complementary research programs whose relationships constitute the ecology of the research field. The size of the research program (in terms of numbers of scientists, citations, publications, revenue spent, or some other measure) is an indication of its dominance within a research field.

As research fields expand and develop, the various research units develop their own histories. Thus, a methodological tradition may develop in one way, whereas a theoretical or

experimental tradition may develop in another way (Galison 1997). However, when viewed synchronically, researchers necessarily, even if not intentionally, assemble a research program whenever they work on a problem because they select from available methods, conceptual frameworks, and archives of solved problems. Thus, a research program is a particular configuration of research units at a given time, but those units do not necessarily develop together over time.

The selection of research programs is guided not only by various types of interests but by the accepted selection criteria or values that are part of the research culture of the field. There are many ways to classify values, but for the present purposes of examining scientific selections from the viewpoint of public interest(s), values will be classified in terms that can be approximated as particularistic or universalistic. The terms will be used here in a sense that is somewhat different from that of Parsons (1951, 58-67), who distinguished value orientations that take into account the social characteristics of the actors or entities in question versus those that do not. The key issue here is whether the values exist with reference to specific social differences (genders, races, occupations, classes, nations, time periods; Hess 1995) or whether they do not (e.g., achievement-oriented, individualist egalitarianism in hiring decisions, evidence and consistency in choices of theories, or efficacy and safety in choices of therapies/ technologies). In other words, the dichotomy will be taken here as a shorthand way of referring to a complex sociological and anthropological literature on modernity under a variety of rubrics, such as community/society, holism/individualism, hierarchy/equality, ascription/achievement, and mechanical/organic.

In contrast to the literature on modernization, universalistic and particularistic values continue to exist in a synchronic and dialectical relationship rather than a merely historical one. The historical dimension of “modernity” is preserved through the increasing legitimacy of the

universalistic side of the equation, which over time and variably across fields tends to encompass the particularistic (Hess and DaMatta 1995). Yet, the culture-power model articulated here holds that under conditions of modernity a process of alignment of universalistic and particularistic values tends to occur, in a matter analogous to but different from the alignment of public and sectional interests discussed above. In other words, universalistic values or selection criteria are usually legitimate and explicit, whereas the particularistic alternatives are often illegitimate and left unstated. Unlike Parsons and closer to DaMatta, the model holds that there are no purely universalistic or particularistic situations but only universalistic and particularistic dimensions to a situation. In the case of science, where universalism dominates the official ideology of the field if not its norms, particularistic values are often left hidden; that is, they tend to be covered up by universalistic justifications when selections of research program units are made public or justified.

The role of both particularistic and universalistic values in science has been documented in the literature (e.g., Allison and Long 1987, Cole 1992, Long 1978), and like most contemporary social institutions, science in practice is not as perfectly modern as it may appear to be in ideology. This insight lies at the core of the social constructivist literature, which is interpreted here to include the role of universalistic values in the justification process that is necessary for new theories, methods, and knowledge claims to become generally accepted in the research field. A theory of scientific selection must be capable of accounting for scientific progress in the sense of improving the "fit of belief to referent" (Campbell 1990, 14), and consequently it must grant a relatively important role for a type of universalistic values called here technical. Those values serve as criteria for theory or model selection, even when universalistic values are less obvious for other levels of selection in science, such as personnel for positions and rewards. In other words, decision-making based on values such as the use of evidence and logic to justify content choices

must have a nontrivial role as causal factors in the explanation of scientific change. At the same time, however, it is well documented that particularistic social values also play a role even in the selection of scientific content, albeit more so for fields that work on issues related to social difference. Whereas philosophers of science have led the way in delineating technical, universalistic values (often by not clearly distinguishing prescriptive from descriptive accounts), feminist science studies scholars have led in delineating the role of particularistic values (e.g., Tuana 1989). The point here, in a framework that takes both standard philosophical accounts and feminist alternatives as a point of departure, is that an alignment tends to occur in the selection process, so that a both-and situation exists, rather than an either-or situation.

Over time a research field develops a culture that consists of more than its structures of special terms, theories, practices, and social relations. The outcome of controversies becomes part of the collective memory of a research field, so that hierarchies occur in the ordering of exemplars (or canons), conceptual frameworks (theories or models), methods, and problem areas. In other words, research units become structured hierarchically as a result of the events in the field's history. To give an example with cancer research,

1. Conceptual frameworks become ordered so that some theories (e.g., cancer as a multistage genetic process) become preferred to others (e.g., cancer is more like a nutritional deficiency disease or an infectious bacterial disease like tuberculosis).
2. Methods become ordered so that some (e.g., the multisite, cross-over, double-blind, placebo-controlled randomized clinical trial) become more highly valued than others (e.g., retrospective outcomes studies or case study series), and in fact a hierarchy or "ladder of methods" may exist in a research field (Hess 1998).
3. Exemplars are organized into canons in ways that reflect the dominant research

programs of the time, and even specific researchers are reconstructed to fit the histories (e.g., William Coley becomes the father of American tumor immunology, not a founder of tumor bacteriology).

4. Problem areas become ordered so that some are highly valued (e.g., oncogene research, Fujimura 1996) and others have a controversial, backwater, or heterodox status (e.g., nutritional or bacterial research programs, Hess 1997).

5. Technological applications are ordered so that some attract powerful interested parties (e.g., the pharmaceutical industry) and others do not (e.g., the orphaned therapies or nonpatentable products).

