S|S|S

ABSTRACT The early 1980s constituted a watershed in science, mainly concerning the extent and nature of globalization and commercialization of scientific research, and its impact upon the university. Considerable debate has arisen about the sources of this transition, but aside from a few lone voices, the scholarly literature has neglected the concurrent rise of the contract research organization (CRO) and its role in the commercialization of scientific research. The CRO warrants wider attention as a modern paradigm of privatized science in the biopharmaceutical sector. In discussing the CRO's technologies, the purposes they pursue, and the legal and policy initiatives that have fostered their rapid rise, we confront the wider implications of the modern regime of commercialized science for the future conduct of scientific research. We identify five areas of innovation: treatment of human subjects, control of disclosure, subjection of research tools to commercialization, redefinition of authorship, and re-engineering the goals of research.

Keywords commercialization of science, contract research organization, ghost authorship, globalization of research, intellectual property, new economics of science

The Contract Research Organization and the Commercialization of Scientific Research

Philip Mirowski and Robert Van Horn

There are two broad reactions in the academic literature to the advancing commercialization of the modern scientific enterprise. One sounds the alarm over:

> an increased dependence on industry and philanthropy for operating the university; an increased amount of our resources being directed to applied or so-called practical subjects, both in teaching and in research; a proprietary treatment of research results, with the commercial interest in secrecy overriding the public's interest in free, shared knowledge; and an attempt to run the university more like a business that treats industry and students as clients and ourselves as service providers with something to sell. (Brown, 2000: 1701)

In this view, the essential attributes that demarcate science from other social endeavors are being undermined and corrupted.[1] These authors tend to subscribe to a Mertonian characterization of the ideal scientific community, so we shall call them the Mertonian Tories. Their writing tends to be long on anecdotal horror stories, but rather short on specifics, be they empirical measures of the nature and extent of commercialization, or

Social Studies of Science **35/4(August 2005) 503–548**

ISSN 0306-3127 DOI: 10.1177/0306312705052103
www.sagepublications.com

theoretical analyses of vulnerable aspects of the scientific process. The second reaction is more sanguine about these modern developments, portraying them as a generic problem of 'technology transfer' from 'basic' research conducted in university settings to their presumed apotheosis as novel commodities in the commercial sphere. Since authors in this literature focus primarily upon the reorientation of the 'outputs' of research into different allocations while treating the 'producers' (universities) and 'consumers' (firms) as persisting relatively unscathed through the process of commercialization, we shall dub them the Economic Whigs. Although their writings are much more variegated and voluminous than the first category, their central tendency is to gather empirical evidence and to argue that the growing modern commercialization of scientific research was 'inevitable', and that there exists little evidence that it has 'significantly changed the allocation of university research efforts' (Nelson, 2001: 14).[2] Many of the Whigs would regard themselves as arguing in favor of the preservation of an 'optimal' sphere of research reserved for open public science and pure unfocused curiosity (a 'separate but equal' doctrine applied to unspecified portions of the university), even though they would also avow that the economy must constitute the ultimate arbiter of scientific success; hence, they cannot really understand what the Tories are trying to accomplish with their overwrought imitation of Cassandra.

Our impression is that, so far, both groups have been talking past one another. Numerous criticisms can be made of both strains of literature, but the one we would like to make suggests that both approaches are unduly restricted by the unexamined presumption that the university is the primary field upon which the privatization of research has played out. We contend that the re-engineering of the structures of scientific research since the 1980s has occurred on many different fronts, that it has been a subset of larger political and economic trends, and that universities have been relative latecomers to the thorough-going privatization of the conduct of science.[3] In many instances, the transformation was nurtured by the creation of new social structures of research, which act as prototypes outside the university: new forms of intellectual property, new communication technologies, new research protocols, new career paths, and new institutions of command and control. If this transformation has indeed come to pass, then it is still very early for universities to exhibit anything like the full consequences of the privatization of science. In other words, universities may not necessarily be the most perspicuous of entities for a study of those consequences. Furthermore, a study of the future implications for science should focus less upon the impact of changes on some narrow construction of the 'products' of research (themselves often capable of being assessed only in the fullness of time) and concentrate more on the process aspects. If we aimed to seriously address the concerns of the Mertonian Tories, then the way to do so would not be through blind adherence to the theoretical commitments and methods of the Economic Whigs. In this paper we begin to develop a third position by triangulating between the previous two, which might be called 'Triggish'. From this

vantage point, we could imagine a scenario wherein science undergoes reorganization, initially at other sites, with the university responding to those changes later and at a distance. We believe that the best way to encourage debate over the possible consequences of the commercialization of science since the 1980s is to pay more attention to functional innovations in the organization of scientific research within the *corporate* sphere. It is there, rather than at the universities, that we should expect to discover the stark outlines of a more thoroughly modern, post-Cold War restructuring of scientific research. In Trig History, 'science' has no atemporal essence, and social structures of research come and go at different centers of innovation. After this alternative model has been delimited and described in some detail, it may become possible to gauge the effects of such modern innovations upon university science.

Clearly, the sphere of corporate scientific research looms larger and is more diverse than the university sector, both now and in the past, confounding any ambition to make hasty generalizations about the commercialization of research. However, it is no accident that one industry has tended to dominate all others in the existing literature on the post-1980 commercialization of science: the biopharmaceutical industry. There one finds a major locus for recent disputes over recent innovations in intellectual property;[4] there stands the industry which presciently organized a coalition in the 1980s to exert political pressure to 'standardize' the international treatment of intellectual property as an important component of US trade policy (Ryan, 1998: 67–69; Drahos & Braithwaite, 2002; Sell, 2003); there abides an industry encumbered with a more-or-less dedicated regulatory agency in the USA, whose remit is not only to supervise the quality of its products, but its research activities as well (Abraham, 2002); and there is situated the industry most strategically located to benefit from the dramatic reallocation of post-Cold War research funding away from physics and towards the life sciences. Without entering into questions of causality here, it should be apparent that the existing literature on the commercialization of science has implicitly identified the biopharmaceutical sector as one major epicenter of innovation in the re-engineering of post-Cold War research. Yet, even there, it would be an error to treat the biopharmaceutical industry as an undifferentiated whole when it comes to science.

Consequently, we shall focus on a novel entity in the pharmaceutical sector, a specially crafted institution that exemplifies the strengths and weaknesses of the post-1980 era of commercialized research. This institution is the 'Contract Research Organization' (CRO), which for most intents and purposes did not exist before 1980.[5] What began as small specialized boutique firms offering narrowly targeted outsourcing services to pharmaceutical clients have come to dominate drug development and clinical trial management.

To our knowledge, there are no published histories of the CRO. Indeed, the only aggregate data we could find come from the industry itself, and therefore must be treated with some caution. One estimate of

TABLE 1
A decade of contract research organizations

	1992	2001
CRO market size	US$1.0 billion	US$7.9 billion
Top 20 CRO revenues	US$0.5 billion	US$4.6 billion
CROs ≥ US$100 million (*N*)	2	16
CRO employees (*N*)	12,000	94,000
Publicly traded CROs ≤ (*N*)	2	19
Enrolled research subjects (*N*)	7 million	20 million

Note: CRO = contract research organization.

the sector's growth in the 1990s comes from Davies (2002) and is presented in Table 1.

Another way to gauge the growth of CROs is to look at recent revenue growth of the four largest CROs (see Table 2).

Perhaps a better way to gauge the growing size and significance of the CROs is to compare the relative proportions of the pharmaceutical research industry research and development (R&D) budget in the specific subsets of clinical research that have been conducted through CROs with the amounts spent on their primary competitors, the Academic Health Centers (AHCs). One source suggests that the percentage of industry-sponsored clinical research captured by AHCs fell from about 80% in 1988 to 40% in 1998 (Davies, 2001). Another source estimates the market share of AHCs dropped from 71% in 1991 to 36% in 2001 (*CenterWatch*, 2002, quoted in Parexel, 2003: 130). A third source estimates that the share of outsourced pharmaceutical R&D going to AHCs was 30% in 1999, and projects that CROs would capture 90% of this market by 2006 (quoted in Parexel, 2003: 29).[6] While there are unfortunately no official statistics on the absolute size of the CRO sector, and even less describing historical trends, it would seem that an extraordinary displacement of AHCs by CROs is underway.[7]

Curiously enough, although CROs have been a subject of concern in the medical literature, thus far the literature on science policy and commercialization of academic research has neglected them. Perhaps this has been due to a fascination with the more glamorous upstream phases of the

TABLE 2
Contract research organizations: individual firm revenue growth

Revenues (US$ million)	2003	2002	2001	2000
Quintiles	2046.0	1992.4	1619.9	1659.9
Covance	974.2	924.7	855.9	868.1
Parexel	619.2	564.9	387.6	378.2
PPD, Inc.	727.0	608.7	431.5	345.3

Source: Hoovers Online at <http://cobrands.hoovers.com>.

biotechnology phenomenon, or a mistaken belief that CRO activity is restricted to a narrower range of clinical drug research in downstream phases. Another neglected aspect of the recent development of CROs is their expansion into nearly every stage of the discovery, developing, and marketing of new pharmaceuticals (Gad, 2003). One survey identifies preclinical research as one of the fastest-growing areas of CRO services (Milne & Paquette, 2004). Their activities range from initial screening of molecules for biocompatibility, in vitro screening, pharmacokinetic modeling, chemical synthesis and analysis, all phases of clinical testing, dosage formulation and pharmacy services, to all aspects of the regulatory process. They are sometimes compared with accounting firms, which have also extended their services far beyond simple record keeping.