For an analysis of a research field to be critical, in both the sense of critically important and nonhagiographic, it should examine the existing configuration of research programs and hierarchies as a comparative problem, that is, against the background of what is needed or what has been left undone. The analysis of the selection processes that generated the historical configuration of research programs within a research field must be done in a realistic way that does not reduce the explanation of scientific action to a simplistic scheme, as tends to occur in some constructivist models as well as some philosophical models. The culture-power model proposed here builds in complexity by viewing a range of possible values and interests as simultaneously acting causal shaping factors in scientific events. In other words, it assumes that the basis of social action cannot be reduced to rational-actor models based on utilitarian calculations of interest; instead, people also orient their action with respect to values embedded in both role requirements and personal philosophies developed over a life history.

By conjugating values and interests in the analysis of scientific change, and by defining values and interests as broad categories that embrace various subtypes, the culture-power model

suggests the complexity of decision-criteria that agents apply to the selection of research programs and their units (providing a type of resolution to the culture and practical reason problem, Sahlins 1976). The model avoids reducing scientists to "interest dopes," rational actors, entrepreneurs, or quasi-military strategists by pointing to the irreducible complexity of action that is based on complex dynamics of values and interests. For example, interests (especially sectional and personal interests) create pressures on selection criteria to bend toward particularism. However, knowledge choices within a scientific community must be justified or legitimated by reference to universalistic criteria. Therefore, excluded sectional and personal interests can combat dominant interests by calling on adherence to universalistic criteria or by recasting alignments of public and sectional interest. However, universalistic criteria as specified in the form of methodologies are themselves organized into hierarchies that tend to reflect the dominant sectional and personal interests. Thus, dominant actors can easily throw the book at advocates of heterodox research programs and yet still appear to remain within the range of universalistic values. In return, excluded sectional and personal interests can challenge the hierarchical ordering of the ladder as based on particularistic criteria and contaminated by sectional interests. In the process, various alignments of particularistic values, universalistic values, personal interests, sectional interests, and public interests will occur.

Historically situated values and interests together shape the agents' decisions that result in the configuration of a research culture at a particular time and its pattern of change over time. For any given scientific event, the model cannot resolve on an a priori basis either the relative casual importance of universalistic versus particularistic values or personal versus sectional versus public interests, or the relative importance of values versus interests; instead, the problem must be resolved through empirical research. Nevertheless, general patterns are likely to emerge from empirical research. Perhaps the most obvious is that applied research fields such as engineering

(Noble 1977), medicine (Moss 1996), and agriculture (Kleinman 1998) tend to exhibit greater penetration of industrial interests. Likewise, as the scale of "pure" research increases to require large capital inputs and the coordination of large teams, funding tends to come from industrial or applied sources, such as defense sources that have shaped the contours of physics in the United States (Forman 1987, Leslie 1993).

A second type of general comment involves the policy implications of the model. The patterns regarding the relationship between applied and large-scale research and industrial interests do not justify a simplistic policy that defends scientific autonomy. Rather, the model developed here would be consistent with a policy standard based on the twin ideals of reducing the influence of particularistic values and sectional interests in the selection of science and increasing the influence of universalistic values and public interest. From this perspective, there are grounds for a type of anti-exceptionalist position regarding the policy of funding agendas. In other words, the public and its designated representatives could, at least in some cases, be better at setting guidelines on funding agendas or hierarchies of problem areas than the expert communities of scientists. This position would be particularly true where it can be demonstrated that the history of research agenda choices in those communities is strongly shaped by particularistic values and/or sectional interests, as in the case of cancer research and perhaps other chronic diseases.

Case Study: Chronic Disease Research

Whereas the classic acute diseases are infectious, either treatable or not, and result in recovery or death, chronic diseases generally are of long duration and have a more complicated and less well-understood etiology. The prestige that biomedicine obtained in the late nineteenth and early twentieth centuries came largely from the harnessing of scientific research to the study

of acute, infectious disease. In doing so, massive changes in mortality were achieved through public health measures for prevention, and likewise individuals benefited from lifesaving therapeutic products for treatment. As countries passed through the epidemiological transition from infectious to chronic disease, the limits of biomedicine have become more evident. In the process, an opening has developed for alternative research programs and affiliated therapies. The cases studied here involve the ironic twist of revisiting the differentiation of acute and chronic diseases as correlating with the infectious/noninfectious distinction.

During the last decades of the nineteenth century, sometimes known as the golden age of bacteriology, peptic ulcers, cancer, rheumatoid arthritis, and multiple sclerosis were all problems that researchers addressed as having a possible bacterial etiology. However, for various reasons the research programs failed, and the family of bacterial research programs became relatively heterodox by the second half of twentieth century. In other words, in the research cultures of the chronic disease research communities, it became "common-sense" knowledge that chronic diseases were not infectious, with a few exceptions (some viral etiologies for cancer). Any theories or research programs that suggested otherwise would be positioned in narratives of scientific progress that cast those heterodox programs as epistemological atavism or cultural survivals from earlier, less scientific times. The situation set the stage for a dramatic consensus shift during the 1980s and 1990s for the etiology of gastric ulcers, duodenal ulcers, and related gastric diseases, which for decades had been viewed as noninfectious. The question that emerges is whether it is in the public interest to dedicate funding for similar reassessments in other chronic disease fields.

This essay will focus on peptic ulcers, cancer, rheumatoid arthritis, and multiple sclerosis, and mostly in the U.S. and a few other English-speaking countries. Left outside the scope are the following problems: 1) comparative analysis across national research traditions; 2) parallel

histories of viral programs for the same chronic diseases; and 3) diseases that have a bacterial etiology but have been recognized more recently, such as Legionnaire disease, Lyme disease, toxic shock syndrome, and, less conclusively, Gulf War syndrome and AIDS, both of which may involve bacterial agents, perhaps as cofactors (Nicholson and Nicholson 1997, Montagnier and Blanchard 1993). The focus here is on long-recognized diseases for which bacterial research programs were once relatively prominent in the research cultures and subsequently slipped into heterodox status.

Peptic Ulcer Research [subheading]

Biomedical researchers now credit the rediscovery of the role of the spiral-shaped bacterium now known as *Helicobacter pylori* in gastric diseases to work by Australian gastroenterologist Barry Marshall and pathologist Robin Warren. Their work was first presented in the early 1980s, although a precursor study in 1975 is also given some credit for laying the groundwork (Steer and Colin-Jones 1975). Marshall demonstrated his hypothesis in a dramatic way: by drinking a glass of water infested with the bacteria and giving himself gastric disease, a test that he devised after failing to fulfill Koch's postulates with experimental animals. Although the Australian Gastroenterology Association rejected his first paper, Marshall was more successful with the International Workshop of Campylobacter Infections, and he and Warren first published their results as letters in *Lancet* (Warren 1983, Marshall 1983). Opinion was at first highly critical or dismissive, but subsequently researchers from New Zealand reported a replication of the experiment (Morris and Nicholson 1987), and gradually replications came in that favored the Australian claim. By 1993 consensus conferences in the U.S. and other countries had recognized the bacterium as playing a significant role in gastritis, duodenal ulcers, and gastric ulcers (e.g.,

National Institutes of Health Consensus Conference 1994). Treatment is a relatively simple and nontoxic sequence of antibiotics and bismuth, known as the "triple therapy," that can usually eradicate the bacterium in less than two weeks (Soll 1996). Furthermore, researchers are increasingly finding linkages between the global infection of the world's population and the incidence of gastric cancers (Parsonnet 1993, 1996).

The rediscovery of *Helicobacter pylori* has prompted some soul-searching among gastroenterologists (e.g., Blum 1996), just as the discovery of bacterial agents in other diseases at first thought to be of unknown etiology (e.g., cat scratch disease, Legionnaire disease, and Lyme disease) has prompted soul-searching in the medical community at large. An editorial in the *Annals of Internal Medicine* by Vanderbilt University physician Martin Blaser (1994) proposed several reasons why recognition of bacterial etiology was delayed for some diseases: difficulty of culturing some pathogenic bacteria, such as *Legionella;* difficulty of distinguishing pathogenic from nonpathogenic strains, such as E. *coli* in hemolytic-uremic syndrome; low bacterial concentrations that are difficult to visualize using conventional stains, such as *Rochalimaea* for cat scratch disease; uncommon sequelae of common infections, such as Guillian-Barre syndrome, which occurs only once in 1000 to 2000 infections of *Campylobacter;* and dogma, such as the belief in the sterility of the stomach that he argues played a role in delaying recognition of *Helicobacter pylori.* The fifth factor, dogma, is in effect a recognition of the fact that research fields have cultures that are hierarchically structured such that some research programs (e.g., the bacterial programs for chronic disease) tend to develop a heterodox status. In itself the dogmas of the research culture do not explain the events; instead, one must ask why the dogmas emerged in the first place.

A thorough history by Mark Kidd and Irvin Modlin (1998) of what is now seen as

Helicobacter pylori provides more specific details on the failure of the bacterial program in the peptic ulcer field. Their research found that spiral organisms in the gastrointestinal tract of animals had been described as early as 1838 (1998: 4). In 1889, the Polish researcher Walery Jaworski postulated a pathogenic role for the organisms, but his views apparently had little impact, perhaps because his original observations were published in Polish (an explanation that points to the nonuniversality of decision criteria in science, which tend to ignore research produced outside the global centers). Kidd and Modlin document that other researchers found other organisms, such as *Staphylococcus,* that, when injected into animals, produced gastric lesions. Thus, divisions occurred within the bacterial research program as some researchers, such as the American Edward Rosenow, advocated a streptoccal etiology, and others, such as the British J. S. Edkins, examined spiral-shaped or "spirochete" organisms. As researchers in this program faced a variety of organisms and some difficulties in culturing them, other researchers advanced a program that defined duodenal ulcers as the result of "hyperacid gastric juice" (Kidd and Modlin 1997, 7). Thus, the first factor in the demise of the bacterial research program was the inconsistency of organisms that was associated with internal divisions among the researchers.

A second factor involved the failure to culture organisms consistently. In 1940, a report identified spirochetes in only 52% of the ulcerating stomachs compared to 14% in nonulcerated stomachs (Freedberg and Barron 1940). While the relative proportion might appear to suggest a causal relationship, it was weak in terms of a model of causality based on Koch's postulates, where the microbe must be present in the diseased organism and not present in the non-diseased organism. The report concluded that there was "no evidence" that the organisms had pathological significance. Another study, which used a less reliable staining procedure, failed to demonstrate spirochetes or similar organisms in samples from over 1,000 human gastric patients (Palmer 1954).