Whatever the cause, this neglect of CROs has been unfortunate, because their successes have catapulted them into the vanguard of a movement that insists that science conducted in a for-profit modality has had no deleterious effects upon the conduct of research. As a major spokesperson for the industry put it:

> Those of us who choose to pursue clinical science within the CRO industry reject the assumption that wisdom and ethical behavior are solely the province of the academy or the government. We reject also the presumption that the pursuit of profit along with the progress of science and medicine is inherently in conflict. In fact, in our experience the marketplace accurately reflects the public's hopes and expectations for science, and is a powerful guardian of behavior. It has little tolerance for shoddy performance or misapplied energies. It is a powerful mechanism for progress, for which no apologies are needed. (Davies, 2001)

In this paper it is our intention to foster greater awareness within the science studies community of the rise of CROs as a paradigm of privatized science. CROs have been the topic of more extensive debate and discussion in the medical literature for more than 10 years, but there is no reason to suppose that they must be restricted to the pharmaceutical industry; indeed, as we shall suggest in the conclusion, there is reason to think that something like the CRO may eventually spread to other regions of commercialized science.

One might object to our approach by noting that widespread commercialization of pharmaceutical research substantially predates the appearance of CROs. Furthermore, there is substantial evidence (particularly in the US context) that some of the 'innovations' we identify later (pp. 26, 33) may have been present in some incipient form as far back as the 1930s, if not earlier.[8] As 'Trigs', we elect to remain temporarily agnostic on this issue, partly because we wonder if the manifestations of these practices really were 'the same' in both eras, but primarily because we do not aspire to provide a comprehensive history of the effects of commercialization upon pharmaceutical research, although such a history is badly needed. Instead, our immediate motivation is to contribute to the dispute between the Mertonian Tories and Economic Whigs by providing an explicit census of how CROs interact with the re-engineering of *modern* laboratory and

clinical pharmaceutical research in both corporate and academic settings.[9] We pull together scattered evidence from journalistic accounts and the medical literature on what might be called a nascent 'mode of production' of drug research rooted in specific legal, social, and organizational structures. Contrary to the Whigs, CRO science differs from what preceded it; but contrary to the Tories, accusations of corruption must be judged on a case-by-case basis, and may not be limited to US conceptions of legitimate research. Perhaps our analysis will persuade scholars: (1) to stop treating the research process as a Platonic essence, independent of its organization and funding; (2) to pose the question of whether the impact of commercialization on scientific conduct is historically contingent upon other (social, legal, cultural) factors; (3) to make use of this theoretical framework to go back and construct richer histories of the ebb and flow of the commercialization of pharmaceuticals research, and indeed, scientific research in other areas;[10] and (4) to raise the historical question of whether Mertonian images of the disinterested operation of science ever actually corresponded to research practices on the ground.

In short, we begin by posing the question: how has research in a CRO been altered by the imperative of commercialization? We then broach the further question: how have these innovations filtered through to modern university science?

Conventional Accounts of the Rise of the Contract Research Organization

It is necessary to gain a rudimentary grasp of the modern drug development process in order to see how it determines the way science is conceptualized and performed by the pharmaceutical industry.

The drug development process in the USA has been effectively standardized through regulations promulgated by the Food and Drug Administration (FDA). This system dates from the 1938 Federal Food, Drug and Cosmetic Act (Marks, 1997: chapter 3; Rasmussen, 2005). However, most observers agree that the real watershed was the Kefauver-Harris Amendments of 1962, which reacted to the Thalidomide controversy (Daemmrich, 2004: 26–29). These amendments mandated that the FDA require drug companies to demonstrate the safety and efficacy of a drug before marketing it. The FDA was authorized to determine the standards and format of testing from the first animal trials through the final human clinical trials. Although immediately attacked by economists and industry as unwarranted government interference with innovation, delaying the marketing of new drugs, the FDA approach gradually became the gold standard of pharmaceutical approval.[11] Initially, because of the dominant size of the US market, but later promoted as part of a process of 'harmonization' of regulatory requirements across the European Union, Japan, and the USA, the FDA-mandated procedures now form the basis of corporate drug testing throughout the developed world (Abraham & Smith, 2003).

Briefly characterized, the FDA-mandated process involves the following steps: the sponsor, in this case the pharmaceutical company, initiates the drug development process. This occurs regardless of whether the idea for the treatment originated in an academic, clinical, or corporate laboratory. The drug development process then comprises four stages: a preclinical (or animal) stage, a clinical stage, a regulatory delay, and a postclinical stage. During the preclinical stage, a new compound to effectively treat a disease is identified and tested on animals in order to ascertain pharmacological effectiveness, and potential for toxicity and carcinogenicity. The FDA has recommended a minimum of 12 months of tests on at least two species (typically mice and rats).[12]

After filing an Investigational New Drug (IND) application with the FDA and receiving preliminary approval, the clinical stage consisting of four standardized 'Phases' begins, with each phase recruiting suitably informed patients.[13] An institutional review board (IRB) oversees procedures and protocols of the clinical trial, and investigators at various academic institutions, hospitals, or (more recently) other sites administer the clinical trial. Phase I, which lasts about one year and involves a few dozen patients, typically aims to identify any deleterious effects on normal healthy patients. Phase II, which lasts several years and involves a few hundred patients targeted for the pathology of interest, determines if the drug has some therapeutic effect on the specific disease – efficacious or deleterious. Phase III, which lasts up to five years and involves thousands of patients, seeks to quantify degree of effectiveness, and can involve masked trials that compare the new drug with a placebo and/or existing rival treatments. If the drug proves promising, then the same firm files a New Drug Application (NDA), and waits for FDA approval to market the drug. Further Phase IV postclinical trials can be conducted after a drug is approved for marketing, perhaps due to concern over its longer-term efficacy, or perhaps because the FDA conceives of a need to monitor safety. In the pharmaceutical industry, the period between the initial Phase I trial and the submission of the NDA is often called the 'developmental cycle time' (Getz & de Bruin, 2000).

In the postwar period, research into drug efficacy became a very formalized and ritualized process. As the demands imposed upon pharmaceutical development have become more elaborate, they also came to be regarded as excessively onerous. Recruiting subjects, managing diverse trials in different settings, monitoring and recording data, subjecting data to statistical controls and higher-level analyses, and writing up the results for publication all absorb vast amounts of time and money. From the perspective of the pharmaceutical corporation, the more time and money spent upon FDA trials and procedures, the less is available for patent protection. Because of a perceived need for speed, and because of the vast sums of money involved – one (possibly exaggerated) estimate put the average cost to develop a single new drug in the 1990s at US$802 million (Tufts Center, quoted in Parexel, 2003: 94) – there arose the impression of a conflict between conventional norms of (academic) science and the

commercial imperatives operating in the drug development process. As one former FDA Commissioner put it, 'Many drug reviewers had become accustomed to working at an academic tempo, largely devoid of deadline pressure' (Kessler, 2001: 40). In order to placate certain organized patient constituencies (especially AIDS activists) as well as address the concerns of the pharmaceutical industry, the FDA made numerous changes to its requirements for drug trials in the 1990s, under some circumstances dispensing with placebo comparisons, and implementing other rule changes which served to shorten the average time from NDA to drug approval. Indeed, one recent study documents a sharp downward trend in approval times in the 1990s, with the percentage of new drugs receiving FDA approval within 6 months from NDA increased from 4% in 1992 to 28% in 1999 (Kaitin & DiMasi, 2000). Some observers treated this as a consequence of the FDA Modernization Act of 1997, while others suggested that the FDA has been pressured continually to bend its procedures to meet the demands of the pharmaceutical companies. Because of various deregulation initiatives, about 12% of the FDA budget is now accounted for by fees paid by pharmaceutical firms to expedite the regulatory process (Abraham, 2002: 1499).[14]

Nevertheless, the pharmaceutical sector criticized these attempts at accommodation in the 1990s for not going far enough, in part because, in the industry view, the problem resided as much in the academic clinical sphere in which mandated drug testing had previously been carried out as it did within the culture of the FDA (Feinstein, 2003). The new automated screening protocols were resulting in a tidal wave of new candidate compounds: the number of drugs in US Phase I clinical trials grew from 386 in 1990 to 1512 in 2000 (Walsh et al., 2003). Even though FDA time to approval from NDA was shrinking, the duration of the clinical developmental cycle was lengthening, at least until very recently (Getz & de Bruin, 2000; Kaitin & Healy, 2000). In the corporate view, the remedy for this prolongation of the clinical phase was a new breed of scientific researcher who was more comfortable with the deadlines, and who focused more intently upon the specifics of the FDA guidelines and less on the complicated range of patient complaints; someone who appreciated the pragmatic importance of narrowly formulated questions as well as cost containment innovations, and was less held in the thrall of academic advancement. The need to recruit ever-larger patient populations seemed to require another kind of entity to coordinate clinical trials. The pharmaceutical corporations preferred to treat drug testing and research as a fungible service conducted in-house or contracted out, leading to a quantifiable output largely defined by FDA parameters, an output that could be monitored for its contribution to the bottom line. The pharmaceutical companies were casting about for a specially engineered research entity to impose cost-constraint, and some far-sighted entrepreneurs provided it in the 1980s: it materialized in the form of the 'contract research organization'.

A small body of literature attempts to explain why in the 1980s corporations began to outsource their drug R&D and testing, particularly in Phase II and Phase III trials.[15] This literature tries to explain why CROs came to dominate the pharmaceutical sphere, displacing not just drug testing in AHCs but also some in-house basic research and cross-firm alliances. Most analysts focus narrowly on financial problems in pharmaceutical corporations, neglecting larger issues such as the reconstruction of the research process, the changing nature of research questions,[16] concomitant revisions of intellectual property, and the consequences of globalization.