According to Kidd and Modlin, Palmer's work, which suggested that spirochetes were part of the normal flora of the mouth, "may thus be credited with the envious distinction of setting back gastric bacterial research by a further thirty years" (1998, 10). Likewise, a historical summary by the physician Cornelius Dooley concludes, "After the publication of this [Palmer] report, interest in gastric bacteria waned" (1993, 2).

In the internal histories of the field, the pattern of consensus shifts—from decline after 1940 to revival in the 1990s—appears to be explained as a product of researchers guided by universalistic, technical values in the face of ambiguous evidence. In other words, the problems of ambiguity in both the type of organism and the frequency of its association with gastric disease weakened the position of advocates of the bacterial research programs. The end result is that, after an historical cul-de-sac, the research field corrects itself and produces a better research program, almost in the form of the return of the repressed. However, the process appears legitimate (in terms of the employment of universalistic values) at both historical junctures. The rejection of the bacterial program was based on ambiguities in the evidence, and the resurgence of the program is ascribed to the emergence of new technologies such as the endoscope and new bacterial culturing techniques that helped make the observations more credible and stable. By implication, because the new therapy is both curative and relatively inexpensive and nontoxic, it is superior to existing antacid therapies and therefore is clearly in the public interest. In other words, universalistic, technical values seem to guide the evolution of a research field that, in the long run and after a historical lapse, produces research and therapies that are both technically progressive and in the public interest.

However, the narrative of undone and redone science probably conceals some undone history. First, as journalist Terence Monmaney (1993) points out, the prevailing view of peptic

ulcers during the second half of the twentieth century was closely linked to indictments of the tense, stressful lifestyles of modern industrial societies, which trigger in some people a reaction of excessive secretion of gastric juice. A scientific claim—that the acidity of the stomach made it impossible for bacterial flora to survive there—that was linked to another claim—stress creates excessive acid secretion—enabled the etiology of peptic ulcers to enter the realm of common sense in the lay and clinical cultures, where peptic ulcers were attributed to stressful jobs or poor marital situations. Noninfectious theories and therapies were therefore supported and justified by values that oppose the *gesellschaft* of a rapid pace and competitiveness. In this sense, particularistic values—selection criteria based on factors other rather evidence and consistency (or safety, efficacy, and cost for a therapy)—came to strengthen the scientific selection of noninfectious theories. The common phrase, "He (or it) is giving me an ulcer," became both a popular explanatory model of illness and a statement about personal or institutional values. In other words, the technical, universalistic values interior to the research culture aligned with particularistic values in the general culture. In this case, however, the particularistic values appear to have emerged after the selection of the noninfectious programs, so that their primary role was not in contributing to the original demise of the infectious program but instead in strengthening the resistance to its resurgence.

Second, the question of sectional interests remains unexplored. Acid-blockers are major money makers for the pharmaceutical industry; in the U.S., peptic ulcer drugs are listed as two of the three top sellers in the $92 billion pharmaceutical industry (Hall 1997, 69). Predictably, the industry did not respond to Marshall's requests for support for his research, probably because the new therapy for *Helicobacter pylori* can be accomplished with generic drugs that are relatively inexpensive and unprofitable (Monmaney 1993). However, as consensus shifted, the

pharmaceutical companies also changed their orientation, and they began to fund clinical trials of new, more profitable antibiotics for the bacterium (Monmaney 1993). Furthermore, the guidelines of the American College of Gastroenterology carefully suggest that clinicians combine treatment for the bacterial infection with conventional pharmaceutical products already in use (Soll 1996). In this way, the new therapy has been brought into general use without directly displacing highly profitable products on the market, and indeed it has created opportunities for new diagnostic devices and new antibiotics. In summary, a complete history of the consensus shifts in the peptic ulcer field might reveal a more complex scenario in which general cultural values and industrial interests supported the stability of the nonbacterial consensus.

Cancer [subheading]

In the cancer field the bacterial research program declined by the first decade of the twentieth century, but it remained as a small minority tradition throughout the century, in contrast with the later demise of the bacterial program in the peptic ulcer field but its apparent dormancy after its demise. As in the peptic ulcer field, universalistic, technical values played a significant role in the deselection of bacterial cancer programs. For example, because bacterial cultures tended to be inconsistent, some researchers were inclined to interpret the purported pathogens as contaminants or opportunistic infections. Furthermore, in the cancer field the bacterial program researchers tended to interpret the differences among bacteria as the variants of a single cancer microbe. By interpreting cancer microbes as “pleomorphic” bacteria (capable of morphological change in response to environmental changes) or, somewhat later, as bacteria that have cell-wall deficient phases, the bacterial programs in cancer research suffered from linkage to the bacterial variation controversies in microbiology (Amsterdamska 1987, 1991; Hess 1997). Likewise,

bacterial cultures were difficult to obtain and required nonstandard techniques.

For the bacterial therapies, anticancer sera and vaccines that were developed under the bacterial programs in the cancer field were difficult to prepare and administer in standardized doses. Questions of safety also emerged for the fever treatment of Coley's toxins, a bacterial vaccine that involved injections of a combination of bacterial that caused a high fever that, in some cases, triggered an immune-system response that led to long-term cancer remission. Likewise, efficacy appeared to vary across tumor type (for example, Coley's toxins worked well for sarcomas), and research that documented efficacy was sparse and often not in the form of clinical trials, itself a product of poor funding.

At the same time, however, the barrier for sera and vaccines was strengthened by a medical culture that was increasingly favoring an industrial value of therapeutic standardization that drew models from a modernist culture and economy of mass production (Hess 1997). Thus, therapies such as radiation treatment and, after the second world war, chemotherapy, could be administered according to standardized doses that met industrial therapeutic selection criteria in which individual differences among patients were minimized. Values such as standardization on the model of industrial-style mass production of therapies went hand-in-hand with industrial interests that favored profitable therapeutic products. In this case, there was a close alignment of a particularistic value (standardization) and a sectional interest (radiation and chemotherapy).

A similar convergence occurred with the view that cell-wall deficient phases of known bacterial species and mycoplasma (a type of bacteria that do not have cell walls) have little pathological importance. Researchers often assumed that bacteria lacking cell walls would rupture in the host due to osmotic pressure, and until recent decades few studies supported the claim that cell-wall deficient bacteria or mycoplasma can play a role in disease (Mattman 1993, Tsai et al.

1995). Universalistic values such as lack of evidence for pathogenicity or lack of consistency with known osmotic pressure phenomena could be used to justify dismissing the theory that cell-wall deficient bacteria could play a role in pathology, yet the failures were based less on negative studies than on undone science. As the research culture of medical bacteriology rejected pathological roles for cell-wall deficient bacteria, the bacterial programs slipped into heterodox status. Researchers who supported the heterodox programs tended to include women to the point that biologists commented on their predominance (Hess 1997). Likewise, cell-wall deficient bacteria were "feminized" as non-aggressive or not dangerous to the host, and such views of the "deficient" bacteria that lacked a cell-wall (parallel to sexist characterizations of female anatomy) became part of the common sense of the research culture. In other words, particularistic, masculine values were mobilized in the construction of the purported cancer microbes as nonaggressive and etiologically unimportant.

In terms of interests, leaders associated with the emerging industries of radiation oncology in the first half of the twentieth century and chemotherapy in the second half were not only outspoken critics of bacterial programs but instigators of incidents of intellectual suppression (Moss 1996, Hess 1997). At the same time, some of them were true believers in the view that radiation therapy and chemotherapy were in the public interest, and the medical journals are full of cases that document remissions achieved with the conventional therapies (albeit mostly temporary and accompanied by side effects). Consequently, an alignment of sectional and public interests occurred; the leaders of the emerging radiation and chemotherapy programs could view their criticism and even suppression of the bacterial programs and therapies as legitimately in the public interest even if they were also economically invested in the dominant therapies and receiving substantial profits from their continued use.

Today, the bacterial programs for cancer occupy a very heterodox position within the cancer field, with a few exceptions. First, the bacterial vaccine of William Coley, a Harvard-educated physician who worked at New York's Memorial Hospital until his death in the 1930s, has undergone some recuperation as he has been reconstructed as the father of tumor immunology. However, the recuperation of the bacterial vaccine has coincided with its disengagement from Coley's own research on bacteria as cancer pathogens. The current medical histories of biological treatments of cancer, which now give a place of honor to Coley, have also downplayed or ignored his role as a supporter of the now discredited view that bacteria can cause cancer (Oettgen and Old 1991, 97). The evidence in support of the efficacy of his vaccine is interpreted as due not to an effect on bacterial pathogens but instead to nonspecific stimulation of the immune system (e.g., Wiemann and Starnes 1994), which the tumor immunologists consider to be inferior to their more toxic, specific therapies such as the interleukins (Rosenberg and Barry 1992, 59). Another exception to the heterodox position that bacterial research programs occupy in the cancer research field is the increasing recognition that the bacterium *Helicobacter pylori* causes not only gastric ulcers and some gastric carcinomas, but also gastric non-Hodgkin's lymphoma (Parsonnet et al. 1994) and some colon cancers (Meucci et al. 1997). Thus, the consensus shift that occurred in the peptic ulcer field may have a spillover effect on the cancer field. The third major, but less generally accepted, exception is the increased interest in the role of the human growth hormone choriogonadotropin in tumor promotion and the possible role of cancer-related bacteria in producing a similar substance (Livingston and Livingston 1974, Acevedo et al. 1987). With minor exceptions in mind, it is safe to conclude that the position of bacterial programs and therapies in the cancer field is extremely heterodox.

Rheumatoid Arthritis [subheading]

The role of bacterial programs in the rheumatoid arthritis (RA) field bears similarities and differences with both the peptic ulcer and cancer fields. As occurred in the peptic ulcer field, there has been a consensus shift during the 1990s, but it is less dramatic. Clinical trials using minocycline in the Netherlands (Kloppenberg et al. 1994) and the U.S. (Tilley et al. 1995) reawakened interested in antibiotic treatment for RA. However, antibiotic therapy for RA has a longer duration than for peptic ulcers—it is a matter of many months or even years rather than days or weeks—and the results from the clinical trials of the 1990s have been only moderate in comparison with existing therapies. Furthermore, as in the peptic ulcer and cancer fields, there are heavy professional and pharmaceutical investments in therapies that assume a noninfectious etiology. Consequently, antibiotic therapy has not displaced existing therapies, even though it is probably safer and may result in recoveries of longer duration. The picture may change as results from studies in early-stage RA patients, which appear to be more dramatic, come in (e.g., O'Dell et al. 1997).