Conventional accounts offer a number of reasons for the rise of CROs in the 1980s and 1990s. Primarily, they emphasize the pharmaceutical industry's drive for increased efficiency and cost savings. Pharmaceutical R&D has grown over the past decade – as evidenced by gross costs climbing precipitously from 2 billion US dollars in 1980 to 30.3 billion US dollars in 2001 (PhRMA Annual Survey 2002, quoted in Parexel, 2003: 1). This increased cost proved burdensome, as a day's delay in FDA approval has been estimated to penalize a firm with more than 1 million dollars in lost revenue (Abraham, 2002: 1498). Consequently, the CRO met the pharmaceutical industry's needs by offering targeted drug expertise, timely clinical trial completion, and eventually 'end-to-end outsourcing support for all phases of clinical research' at a comparatively low cost. Further, CROs offered the ability quickly to start or cancel clinical trials by smoothing the stop–go cycles of drug development and minimizing idle in-house research capacity.

Furthermore, the 1980s witnessed a gale of creative destruction in what has been dubbed 'Big Pharma', with firms seeking to control emerging technology and establish global market share through buyouts and takeovers.[17] In the economic climate of the 1990s, the CRO industry rode the merger wave by acceding to the demands of the surviving pharmaceutical companies' desires to shed a portion of their labor force and cut back on expensive laboratory capacity. Because proportionally fewer candidate molecules were panning out as successful new drugs, increased speed and ruthlessness in terminating unpromising trials would help contain costs. This would prove easier if the research was not conducted in-house or by quasi-independent academic contractors. Therefore, to maintain managerial prerogatives and save costs, the pharmaceutical firms outsourced much of their routine research to CROs.

The conventional accounts acknowledge that some aspects of globalization play a role in fostering a niche for the CROs. Pharmaceutical firms lack expertise on foreign relations and regional regulatory differences in a globalized world, and thus required a full-service provider to coordinate clinical research across national boundaries. Some US pharmaceutical firms engaged in regulatory arbitrage by pursuing a Europe-first strategy for drug approval in order to leverage a first-mover advantage for getting their drugs to market more rapidly. Moves to 'harmonize' drug evaluation procedures across major markets, such as Japan and the European Union,

only rendered this activity more attractive. Again, it made sense for these firms to outsource at least some of their clinical trials, rather than maintaining a far-flung research and regulatory capacity. The CRO industry leapt in to supply the relevant cross-cultural expertise in international clinical studies. CROs reduced the time needed to find investigators and recruit patients, and thus encouraged the clinical trial to proceed with relative celerity under diverse sets of regulatory circumstances.

Another conventional explanation of the rise of the CRO is that it was better positioned than pharmaceutical companies or hospitals to take advantage of major technological changes in the way drugs were screened and tested. Some analysts suggest that pharmaceutical companies did not accord high priority to elaborate instrumentation specially geared towards evaluation of drug efficacy: 'pharmaceutical companies are not in the instrument business' (Lester & Connor, 2003). Examples of such specialized technologies include custom-made information technologies, and integration of genetic screening into the clinical process. An example of the former, PharmaLink, a CRO providing internet-based clinical trial management, represented the vanguard of paperless clinical trial management via e-technology. This approach promised to ensure more accurate data collection, providing clients with instantaneous data access and expediting the clinical trial process (*Business Wire*, 2002). In the case of expediting the clinical trial process, pharmacogenetics has been developed as the 'study of the variability in drug responses attributed to hereditary factors in different populations', and pharmacogenomics is 'the determination and analysis of the genome (DNA) and its products (RNA and proteins) as they relate to drug response' (Roses, 2001: 2262). Numerous biotechnology firms and pharmaceutical companies in both Europe and the USA are developing pharmacogenetic technology (Hedgecoe & Martin, 2003), and the use of pharmacogenetic technologies for drug development would require, among other things, large genetically screened patient pools and technologically complex clinical trials – an ideal task for a CRO. For example, PPGx, one such joint venture, 'is one of the first attempts to build an integrated pharmacogenomics operation, including proactively genotyping healthy volunteers for Phase I.'[18] Both pharmacogenetics and pharmacogenomics, however, have opened up further opportunities for CROs to displace AHCs.

Thus, according to the canonical story, it was primarily external economic factors bearing down on pharmaceuticals that contributed to the rise of the CRO industry, opening up new avenues and encouraging a new niche entity to augment efficiency and reduce cost. However, the portmanteau term 'cost' covers a multitude of sins: analysts of CROs rarely explore the possibility that the reconstruction of clinical research itself was the immediate raison d'être for the rise of the CRO; nor do they examine why the innovation had to assume the format of a freestanding commercial entity rather than a restructured in-house research capacity. Costs could have been reduced by conducting an invariant science under transformed economic circumstances, or alternatively, by changing the kind of science

that was performed. In the case of the latter, an arm's-length relationship to the originating pharmaceutical firm would be necessary for restructuring the research process within a more thoroughly privatized framework. This turned out to be one of the most salient consequences of CROs, even if it was not paramount for the particular entrepreneurs who created the new institution.

How Contract Research Organizations Have Influenced the Conduct of Scientific Research

CROs generally resist any suggestion that privatized drug testing and prospecting have undergone profound transformation. Instead, they prefer to promote the advantages of cost and convenience, rather than any alterations in the conduct of science. The existing literature's stubborn concentration upon the rationale of cost savings reinforces that tendency and discourages inquiry into the changing character of biomedical research. There are at least three reasons to be skeptical of the popularity of narrowly defined 'economic' explanations of the rise of the CRO. First, they tend to divert attention from the actual means through which the promised cost savings could be realized. In their commercial presentations, CROs frequently compare the cost of their research with that of AHCs, rather than research costs internal to the pharmaceutical industry. Such invidious comparisons with the previous era of drug research in university or other teaching hospitals – implying that CROs were intended primarily to displace academic science – only obliquely concede that pharmaceuticals research has been re-engineered. However oblique, such concessions present us with major clues about the structural effects of privatization on clinical research. Second, one of the major selling points of the CROs, again highlighted in their commercial presentations but escaping the conventional wisdom, is that data concerning the conduct of drug trials were rendered more dependably proprietary. Consequently, information on the conduct of CRO research has become even more inaccessible to interested outsiders than similar information would have been under the earlier academic regime. Unfortunately, this precludes us from giving detailed quantitative information on pharmaceutical research conducted exclusively within CROs. A third reason for remaining skeptical about 'cost savings' explanations is that when pharmaceutical executives were surveyed about the reasons for their own decisions to outsource clinical trials to CROs, they ranked cost-savings as relatively low on the scale of importance (Pichaud, 2002). Indeed, difficulties with holding CROs up to consistency and quality standards, together with the risks of noncompliance, have given rise to the pharmaceutical catchphrase: 'A CRO is only as good as its last contract' (Azoulay, 2003).

We contend that the conduct of scientific research has been profoundly altered by the rise of the CRO, but that the CROs did not accomplish this feat single-handedly or in isolation. Few if any of the transformations that we shall enumerate would have taken place without the across-the-board

push to expand the boundaries of intellectual property, the international drive to impose harmonization, and the political will to render science less subordinate to parochial national objectives and more responsive to global initiatives. These movements occurred on top of wrenching alterations in the largesse bestowed upon individual sciences by the state (and especially the seemingly inexorable elevation of the biomedical over the physical sciences), and changes in the cultural validation of 'science for its own sake'. Nevertheless, in this environment, the CROs managed to convert a set of research protocols constructed around the prerogatives of the individual scientist, and to a lesser extent, the concerns of the medical community, into a second set of protocols more suited to controlling the developmental cycle of new pharmaceuticals. The CROs conjured up a set of research practices that more effectively adjusted to the traffic and rhythms of corporate privatized science. These reasons help to explain the undeniable success of the CROs in capturing the bulk of clinical drug trials away from AHCs.

This new breed of scientific research has been the subject of extensive commentary in the medical literature, but strangely enough it has not become a subject for the debate between the Mertonian Tories and the Economic Whigs.[19] Perhaps this can be attributed to the fact that much of the medical literature tends to discuss CROs as 'pathologies of pharmaceutical science', rather than as structural consequences of a wider commercialization imperative. If we avoid viewing these phenomena as the dubious behaviors of a few misguided individuals or transgressions of the terminally greedy, and instead approach them as structural changes in the organization of science, then it will become possible to regard them as harbingers of the future of privatized science.

The medical and legal literatures discuss the new regime of industrialized research under five headings: (1) transformations of research on human subjects; (2) restructured controls over disclosure and confidentiality; (3) management of intellectual property, especially in the case of 'research tools'; (4) transformations of the role and functions of publication, and the systematic appearance of ghost authorship; and (5) reordered goals of scientific research. Rather than provide a comprehensive survey of what these literatures say about each of these categories, we shall simply cite a selection of exemplary papers and arguments. What we add to this summary is an analysis of the ways in which each phenomenon is linked to CRO functions.

Research on Human Subjects

Research on human subjects in the pharmaceutical industry has perhaps been the most contentious source of problems in the drive to speed up the developmental cycle, and as such, has drawn the most attention in the popular press.[20] Examples such as the perverse 'experiments' of Nazi doctors on concentration-camp inmates in World War II, the Tuskegee Institute syphilis experiments, or the plutonium injection experiments

commissioned by the Atomic Energy Commission (Goliszek, 2003) remain paradigmatic of 20th-century 'science' gone haywire. Responding to a conviction that not every scientist could be trusted to treat subjects in a humane fashion, the US Congress passed the National Research Act of 1974, requiring that every institution that accepted federal funding must set up an 'Institutional Review Board' (IRB) to monitor the treatment of human subjects. The Department of Health and Human Services also mandated to provide oversight and guidance for the IRBs. The need for specialists to staff these academic IRBs led to the rise of the 'bioethicist', and one of the few growth areas in the discipline of philosophy in recent decades, 'medical ethics'.