Even if antibiotic therapy were to replace conventional therapies for RA, it would probably end up disengaged from research programs on bacterial etiology. Current opinion in the RA field probably favors nonbacterial mechanisms, such as inhibition of collagenase enzymes, as the explanation for the apparent efficacy of antibiotic treatment (e.g., Breedveld 1997). Although the delinking of the therapy from the bacterial etiology is analogous to what occurred in cancer research with bacterial vaccines such as Coley's toxins, bacterial vaccines are more controversial in the cancer field than antibiotic therapy is in the RA field. The relative ease of acceptance of antibiotic therapy in the peptic ulcer and RA fields in contrast with the continued controversial status of bacterial vaccines in the cancer field suggests that antibiotics represent a more promising

therapeutic linkage for bacterial research programs, not only because antibiotics (even generic ones) are more acceptable to the pharmaceutical industry but also because antibiotic therapy is more consistent with the industrialized, standardized treatment values of the culture of contemporary biomedicine.

Like the cancer field and unlike the peptic ulcer field, no single, stable organisms emerged as a candidate pathogen for RA. Although peptic ulcer researchers in the late nineteenth century and first half of the twentieth century also found a variety of candidate organisms, spiral-shaped organisms were consistently found, and in the 1990s, the field was able to stabilize around a single organism. In contrast, according to a medical history of RA by R. A. Hughes, proposed bacterial agents for RA changed over a history that he broke into three periods: a variety of small bacilli from the late nineteenth century through the 1920s, a focus on streptococci until the late 1930s, and attention to mycoplasma after the 1930s (1994b, 363). During the middle period, research was led by the Mayo Clinic's Edward Rosenow, who was mentioned above in the context of peptic ulcer research and was also peripherally involved in some of the bacterial research for cancer. Rosenow was also an advocate of bacterial variation or "transmutation." His studies of bacterial variation and the subsequent research on mycoplasma suggest parallels, at the level of proposed organism, between the bacterial programs in RA and cancer rather than RA and peptic ulcers. Unlike the peptic ulcer field, the bacterial programs in the RA and cancer field tended to focus on more ambiguously defined bacterial agents, thus making it easier to question their existence or pathogenicity. In other words, universalistic, technical criteria for theory choice were legitimately employed in the RA field to reject the bacterial research programs.

Moreover, the bacterial therapies that emerged in the RA field faced severe problems of safety and efficacy. Under the popular focal infection variant of the bacterial etiology theory, doctors and

dentists treated diseases such as RA by removing infected teeth, tonsils, or other organs. The theory and therapy were under attack by the late 1930s and fell into disrepute by the 1950s (Hughes 1994a, 375-76). As Hughes relates, "Nails were driven into the coffin of focal infection by abreaction amongst both patients and doctors opposed to the wholesale removal of organs and also by papers failing to confirm that streptococci were isolated more frequently from tissues of patients with RA than from those of a control population" (Hughes 1994b, 363, citing Dawson, Olmstead, and Boots 1932). Hughes points to one study (Davidson 1949) that found a nearly equal incidence of focal infection in RA and control patients, but by that point medical opinion had largely turned against the focal infection theory. In some cases, advocates of the focal infection theory treated arthritis by removing all teeth, only to find that the arthritis remained. Furthermore, the emergence of antibiotics made it possible to treat purported focal infections without operating. Therefore, safety and efficacy concerns for the surgical therapy appear to have been more significant than lack of evidence for the focal infection theory, although the two concerns ran together. In short, universalistic criteria, particularly safety and efficacy concerns for the therapy, and public interest concerns legitimately led to the rejection of the bacterial surgery therapies.

However, during the next generation, a reconstructed minority research and therapy tradition continued within the RA field, and the play of values and interests became more questionable. The minority tradition focused on cell-wall deficient bacteria and mycoplasma as possible etiological agents and antibiotics as the therapy of choice. The minority tradition in the U.S. was led by the physician-researcher Thomas Brown, who was chair of the Department of Medicine at George Washington University. Brown claims that the bandwagon that developed around cortisone research in the late 1940s and into the 1950s made it extremely difficult for him to win any interest in the mycoplasma theory, even though he was achieving good results (Schammell

1993, 75-76). Furthermore, he probably further marginalized himself by becoming an early critic of the dangers of cortisone. Although his concerns with safety proved to be accurate, he was removed from a key committee of the American Rheumatism Association for his position against cortisone, and his funding for research on the bacterial etiology disappeared. Because the American Rheumatism Association had been founded in part to combat the abuses of surgery in the treatment of arthritis, the organization apparently had a strong bias against infectious theories of any sort, including a program linked to antibiotic therapy rather than surgery. Even in the late 1980s, the organization developed a campaign against Brown's book on the mycoplasma theory and tetracycline treatment (Scammell 1993, 35). After the weaknesses of cortisone treatment were recognized, the organization continued to support other drug treatments not based on infectious theories, such as nonsteroidal anti-inflammatory drugs and the cancer drug methotrexate (98, 155). Thus, conventional therapy for RA during this period was similar to that for cancer and peptic ulcers: patentable, profitable drugs that were not based on infectious theories.

The factors leading to the rejection of Brown's research program and therapy were therefore complex. The history of unsafe, inefficacious surgery that had accompanied the focal infection theory led to rejection of surgical treatment based on universalistic values (lack of proof of efficacy) and public interest concerns (harm to patients). Yet, the replacement of infectious theories by new research programs, such as the auto-immune disorder program, became linked to profitable therapies that were supported by the pharmaceutical industry. In other words, whereas universalistic values and a notion of general public interest (in therapeutic safety) guided the demise of the bacterial programs, sectional interests (pharmaceutical industry profits) in new drugs would tend to keep Brown's alternative formulation of the bacterial program from receiving fair consideration within the research field.

Of course, the justification for that rejection would not explicitly make reference to sectional interests; instead, it drew on universalistic values, in fact even more so than usual. In other words, the stabilization of the research culture as the outcome of the closure of the controversy prior to Brown meant that any attempts to revive the defeated bacterial program would be subject to the toughest of technical evaluation criteria. As occurred with other excluded or heterodox programs and therapies in cancer research, Brown would get the book of universalistic criteria thrown at him, while at the same time he was stripped of research funding that would allow him to meet those standards. Thus, universalistic values can aligned with sectional interests so that the research field is proceeding according the highest of scientific standards along a pathway defined by sectional interests. In turn, that pathway may lead to another research and therapy cul-de-sac, as occurred in the peptic ulcer field.

However, Brown also suggests that technical problems made it difficult for him to win support for his therapy. In other words, even if scientists were motivated to throw the book at him, they would not have to overplay their technical values by much to reach a grounded conclusion of rejection. For example, when Brown first published on the mycoplasma theory in 1939, it was difficult to culture mycoplasma, and other researchers suspected that his successful cultures were contaminants, a view that is widely shared even today (Scammell 1993: 28).

Even more complex was the relationship of the excluded program to the hierarchical structure of methods in the research field. Clinical trials represent the top of the ladder of evidence in the evaluation of therapies, in contrast with retrospective outcomes assessments or case study series. There are many ways in which clinical trials can bias measurements of efficacy against nontoxic therapies (see especially the interview with Houston in Hess 1998). Brown called attention to one biasing factor that affected the evaluation of his alternative antibiotic therapy: the

tendency for clinical trials to last only six months created a bias in favor of ineffective, toxic drugs and against his alternative. At the six-month interval, toxic, symptom-masking drugs tended to produce successful, short-term results. In contrast, the effects of his tetracycline treatment were often not yet evident, and patients could even be in a worse condition due to a healing process known as the Herxheimar reaction, in which patients worsened before they got better. Brown argued that if the endpoint for clinical trials had been extended to two years, the lack of safety and efficacy of conventional treatments would be evident, whereas his alternative would have proven safer and more efficacious (1993, 165). This problem also occurs with cancer research, where radiation and chemotherapy often demonstrate short-term responses but have very poor prognosis at long-term endpoints, especially at the five- and ten-year mark. The problem suggests again how the hierarchical structuring of research methods (where, for example, Brown's huge case study base of 10,000 patients could be ignored in favor of short-term clinical trials) created biases in the selection of therapies. An alternative hierarchy of research methods that used long-term measures as the method of choice would have dramatic epistemo-political implications for the heterodox status of alternative therapies in the RA field, and other disease fields as well (Hess 1998).

Today, rheumatologists recognize a variety of microbial agents for the etiology of several types of rheumatic disease (Espinosa 1993), but they are skeptical that RA could be caused by a single bacterial agent, as in the case of Lyme disease or rheumatic fever (Harris 1997, 41). Cell-wall deficient bacteria or mycoplasma found in the joints of RA patients still tend to be rejected as contaminants, as occurred with similar bacteria found in tumors, although there is some interest in the immunological role of bacterial components as contributing factors to RA (Harris 1997, 43). To the extent that the minocycline therapy becomes widely accepted, it will probably happen, at least in the short-run, after the therapy is disengaged from theories of bacterial etiology.

Multiple Sclerosis [subheading]

The MS field is intriguing as a fourth point of comparison because of the long history of researchers who considered MS to be a "spirochetal" disease. Although the classification would seem to situate MS in a family of diseases similar to syphilis and yaws rather than peptic ulcers, much of the early terminology is ambiguous, and the agent seen in the early studies might have been more similar to *Helicobacter pylori.* The point is that the categorization of the bacterial agent for MS does not suffer from the ambiguities of complex pleomorphic bacteria, as in cancer, or mycoplasma, which characterized the RA field.

The rejection of the bacterial program in the MS field appears to be the result of historical contingencies rather than considered argumentation based on universalistic values. According to one of the current advocates of the spirochetal theory, Vincent Marshall, the largest concentration of researchers during the period prior to World War II was from Germany, and many of them disappeared in the Holocaust or the war (1988: 89). He adds that in the late 1950s, an American researcher published on the subject but then issued a retraction, explaining that the positive cultures were due to contamination:

> This paper was then repeatedly refuted in numerous journals by her fellow researchers ...This occurred in the early years of the National M.S. Society and resulted in a total stonewalling of all spirochete research funding for the last 40 years (Marshall 1988: 90).

Instead, research funding was directed toward various hypotheses of viral etiology. Viral programs had been in existence in cancer research since the first decade of the twentieth century, and they were popular during the period following the polio vaccines and prior to President Nixon's declaration of the end of research on biological warfare agents. As occurred with the quest

for viral etiologies for the major human cancers, for MS the various attempts to find a viral etiology have not been successful, although viruses remain of interest as cofactors that may contribute a triggering role (Cook and Dowling 1996).