Until 1981, the local IRBs, which at the time were housed mainly at universities and not-for-profit institutions, oversaw clinical trials. Yet the whole concept of a locally based IRB had been predicated on an older, obsolete version of scientists as lone investigators running small-scale self-contained clinical trials at geographically isolated AHCs. There was a myriad of reasons for pharmaceutical firms to be dissatisfied with local IRBs: they imposed idiosyncratic protocol guidelines; they had no appreciation for cost and speed considerations; their legal status was too uncertain; and so forth. Consequently in 1981 the FDA permitted the creation of independent IRBs in order to 'provide oversight to investigators doing FDA-regulated research in their offices or in institutions too small to support an IRB' (Forster, 2002: 517). This led, in turn, to the creation of a novel occupation – bioethics consultant – which gave rise to contradictions of its own (Elliott, 2002). This new for-profit niche market provided services to CROs from their inception. Before 1981, a CRO would have had to create its own IRB or use one from a sponsor, an awkward arrangement at best.[21]

Independent IRBs hold several advantages for CROs:

1. Compared with independent IRBs, local academic IRBs have more lengthy mean approval times: 37 versus 11 days (*CenterWatch 2000*, quoted in Parexel, 2003: 139).
2. Local IRBs are regulated by the National Institutes of Health, the Office for the Protection of Research Risks, and the FDA, whereas independent IRBs only have to conform to FDA requirements.
3. Independent IRBs proved capable of financial expansion commensurate with the volume of research reviewed. Some academic IRBs have been known to supervise more than a thousand clinical trials simultaneously, devoting no more than two minutes of discussion per study. Local IRBs were saddled with the same financial resources regardless of the volume of research supervised, placing severe strains on them as the volume increased (Forster, 2002).
4. Academic bioethicists in local IRBs could raise questions about conflicts of interest and include them in their recommendations, a possibility that was anathema to the pharmaceutical industry.[22]

The independent IRB, with its bioethicists for hire, proved a boon to the CRO industry, giving it a substantial competitive edge over rival research institutions. As a prerequisite for the full privatization of clinical research, ethical oversight of human subject research had become transformed into a fungible commodity. Unlike CROs, AHCs and other not-for-profit institutions did not fully benefit from the creation of independent IRBs. According to the preamble of the FDA regulation approving independent IRBs, 'A sponsor-investigator who is unaffiliated with an institution with an IRB can comply with this requirement by obtaining review at an institution whose IRB conforms with these regulations or by submitting the research proposal to an IRB created under the auspices of a local or State government health agency' (quoted in Forster, 2002: 517). Most AHCs already had their own IRBs, complicating or precluding their use of independent IRBs. Universities thus faced a contradiction: while they were happy to encourage bioethicists on their faculty to augment their salaries, their own AHC researchers were prevented from using for-profit IRBs to expedite their research.

From Big Pharma's point of view, even this competitive advantage did not come to grips with what they perceived as the panoply of drawbacks of human research. A number of high-profile failures of IRBs in the 1990s, which led to federal sanctions at Oklahoma, Johns Hopkins, Duke, Colorado, and other universities, suggested that human subjects' oversight was likely to attract even more costly regulation. In 2002, Representative Diana DeGenette introduced a bill in Congress to grant humans the same legislative protections already covering animal subjects; others began to question the entire concept of 'informed consent' when surveys revealed that patients did not comprehend the risks of enrolling in clinical trials. Numerous surveys showed that the media coverage of problematic clinical trials discouraged average Americans from taking part in clinical research. Previously, the FDA had accepted drug applications supported by data from foreign clinical trials as a way to get access to larger populations of patients. Such overseas trials also could circumvent the more onerous restrictions imposed on US trials. This unintended consequence of US restrictions on human subject research provided yet another competitive advantage for the nascent CRO industry: unlike an AHC, a CRO was not tied to a particular geographic locale or academic setting. Furthermore, it could engage in regulatory arbitrage, using its superior economic and political clout in poorer, less-developed countries to negotiate lower costs.

The muckraking literature on 'foreign bodies for sale' has grown in the medical and news media; it has broken out into a major policy controversy.[23] According to one news article, '[t]he FDA has accepted new drug applications supported by foreign research since 1980. By last year, nearly 27% of them contained a foreign test result – about three times as many as in 1995' (Flaherty et al., 2000). A more recent estimate puts the percentage of foreign test results at 37% (Datta, 2003). While the trend has many implications, we shall focus on how it has been implicated in the way

CROs have re-engineered scientific protocols. First, it has enhanced the speed of Phase II and Phase III trials: many of the factors counseling caution and deliberation in developed-country trials are obviated or ignored in Eastern European or Third World trials. Countries such as China and India encourage Western provision of medical treatments by offering direct subsidies to the CROs. Informed consent in such situations often is impossible, so that a level of coercion of patients prevails that would be unthinkable in the developed world.[24] Significantly, some of these countries waive or reduce the requirement of pre-clinical animal trials, further truncating the drug-development profile (Shah, 2003; Sharma, 2003). While the FDA uses various tools to police domestic clinical trials, with foreign research it can do little more than disallow the results. In more than 90% of the cases, the FDA is not notified that foreign clinical trials have been initiated, and it has essentially no control over their conduct. Consequently, many analysts question the quality of the data generated in such clinical trials (DeYoung & Nelson, 2000; Pomfret & Nelson, 2000; Stephens, 2000).

Another unintended consequence of the commercialization of human subjects research is that patients in developed countries have begun to realize that CROs sometimes pay recruitment fees to physicians of US$12,500 or more per subject (Drennan, 2002). Patients have begun to rethink their own roles in clinical trials, and are beginning to demand direct payment in order to participate (Fisher, 2003: 260). Not surprisingly, such demands are strenuously resisted by the CROs, and they provide further incentive to shift Phase II and Phase III trials overseas, where patients are far less obstreperous.

Disclosure and Confidentiality

It is a commonplace that academic and commercial scientists differ in their willingness to disclose research information and results; indeed, this is the major thesis of David & Dasgupta (1994). However, our 'Trigs' approach would argue that the actual structures of disclosure and confidentiality in biomedical research have become much more complicated than these authors' game theoretic model of science suggests. David & Dasgupta's model is a matter of 'choosing' an optimal amount of 'open science' from column A relative to the amount of commercial science from column B, whereas Trigs argue that, once commercialization gets institutionalized, a completely different menu of possibilities is on offer. Much of the medical literature treats this problem under the rubric of 'conflicts of interest', and pays insufficient attention to the dynamical interplay between CROs and AHCs. Conflicts of interest may trouble academics, but they do not seem to present obstacles for CROs. Once CROs entered the arena, AHCs could no longer engage in older vintages of 'open science'.

According to some estimates, one-third to one-half of the clinical trial contracts in the 1990s with AHCs such as the Massachusetts General Hospital (Bodenheimer, 2000) or the Geffen School of Medicine at the

University of California Los Angeles (Kupiec-Weglinski, 2003) contained restraint clauses, confidentiality provisions, publication embargoes, and a host of other legal controls over proprietary information. Fiduciary officers of AHCs have in the past often regarded it as their duty to renegotiate such clauses, but their efforts to set themselves up as a last line of defense for open science had curious consequences. University administrators were not well positioned to police open science: to expunge secrecy from the legal documents did not mean that investigators would hew to the canons of open science. It has been demonstrated that scientists with industry support are more likely than those without it to deny others access to data or research materials (Blumenthal et al., 1996: 1737). Yet in recent years, even university administrators have succumbed to pressures to accept restrictions on proprietary information. One consequence has been a growing conflict at AHCs between offices of technology transfer and university officials, with the former being more willing to condone restraints on contracts, because of their experience in dealing with patent attorneys (Eisenberg, 2001: 239–41). Another consequence is that AHCs have attempted to 'reform' their practices to better resemble those of the CROs, in order to recoup lost pharmaceutical contracts (Campbell et al., 2001; Pollack, 2003).[25] With these practices, universities have managed to invoke the ideal of open science while proving unable to maintain it in practice.

The pharmaceutical companies have not hesitated to exercise their legal powers to restrain disclosure. Some widely cited attempts to muzzle researchers and block publication include the cases of Dr Betty Dong at the University of California San Francisco (UCSF) and Dr Nancy Olivieri at the Toronto Hospital for Sick Children.[26] Although few clinical researchers experience such crude attempts at force majeure to intimidate them to trim their research to fit company demands, it is well documented that, '[u]sing financial, contractual and legal means, drug manufacturers maintain a degree of control over clinical research that is far greater than most members of the public (and, we suspect, many members of the research community) realize' (Morgan et al., 2000: 661). They do this through selective disclosure and restraint on almost every aspect of the clinical trial process. The most replicated finding in the last 15 years of meta-analysis of published clinical studies is that industry funding is highly correlated with results favorable to the drug owned by the study's sponsor. One survey of research papers on the cost-effectiveness of six oncology drugs showed that 'pharmaceutical company sponsorship of economic analyses is associated with reduced likelihood of reporting unfavorable results' (Friedberg et al. 1999: 1453). Another study (Stelfox et al., 1998) found that 96% of authors supporting the use of calcium-channel blockers had financial ties to manufacturers. A similar result was found for anti-inflammatory arthritis treatments (Rochon et al., 1994). One recent examination of published surveys and meta-analyses of drug efficacy found that '[s]tudies sponsored by pharmaceutical companies were more likely to have outcomes favoring the sponsor than were studies with other sponsors'

(Lexchin et al., 2003: 1167). Another survey took into account industry affiliations of the academic unit (such as equity ownership) and individual corporate and consultant relationships, and found that 'approximately one-fourth of investigators have industry affiliations and roughly two-thirds of academic institutions hold equity in start-ups that sponsor research at the same institution . . . these articles showed a statistically significant association between industry sponsorship and pro-industry conclusions' (Bekelman et al., 2003: 454).

Some commentators are offended by the implication that trained clinicians can so easily be swayed to produce scientific results on demand, but others insist that the problem is not that investigators are crudely falsifying the data or otherwise abandoning their commitment to truth. They concede that when research is spread over vast numbers of clinicians and disparate geographical sites, then there are simply too many individually small but cumulatively decisive ways for the data to be biased in a 'positive' direction. Such sources of bias include the selection of subjects, strategic choices about how to treat drop-outs, protocols for handling and reporting side effects, deciding whether to use placebos instead of competing treatments, the administration of rival doses, decisions about what constitutes a drug's efficacy (sadly, there are rarely clean 'cures' for most of the syndromes in question), and decisions about when to end a trial.[27] While such biases have always beset clinical trials, the privatization of science tends to insulate them from internal and external critique. As one researcher, Dr Curt Furberg of Wake Forest, has observed (quoted in S. Hughes, 2002: 6):

> companies used to do ten trials and then just pick the two they liked the best to submit to the regulatory authorities. Then this was stopped, and the agencies demanded to see all the data. The companies then needed to have more control, and the whole issue of academic freedom hit them. So to avoid this they have taken two routes – the use of clinical research organizations (CROs) and developing countries .... CROs bypass the issue of academic freedom altogether, as the CRO wants to please the company it is working for and so constitutes no safeguard whatsoever. And the developing countries have no money, so an industry dollar goes a long way. Investigators are very anxious to please.

Another source for the bias in results is the rarely acknowledged 'sweatshop' character of work in CROs. Compared with their counterparts in large pharmaceutical firms, researchers in CROs are lightly trained, poorly paid, and discouraged from exercising any initiative, which is why they have extremely high rates of turnover (Azoulay, 2003). Curiosity is not conducive to the health of the bottom line. As one outsourcing manager admitted (in Azoulay, 2003: 22):

> There is a line-by-line definition of the CRO's responsibilities. That means that the CRO is less likely to notice stuff that might be going on at the sites. There are no incentives for the individuals at CROs for capturing 'soft data', unlike here, where you get rewarded at every level. At a CRO, you might work for two or three sponsors at the same time. So it's all about hard deliverables. Anything beyond the contract you do not get.

Conflicts of interest have recently become varied and baroque, even as they have become more pervasive.[28] One major perplexity has been to come up with an adequate definition of 'conflict of interest' in a world in which distinctions between academic and corporate institutions have tended to dissolve. Ironically, because the contractual relationships between firms and employees are more formally codified in the case of CROs, conflicts of interest may actually be less intrusive than in supposedly disinterested academic clinics. However, this may not be cause for optimism.

The problem with 'conflict of interest' in science is that it turns out to be a Pandora's Box: once opened, it is nearly impossible to close; and 'disclosure' offers no panacea, since it is unclear what must be disclosed, and to whom and under what circumstances. Should direct payments from the industry sponsor to the researcher be disclosed under all circumstances? Should it be expanded to include stock ownership or, even trickier, stock options? What if the investigator has an executive relationship, or sits on the board, of the sponsoring company or some interlocked firm? Does it cover indirect payments, such as consultant fees, honoraria, trips to resorts, 'gifts'? What if the sponsor supports students or others designated by the researcher? These and other questions have been raised on a regular basis in the past two decades. To stem the tide, most universities have clad themselves with some form of conflict of interest policy, but there is no standardization from one institution to the next (Cho et al., 2000), and no serious enforcement. Indeed, one study demonstrated that fewer than half of the clinical investigators interviewed at UCSF and Stanford could even correctly state the provisions of the conflict-of-interest policy at their own institution (Boyd et al., 2003). Perhaps what is remiss at the university level can be rectified at the publication level. At least that seems to have been the rationale of the International Committee of Medical Journal Editors (ICMJE) when they promulgated 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' in 2001.[29] Unfortunately, this praiseworthy crusade by the journal editors to expose author ties to sponsors does not sufficiently take into account the larger forces transforming the very structure of publication and authorship in privatized clinical science (see p. 25). A recent study suggests that this well-intentioned attempt to legislate disclosure has not succeeded, because 'academic institutions routinely participate in clinical research that does not adhere to ICMJE standards of accountability, access to data, and control of publication' (Schulman et al. 2002: 1339). Worse, the *New England Journal of Medicine* was embarrassed in June 2002 into revoking its prohibition against authors of review papers having any financial ties to the drug companies whose medicines were being assessed. The reason the *New England Journal of Medicine* gave was that they could no longer find such putatively independent experts (Newman, 2002). If 'conflicts of interest' have become so ubiquitous, then 'disclosure' can do nothing whatsoever to address the systemic bias that besets pharmaceutical evaluation.[30]

The whole question of the role of conflicts of interest in science is fascinating due to its labyrinthine complexity, and it deserves more attention than philosophers and science policy analysts have given it.[31] The fundamental stumbling block seems to be the tendency to cast the problem as a matter of individual responsibility, rather than a structural problem in the organization of science. In the conventional treatment, truth is a communal goal that is impeded by biases clouding individual judgment. The weakness of this diagnosis is that no successful scientist believes that he or she is biased, however much they might believe it about others. Some interview transcripts evoke this viewpoint (in Boyd et al., 2003: 772–73):

> It's a delicate thing. You have to decide for yourself. For example, I'm getting money from [a pharmaceutical company] for a study I'm working on. They also have me on speaker's bureau. I feel comfortable with this relationship as long as the slides I use are my own, and I'm speaking about my own research and opinions. I don't think the information I present has anything to do with what [the company] wants me to say. The system can be, and is, abused. Some people do give canned talks prepared by the companies that are paying them.
>
> [US]$10,000 here or there is not a big deal. Personal financial relationships with sponsors are necessary for growth. People have to look at the big picture and see the benefits that come from academic–industry relationships.
>
> There is the risk that I become a complete whore and begin saying things that I don't believe. I'd hope I'd recognize this if it were happening to me, but it is hard to know. The risk to the public is one of fraud – scientists say something is true when it isn't. I don't think conflict-of-interest rules can mitigate either of these risks – it is basically up to the individual investigator to act ethically.

The problem with the privatization of research is not that people may have personal biases or special interests, or even that they develop self-serving rationales for them. No one would be surprised at this. 'Disclosure' has become an issue in modern biopharmaceutical science because one set of social structures for navigating the shoals of human cognitive weaknesses was slowly being traded for another entirely different one. In the interim, it remained in some actors' interests to blur the distinctions between the two. Although conflicts of interest would seem to be pervasive in the CRO sector, we have seen little evidence of worries over disclosure and confidentiality, while the CROs have gradually taken over clinical drug testing. At the most superficial level, this follows from the fact that analysts understand that researchers at CROs are first and foremost *employees*, and their motives are expected to be subordinate to the objectives of the firm. The firm, in turn, must be unyielding in its insistence on the immediate objective to supply clinical data to the contractor in a timely and cost-effective way that meets FDA and NDA requirements. The individual employees of the firm will also bear their own personal conflicts of interest with these specific objectives of the firm – ranging from their own idle curiosity to concern over patients' general well-being to bureaucratic

infighting to conceptual biases – but no one would ever expect such conflicts to be rectified by codes of ethics, medical journal strictures, or the intervention of academic committees. The CRO's predominant interest is simply to deliver a product on time and under budget. In CROs, conflicts of interest are not perceived as a problem requiring special remedy or concern, *because the new format has built-in means to discipline them*. This is a consequence of the change in the organization of science.

Intellectual Property and Research Tools

The literature on the impact of recent intellectual property law on science already is massive, and it threatens to grow even larger.[32] Rather than try to address this vast body of arguments, we again shall focus on CROs, their relationship to biotechnology and pharmaceuticals, and their influence on the academic sector. Our Triggish observation is that very few of the standard explanations address the specific timing of the rise of CROs around 1980. We suspect that it has been no mere coincidence that the year 1980 not only marks a shift in government policy toward private patenting of publicly funded research – the Bayh-Dole Act and a host of subsequent legislation – but is also the year that the US Supreme Court decision *Diamond v. Chakrabarty*[33] opened the floodgates to patenting biological organisms. It also was the year that Stanley Cohen and Herbert Boyer received one of the first lucrative biotechnology patents for a recombinant DNA research tool. At that time, the pharmaceutical industry was neither an innocent nor disinterested bystander. In an amicus curiae brief to *Diamond v. Chakrabarty*, both Genentech and the Pharmaceutical Manufacturers' Association argued for permitting patents on living organisms in order to keep genetic engineering 'out in the open', because patents would compel publication (Kevles, 1998: 67). But far from reflecting an altruistic motive to expedite 'technology transfer', their support for this unprecedented extension of intellectual property (IP) may have aimed for more direct corporate control over scientific research. For example, the Cohen/Boyer patent was used extensively by Big Pharma even before Stanford and the University of California began formal licensure (so much for the need for IP to expedite 'transfer': see Reimers, 1998). This agenda also operated behind the scenes with the Bayh-Dole Act. A little-known fact is that a provision of this act, which encouraged universities to patent publicly funded research and license the patents to *small* companies, was quietly extended to *large* corporations by means of a 1983 executive memorandum by President Reagan (Eisenberg & Rai, 2003).

In the late 1970s and early 1980s a few far-sighted individuals in the pharmaceutical industry envisioned profound breakthroughs to be brought about by re-engineering the entire research process in order to more quickly get really lucrative discoveries in a way better suited for drug development. In part, this involved creating novel partnerships with entrepreneurial academics, but it also involved a reorganization of drug research, development and testing, as eventually embodied in the CRO. Our

Trig story describes new forms of IP and new structures of CROs, which act as logical complements in the pharmaceutical industry arsenal. Sometimes the CRO itself made use of the novel IP regime, while at other times the pharmaceutical firm did so because the CRO made such access significant and profitable. Neither alone proved necessary and sufficient to expand control over the research process; together they were an unbeatable combination.