Why would a single failed study in the MS field negate several other previous studies and lead to the failure of a research program? If the history of the American Cancer Society—which held a patent for a major chemotherapy drug (Moss 1996)—is any guide, the history of the National Multiple Sclerosis Society might reveal some interesting ties to the pharmaceutical industry. The tone of blanket skepticism toward metabolic, nutritional, and infectious theories of MS that appears in an official publication of the society (Sibley and Therapeutic Claims Committee 1996, 21) is reminiscent of the American Cancer Society's approach (American Cancer Society 1960, 1990). The leading U.S. nonprofit cancer research organization maintains a list of "unproven therapies," a blacklist directed against several bacterial therapies as well as other "alternative" and metabolic therapies. A position on the list tended to coincide with loss of FDA approval. In general, industrial interests have captured nonprofit organizations in the chronic disease field (Bennett and DiLorzenzo 1994), and their control creates a ventriloquism whereby the nonprofit sector does the work of aligning sectional and public interests, in effect by distorting the latter to correspond to the former. However, the history of the industrial capture of the Multiple Sclerosis Society remains hypothetical at this point. Once again, the problem of undone science runs up against the sibling problem of undone history of science.

Conclusions

The history of the demise of bacterial research programs for chronic disease is a historical and social science puzzle with policy implications. If the rejection of the bacterial programs was not

well justified—that is, if particularistic values and sectional interests played a significant role in the history—then grounds can be established for a legitimate policy intervention (via funding priority changes) that would provide fair evaluation of the relative merits of the lost or undone science. In this sense, science and technology studies can be more than an exercise in historical explanation; it can help to articulate the public interest in science research and science policy and locate points where alignments of values and interests may have obscured the production of research and availability of therapies that are in the public interest.

So does the history of a dramatic consensus shift for peptic ulcers provide a model for other chronic diseases with a history of bacterial programs? Unfortunately, where the case is strongest for demonstrating the role of particularistic values and industrial interests—cancer research—the case for the bacterial programs is also the weakest from a perspective of universalistic, technical values such as evidence, consistency, and, for therapies, safety and efficacy. It is now generally recognized that genetic and noninfectious environmental mutagens (such as cigarette smoke or radiation exposure) play an important role in the genesis of some tumors. It seems likely that if cancer-associated bacterial pathogens play a nontrivial role in cancer, they are tumor promoters, not initiators, although the recent research mentioned above on *Helicobacter* suggest that bacteria may also be tumor initiators for some cancers, particularly those of the digestive tract. Nevertheless, even the more moderate claim that bacterial pathogens may serve as tumor promoters seems to warrant investigation, particularly if relatively safe therapies such as vaccines and antibiotics may contribute to cancer control. Indeed, the comparative analysis across chronic disease fields suggests that long-term use of antibiotics in the tetracycline family may be a potentially new alternative therapy for cancer that has been attempted rarely, if ever. (In my fairly exhaustive historical research, Gregory (1952) may be the exception.)

In the case of RA, the relationships are somewhat reversed. Whereas the undone history may yet reveal a substantial role played by industrial interests in the decline of bacterial programs, there seems to be—given the existing state of historical knowledge—more evidence to support the role of universalistic values in guiding the rejection of bacterial programs, at least for the middle period of bacterial programs and therapies associated with focal infections and unnecessary surgery. In the subsequent period of research directed toward mycoplasma and cell-wall deficient bacteria, the story of Thomas Brown suggests suppression by industrial interests and their aligned professional bodies and organizations. However, the research on mycoplasma as etiological agents remains incomplete and inconclusive, largely due to lack of funding. Nevertheless, the growing acceptance of minocycline therapy suggests that the program *may* have some validity and would warrant further evaluation independent of funding for antibiotic therapy.

Finally, the case of MS seems in some ways to be the most parallel to peptic ulcers. The research on "spirochetes" suggests the possibility that a bacterial agent similar to *Helicobacter pylori,* and without the controversies and ambiguities associated with mycoplasma or cell-wall deficient bacteria, may be an overlooked etiological agent. Furthermore, the apparent bias of a major funding source and the role of historical contingency in the demise of the program (the death of the German researchers during World War II) suggest that universalistic values did not guide the rejection of the program. Whereas in the cancer and RA fields, bacterial etiologies have become disengaged from their formerly associated therapies and, free from the bacterial etiology stigma, are better positioned to regain acceptance in the medical community, in the MS field bacterial vaccines and antibiotic therapy have not been widely reported. (A search on Medline, for example, revealed that antibiotics were being used to treat only opportunistic infections in MS patients.) Consequently, there appears to a great opportunity here as well.

From the perspective of building a science policy that more closely approximates the public interest, the comparative analysis across research fields suggests not only the opportunities to repeat the consensus shift that occurred in gastroenterology but also the possible reasons why such shifts may not be difficult or impossible. Clearly, a successful replacement of current therapeutic regimes in cancer, RA, and MS with effective, inexpensive, and safe alternatives—as occurred with the short-term course of generic antibiotics for the treatment of *Helicobacter pylori*—would be aligned with most definitions of the public interest. Likewise, it seems that if the dominant researchers are left to their own preferences, they will guide research away from the bacterial programs because of the stigma that the programs have accrued in the research cultures over the course of time. Consequently, ear-marking public funds for further evaluation of the minority research programs with their affiliated low-toxic therapies would seem to be an appropriate intervention that could be defended as in the public interest.

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