In our view, it is difficult to separate the profound efforts to reengineer clinical testing from the pharmaceutical industry's recent efforts to discover new drugs.[34] In the 19th century the industry tended to prepare 'extracts' of compounds from naturally occurring materials, but in the early 20th century synthetic chemistry was used for producing compounds that had not previously existed in nature. The third great transformation of the industry came late in the century with the integration of microbiology and information technology into research protocols for designing molecules to block or enhance the operation of receptors or proteins.[35] Such research could be automated on an unprecedented scale, with High Throughput Screening testing hundreds of compounds on genetically engineered sequences or protein targets. As the metabolic pathways became more differentiated, so too did the ability to detect and monitor them in clinical settings. Hence the CRO should not be regarded as a niche firm, as it often is; instead, it is an indispensable component of a more comprehensive research portfolio, one simultaneously 'high-tech' and organizationally novel. This portfolio was predicated not only on the commercialized 'products' of genetic manipulation, but also on the upstream 'targets', and the array of research tools and materials for advancing biological research. Consequently, from our perspective, abstract arguments over which parts of science should more correctly or appropriately be relegated to a 'public' versus 'private' sphere (Maurer, 2002) have landed far from the mark; the coalition of the pharmaceutical and biotechnology industries has shifted the boundaries of what counts as 'public' or 'private' in biological research. As Diana Hicks (1995: 401) has perceptively observed, 'because there is no natural distinction, academic and industrial researchers construct the distinction between public and private knowledge in such a way as to provide themselves with maximum advantage.' This is nowhere more evident than with so-called 'research tools'.

There is a comforting myth (sometimes recounted by the Mertonian Tories) that in some long-lost golden age of science there existed completely free and unfettered exchange of data and research materials. We doubt that this completely altruistic 'gift community' ever really existed.[36] But, what is beyond dispute is that some of the earliest breakthroughs in genetic research were processes or entities that enabled genetic manipulation: the Cohen-Boyer recombinant DNA technologies of Genentech; the polymerase chain reaction (PCR) controlled by Hoffmann-La Roche; and the Harvard Oncomouse – none of which were downstream products aimed at a consumer market.[37] Therefore, some of the earliest money made

from biotechnology was in the area of 'research tools', rather than fully-fledged therapies. The IP innovations of the early 1980s could only be applied to entities that *might* have been shared with other scientists under the previous academic culture, but it still would have been an open question as to what might legitimately fall under that rubric.[38] The biotechnologies and pharmaceutical firms, and the CROs, did not want the question to be left open, however. Considerations of improving the bottom line suggested extending commercialization into the *process* of research, and not just its products, well beyond anything that might have existed in the informal research economy.

This trend has, if anything, intensified in importance: an investigator who examined all US patents issued in 1998–2001 relating to DNA sequencing estimated that as many as one-third were research tools rather than diagnostic, therapeutic, or other innovations (Scherer, 2002). Biotechnology startups plumped for the narrowest possible construction of laboratory entities that should be freely shared amongst scientists, and sought to patent their research tools. CROs followed suit, claiming expertise in monitoring IP and research tools. CROs often promoted their special information technologies that would monitor real-time patient data, dosage profiles, investigator databases, and clinical trial data. More significantly, unlike an AHC, a CRO contractually stipulates that it will not seek to patent research tools arising from its research.[39] A CRO has an advantage over its academic counterparts in what it can provide its clients: management of a package of the IP consequences of research tools.

The US Patent and Trademark Office reinforced the trend toward privatization of research tools by expanding the jurisdiction of the patent system, to the extent of 'treat[ing] software just like chemicals, and treating business concepts no different from pharmaceuticals' (Kahin, 2001). Yet this expansion of IP in conjunction with the coordinated campaign to privatize in both upstream and downstream directions in biopharmaceuticals gave rise to a much more dramatic revision of scientific research organization. Suppose someone seeks to patent a previously unknown cell receptor (by specifying a generic diagnostic 'use'), because it might be useful as a future pharmaceutical product. It might equally be useful as a research tool, for example to screen assays in order to detect previously unknown hormones. Because of its multiple nature, it became possible for biotechnology firms to capture more of the potential revenue stream while the patent for the receptor was in force by negotiating 'reach-through license agreements'. The licensee in such an agreement for hormone research would pay royalties on any new hormone discovered in reference to the receptor.[40] Biotechnology and Big Pharma were united in seeking to rein in the free dissemination of research tools. Research tools were turning out to be the financial lifeblood of small biotech startups; but they also were pivotal for a strategy of patent-oriented research that emphasized secrecy. For instance, the pharmaceutical firms were wary of the possibility that academic researchers give freely provided research tools to competitors; that tool users would publish proprietary information and thus

undermine future patent claims; or that they would reveal harmful side effects of a tool that doubled as a drug, and therefore create regulatory headaches. Their attempt to muzzle users and/or benefit from their successes was a significant departure from previous uses of patents in the pharmaceutical industry, because it broadened the scope of patents to control upstream developments.[41] From the viewpoint of the pharmaceutical industry, this was merely an extension of IP to control and coordinate invention; but atypically, the patent office balked, declaring reach-through claims as 'not patentable because they do not satisfy the requisite disclosure criteria for obtaining a patent .... Reach-through claims are inconsistent with the purpose of the patent statutes' (Kunin et al., 2002: 637–38).

This temporary setback did not deter the pharmaceutical industry from deploying IP to control drug design and testing. Because reach-through provisions on patents proved too slow and uncertain for privatizing research, the biotechnology industry created a legal entity known as the 'materials transfer agreement' (MTA). MTAs are legal and pecuniary contracts that formalize the commercial exchange of research tools between scientific institutions, such as corporations, universities, non-profits, or even the federal government. They may stipulate payment for using a device, organism, reagent, database or software program; but generally they demand much more. MTAs have become the most common means to impose prepublication review, disclosure restrictions, liability indemnification, or restrictions upon actual use. And, most significantly, they often extend 'reach-through' or 'grantback' provisions. They can be used to impose reach-through provisions, which used to be incorporated into patent licenses, because they are quicker and more flexible, and potentially offer greater scope for pinpoint control of IP. According to Richard Posner (2002: 6), 'if the only people who have access to your property happen to be the people with whom you have a contract, you can regulate their access by means of contract and forget about property law.' For many critics, this is one of the most stunning developments in the new IP regime (Marshall, 1997): it locks in the identification of research with a marketplace governed by contract law. This practice has ballooned with stunning rapidity, with a mid-size academic technology transfer office, such as the one at the University of Pennsylvania, processing nearly 500 MTAs per year by 1999 (Enserink, 1999). Other academic offices, like the University of California campuses, arranged approximately 2000 MTAs in the financial year 2002, more than a 30% increase from the previous year (Streitz et al., 2003).

One of the most discerning critics of the MTA has been Rebecca Eisenberg. Her experience on the NIH Working Group on Research Tools in 1997–98 should provide some clarification of the challenges that MTAs pose for the conduct of science (Eisenberg, 2001). She has been a major proponent of the concept of a 'research anticommons' (Heller & Eisenberg, 1998): the notion that restrictions and reach-through provisions of MTAs can be so onerous, and yet dispersed throughout a population of

claimants, that negotiations over research tools become prohibitive, with science held hostage to a phalanx of property managers. Eisenberg (2001: 230) makes the point that repeated granting of reach-through provisions would be chaotic: 'a user cannot promise an exclusive license to future discoveries more than once in the course of a research project before creating conflicting obligations.' The fact that pharmaceutical research has not actually frozen into immobility after more than a decade of MTAs suggests that a simplistic 'transactions cost' approach does not begin to get to the heart of the matter. Although university technology transfer offices may regard MTAs as a money-spinner, the pharmaceutical industry regards their major purpose to be that of obstructing certain lines of research, while maintaining control over others.

Several representatives of private companies said that they would only use an MTA if the company has little or no interest in the research of the scientist to whom it is lending a research tool. If the company anticipates that the scientist's research will yield valuable results it would propose a more substantial relationship, perhaps involving research sponsorship or collaboration. Exchanges for which an MTA is used are thus typically of low value to the provider of the material (Eisenberg, 2001: 232).

In many circumstances, an MTA is a special signal that commercial firms emit to academics when they are unenthusiastic about the request to collaborate; they deploy other emoluments from their IP arsenal when they feel otherwise. The purpose of MTAs is not to *remove* obstacles to research, but to *improve* their precision and accuracy. This observation helps clarify the response of a pharmaceutical representative when confronted with the accusation that his corporation was blocking certain lines of research: 'They complain, "How can we do research?" I respond, "It was not my intent for you to do research"' (in Walsh et al., 2003: 27). Another 'representative of a different biotechnology company reported that her firm only cares about approximately 100 MTAs out of the 2000 that she processes annually, and these agreements always get done' (Eisenberg, 2001: 232). This rationale also explains why the most frequent stumbling block to negotiating MTAs, especially between firms and university researchers, is not generally monetary costs, but other terms and conditions of the agreement.

MTAs are one of the more draconian innovations in modern pharmaceutical research, but they are the logical complement of the CRO. The CRO is prohibited by its original service contract from appropriating IP; the academic researcher is dissuaded from seeking to appropriate IP through the MTA contract. Consequently, the pharmaceutical firm can play the academic thoroughbred off against the 'data mule';[42] shifting contracts between them to insure that it maintains control over any intellectual property arising from most aspects of the research process. CROs apparently have yet to impose their own MTAs, although the unintended consequences of the full commoditization of research have yet to come to fruition.

The Vicissitudes of Publication and Authorship

It would be erroneous to approach scientific publication as simply a matter of disseminating newly minted information, perhaps after the fashion of the 'new information economics'. From the Trig perspective, publishing research performs many interlinked functions. For instance, the appearance of a paper in a particular journal signals something about its significance; the names appended to the paper lay claim to whatever benefits may accrue to the publication, at least within the parameters of current IP restrictions. Publication also furnishes an option for 'scientific credit', a contested and controversial entity in the best of times. However beset with multiple functions, the commercialization of science wreaks havoc with older notions of the scientific author and her roster of publications. We are nonplussed that the literature on the privatization of science seems to have passed this phenomenon by, even though it has been the subject of extensive debate and anguish among researchers in biomedical fields. Again we discover that journalists have more frequently ventured where academics fear to tread.[43]

Once more, we take issue with Whigs such as David & Dasgupta (1994), and note that the commercialization of science has not only had an impact on the level of disclosure of findings, but is also slowly changing the very meaning of the 'scientific author'. Their model treats the scientist/author as an invariant entity. The simple integrity of the rational authorial agent is something that modern economists would tremble to question, even in their most fetid nightmares. And yet, far from being some passing postmodern fantasy, the editors of some of the most prestigious medical journals have found themselves impelled to convene special conferences and retreats to debate the vexed Triggish question of 'What is a scientific author?'.

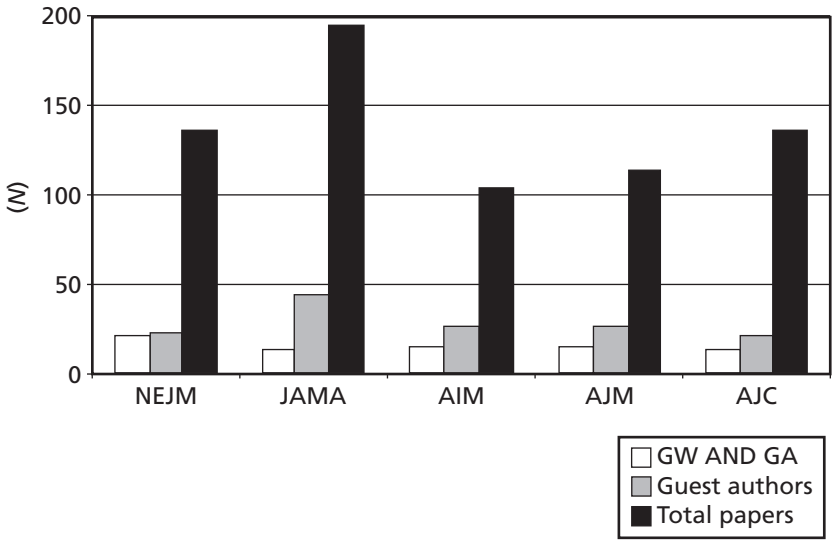
The first exploratory discussion was held at Nottingham, UK, in June 1996. Consequently, the fifth revised version of the ICMJE 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' was promulgated in 1997; a follow-up conference sponsored by leading medical journals was held in February 1998 in Berkeley, CA. There, the ICMJE formed a 'Task Force on Authorship' which met in May 1999.[44] Further attempts to clarify the expected 'role of contributors' were promulgated at the *Journal of the American Medical Association* in 2000 because 'rules regarding authorship, for example, those of ICMJE ... were commonly ignored and flouted', although this initiative was not made uniform at other journals (Rennie et al., 2000: 89). This initiative was a reaction to a study by Rennie in the latter half of 1997, in which it was found that a full 44% of the names on the bylines of papers in the *Lancet* did not qualify for authorship even under a lenient interpretation of the ICMJE criteria (Yank & Rennie, 1999). What provoked this flurry of activity? It was first sparked by a number of high-profile cases of scientific fraud in which certain reputable authors sought to repudiate faulty published papers that had their names appended as co-authors, on the grounds that they had not

sufficiently monitored or supervised the empirical procedures which had been exposed as bogus. This led to reconsideration of the phenomenon of 'gift authorship' or 'honorary authorship', where famous or otherwise influential figures were listed as co-authors, even though they had not contributed 'significantly' to the project (Bhopal et al., 1997). Subsequently, journal editors such as Frank Davidoff found that some authors submitting papers refused to tone down their interpretations of results, or even take full responsibility for provision of data sets, because of prior but unacknowledged conditions imposed by their industry sponsors. Further inquiry revealed that many listed co-authors would refuse to endorse the full text of published papers due to lack of agreement over methods, statistical analysis, interpretative commentary, directions for future research, and so on (Horton, 2002). Embarrassing cases arose in which clinical data provided in the published papers differed substantially from those reported to the FDA (Okie, 2001). Things appeared to be coming apart: authorial voices seemed to have become unhinged from authorial identities. At that point, it became apparent that other IP considerations also influenced attributions of authorship, particularly as scholarly journals contended with copyright issues in connection with electronic publication, only to realize that stakeholders other than the putative authors also held rights over texts and supporting data. In our opinion, however, the straw that broke the editors' backs was the phenomenon of 'ghost authorship': the practice through which researchers agree to put their names on texts that had been composed by unnamed third parties, who held final control over the content of the manuscript. Instances of ghost authorship had begun to surface in transcripts of trial proceedings of lawsuits against pharmaceutical companies (Giombetti, 2002; Healy, 2003).[45]

The incidence of the 'Guest-Ghost Syndrome' in the medical literature would now appear to be approaching levels rarely seen outside of sports autobiography. The specter has been raised that the medical journals are teeming with the 'non-writing-author/non-author-writer' as a major persona. As one can readily appreciate, the extent of this phenomenon would be difficult to gauge because of its very nature: imposture and concealment would not be worth the effort if it could be readily unmasked. Testimony to the concern of the medical community was an elaborate attempt to measure the extent of guest and ghost authorship by surveying all the authors in six different journals in 1996 (Flanagin et al., 1998). The results of part of the survey broken down by journal are presented in Figure 1.

In the aggregate, 19% of the papers had evidence of honorary authors, 11% had evidence of ghost authors, and 2% seemed to possess both. Curiously, the prevalence of guest-ghosts did not differ significantly between large-circulation and smaller-circulation journals. In a web-based survey focusing on the 1999 reports of the Cochrane Library (an international organization devoted to maintaining systematic reviews of risks and benefits of particular therapies employing a common methodology), a research team found that 39% of the reviews had evidence of honorary authorship, while 9% had evidence of ghost authorship (Mowatt et al.,

FIGURE 1
Extent of guest and ghost authorship in five journals in 1986.



Source: Flanagin et. al. 1998.

Notes: NEJM, *New England Journal of Medicine*; JAMA, *Journal of the American Medical Association*; AIM, *Annals of Internal Medicine*; AJM, *American Journal of Medicine*; AJC, *American Journal of Cardiology*. Guest author: an author not meeting all of the utilization review (UR) criteria for authorship. Ghost author (GA): an individual who was not cited as an author but made a contribution that merited authorship. Ghostwriter (GW): an unnamed individual who participated in writing the paper.

2002). Other evidence of ghost authorship has been exposed through the disciplinary actions of medical journals: for instance, in February 2003, the *New England Journal of Medicine* retracted a paper it had previously published because several listed authors insisted that they had little or nothing to do with the research (Johnson, 2003). In a different survey design that focused upon a specific drug rather than specific publication outlets, Healy & Cattell (2003) began with information from a medical communications agency that specialized in the drug sertraline. Using Medline and Embase, they then collated a list of all sertraline publications in 1998–2000. They were able to establish that 55 published papers had been coordinated by the agency, whereas 41 had not. However, only two of the 55 papers actually acknowledged that the agency had provided 'writing support'.[46]

Certainly this proportion might seem outlandish to anyone who is himself a scientific author, as we suspect it does to many of the readers of this paper, but a factor omitted in their calculations would be the contemporary dominance of CROs in clinical pharmaceutical research. One major reason for the epidemic of guest-ghost authors in the recent medical literature is the rise of the CROs in pharmaceutical research.[47] The logic of ghost authorship for CROs is quite straightforward. The raison d'être of

the CRO is to fragment into its component parts and rationalize many of the scientific functions previously performed by the academic clinician or professor of medicine, and one of those functions is authorship. The attribution of authorship in Big Science has presented a number of practical problems (Biagioli & Galison, 2003), which may partly be attributable to the increased scale of research, but the privatization of research also introduces some special considerations. The basic fact about CROs is that they are not teleonomically oriented towards academic authorship: the doctors administering clinical trials for pay are uninterested in authorship, as are the bioinformatics specialists, the patient recruitment team, the in-house statisticians, the engineers, and the host of other specialists employed by the CRO to organize and conduct drug trials. Since IP is stringently controlled, and personnel turnover is so high in a CRO, it would be quixotic for an employee of a CRO at most stages of research contract to expect credit for a publication. Their careers do not stand or fall by the number of journal papers listed on their curriculum vitae. Furthermore, the modern production of clinical data is governed in the first instance by the requirements of FDA approval; academic publications may be viewed, more often than not, as 'infomercials' that aid the marketing of the drug. The confidentiality provisions and publication embargoes covered earlier in the sections on pp. 15 and 24 reveal that dissemination of scientific information is subordinate to a larger agenda in the world of corporate science: commercialized research needs to be subjected to selective disclosure and closely controlled discussion. How better to deploy the required discretion than to hire commercial ghostwriters to produce the desired texts to order? Hence the proliferation of 'medical communications companies', themselves often CRO subsidiaries, can be regarded as a concrete manifestation of the commercial outsourcing of scientific research. And instead of trying to 'censor' or otherwise muzzle obstreperous academics who participate in the research after the fact (and risk the adverse publicity of the Olivieri and other cases), how much more 'Pareto optimal' to provide them with pre-authored 'drafts' of clinical summaries that are structured to highlight the results deemed useful by the drug company – papers that they can then proceed to publish under their own names, the more readily to further their own academic careers?

The way medical ghostwriting works has been illuminated by a Canadian Broadcasting Corporation report. The team interviewed a number of ghostwriters who insisted that their identities be kept confidential, so the broadcast reported an interview with an unidentified writer whose annual salary exceeded US$100,000 per year, and who said that a paper in a top medical journal would net him payment in the neighborhood of US$20,000.

> [Writer]: I'm given an outline about what to talk about, what studies to cite. They want us to be talking about the stuff that makes the drug look good. [Interviewer]: They don't give you the negative studies? [Writer]: There's no discussion of certain adverse events. That's just not brought up .... As long as I do my job well, it's not up to me to decide how the drug

> is positioned. I'm just following the information I'm given. [Interviewer]: Even though you know that the information is often biased? [Writer]: The way I look at it, if doctors have their name on it, that's their responsibility, not mine. (Johnson, 2003)

Popular and journalistic outlets often approach such phenomena as instances of the breakdown of ethical standards and editorial oversight, but this unduly personalizes what is clearly a structural phenomenon. Such commentators (and even the medical editors of the ICMJE[48]) are still operating within the parameters of an older conception of science, in which authorship credit in journals is framed as a 'reward' for scientific effort, linked to an identifiable personality: the buck stops at the author. But the CROs participate in an altogether different kind of economy, in which various claims about drugs are being 'sold' to regulators, doctors writing prescriptions, and increasingly, to the patient end-user. Should these claims of efficacy be challenged, they could then potentially be litigated in a court of law and negotiated in terms of monetary liability of a corporate entity. The 'responsibility' in question is not that of some free-floating intellectual to an abstract 'republic of science',[49] but rather that of a commercial corporation to its shareholders, the regulators, and (to a lesser extent) its customers. When medical editors propose something resembling 'film credits' be appended to paper reporting clinical trials in order to reveal where the buck stops, they have begun to address the complex realities of collaborative science, but have unaccountably neglected the realities of commercialized science. One should not prematurely confuse the two. Especially for the CRO, there exists no single person or small number of people whose probity stands planted firmly behind the information disseminated (after all, mostly they are merely employees; many have moved on even before the project was completed; and corporate officers are not personally liable for product negligence); there are only the contractual obligations of the corporation. As the anonymous ghostwriter put it in his interview, it's just not his problem. The scribe who puts her pen to paper is just one more employee, enjoying the same social obligations and dispensations as the laboratory technician (with probably commensurate job security). These are among the most far-reaching consequences of the commercial outsourcing of research for the brave new world of privatized science.

The Feedback of Ends upon Means

There is a strong tendency in the literature commenting upon the contemporary regime of commercialized science, as we noted in the first section (p. 2), to discount its impact by suggesting that, at most, industry funding may have had some minor influence on changing the *means* by which research is prosecuted, but by no stretch of the imagination has it transformed the *ends* of science. Not only is this assertion made by Mertonian Tories warning of the dangers of commercialization,[50] but, perhaps also more incongruously, it is made by authors located in the constructivist

wing of the science studies community. A recent instance can be found in a review by Steven Shapin (2003: 19):

> Throughout history, all sorts of universities have 'served society' in all sorts of ways, and, while market opportunities are relatively novel, they do not compromise academic freedom in a way that is qualitatively distinct from the religious and political obligations that the ivory tower universities of the past owed to the powers in their societies.

For the Trig analyst, the indisputable fact that academic scientists and their institutions have always had to 'pay the piper' in one form or another throughout history does not imply that the modern trend towards the commercialization of science need not and will not alter the very definition of the 'outputs' of the scientific process. The qualitative effects of 'the market' (itself a reification) upon scientific research remain very much an open issue. Perhaps here, as elsewhere, the rush to discount modern qualms is rooted in too narrow a focus upon the university, with insufficient attention paid to the 'centers of excellence' where the scientific institutions of tomorrow are being forged. We have already suggested earlier that commonplace notions of 'freedom of inquiry' have undergone wrenching revision for some researchers, especially in the precincts of the CRO and the AHC. Yet the effect of commercialization upon the very goals and motivations behind research runs deeper than even this.

The biggest fallacy of the Economic Whig is to simply presume that the 'output' of scientific research, no matter what the circumstances, is always and everywhere generic 'knowledge', indifferent to the uses to which it might be put. This is merely a reification of the metaphor that compares information with a vendible physical item; a metaphor that is frequently deployed as a prelude to the application of standard neoclassical microeconomic analysis. A more threatening aspect of the mis-application of this sort of 'new economics of science' resides in the possibility that the commercialization of science actually changes whatever it is that we get at the end of the process: mutant 'outputs' that possibly didn't even exist under the older academic formation. This section suggests that we observe three such phenomena in the pharmaceutical sector, having to do with the drugs produced, data suppressed, and forms of marketing pursued, and that in each case their appearance is intimately bound up with the recourse to CROs to conduct the clinical trials.

What is the purpose of a clinical trial at the dawn of the 21st century? If you would answer 'knowledge of the effects of various treatment regimens', then you would be missing much of the activity of CROs. The bottom line for CROs, as we have already suggested, is the facilitation of the approval process for new drugs for the pharmaceutical industry. Their vaunted advantages over the AHCs reside in the efficient performance of this function, as they would readily admit. Yet it would be too hasty to simply point to gross numbers of drugs approved and average speeds of development cycles as indices of global 'success' of privatized science. The

major irony that haunts the recent re-organization of clinical research is that all the infusions of corporate funding and all the stress on 'efficiency' promulgated by CROs have produced fewer and fewer truly *new* drugs – that is, drugs that are not merely new molecular entities relative to those previously under patent protection, but are also substantially different from anything that had been established in therapeutic regimens (Nightingale & Martin, 2004). Even some researchers within the pharmaceutical companies have begun to talk of a 'clear fall in productivity' (Pollack, 2002; Berenson, 2004). As one source reports, 'the number of innovative drugs reaching the market has actually declined over the past several years, from a high of 53 per year in 1996 to 27 in 2000' (Angell & Relman, 2002: 106). The number declined further to 21 drugs in 2003, even as the industry had nearly doubled its spending on development over the interval (Berenson, 2004). This has happened while the number of FDA drug approvals has been on the increase. The FDA approved 368 NDAs from 1991 through 1995 and 523 NDAs from 1996 through 2000 (*US Regulatory Reporter 2001*, quoted in Parexel, 2003: 255).

The disparity between gross approvals and real novelty is easy to explain: the new drugs consist primarily of 'copycat' or 'me-too' drugs: molecules which do not differ very much from previously existing drugs, either generics or entities controlled by a competitor; they might even be existing proprietary drugs administered in different doses for different diseases; they are drugs possessing similar therapeutic benefits, but which are different enough to warrant patent or other IP protection. Examples would be Claritin, one of a large family of well-understood antihistamines; Zocor and Lipitor, members of the family of statins; or Zoloft and Paxil, which belong to the same family as Prozac. The provision of copycat drugs dates at least from the middle of the last century, and the recourse to combinatorial chemistry has only rendered their production better understood. Another recent phenomenon is the 'recycling' of drugs (Pollack, 2004): scanning castoff drugs from other pharmaceutical companies for side effects which might be marketed as novel therapies, or exploring cocktails of failed drugs, or drugs deleted from rosters due to industry consolidation. '[A]s big companies have merged, overlapping projects have been cut. Some companies have decided it is better to get a return on these redundant or minor drugs by letting someone else sell them' (2004: 9).

The relevance of this phenomenon to the present discussion is that the commercialization of clinical science has actually promoted the growth of copycat, recycled, and retooled drugs. Clinicians and academic researchers in AHCs have generally given a wide berth to research into copycat and recycled drugs (although, it must be admitted, not eschewed them altogether), since in their view, there were so many more pressing needs in healthcare than simply the quest of pharmaceutical companies to keep existing blockbuster drugs under patent. Further, from an academic perspective, their scientific interest frequently verges on nil. CROs generally do not share such scruples. Thus, while the regime of privatized science is

not strictly responsible for the phenomenon of copycat drugs, it has been much better structured to facilitate their development. For instance, drug companies may themselves want to have access to data on the effectiveness of their copycat molecule relative to existing treatments, but they would not want those data made public (Pear, 2003). CROs are quite happy to maintain these patterns of secrecy and disclosure. Consequently, vast sums of money have been poured into research into copycat and recycled molecules, which have been of dubious benefit to the overall public health, and arguably, communal welfare. Therefore, when champions of the bracing virtues of commercialized science point to the munificent increase of private investment in biomedical research, it may be prudent to recall that not everything that comes out of a drug assay or clinical trial is 'knowledge' in the conventional sense of deepened understanding of the mechanisms nominally at issue.

One might be tempted to aver that this caveat is too harsh, and that at the very least what the pharmaceutical firms and CROs are providing is a vast archive of clinical knowledge of tested molecules, which may provide important clues to further developments in the future, even if they appear at present to be little more than the validation or elimination of a host of copycat or recycled molecules. But even such an attempt to exonerate the privatized regime ignores the fact that, when clinical trials are run for the more restricted purposes of drug development under the modern IP system, then information that does not further those immediate goals is superfluous, and therefore, a source of inefficiency in research. When clinical trials seem to suggest that a line of drug development is not panning out, then the optimal thing to do for commercial reasons is to terminate the trial (Psaty & Rennie, 2003). Not only does this result in a callous and cynical treatment of the patient population, and an apparent violation of the Helsinki Declaration, but it demonstrates that the purpose of clinical research does not include following lines of inquiry wherever they may lead, or contributing to an common archive of 'negative' results, which might in the future be incorporated into larger therapeutic contexts. Perhaps this is why the pharmaceutical industry has resisted repeated calls to register clinical trials, so that outsiders would be able to know that a particular regimen or molecule had ever undergone scrutiny (Dickerstein & Rennie, 2003).[51] The vast volume of clinical trial information that never leaks out from proprietary boundaries, much less actually gets published, can never be considered a 'contribution' to medical knowledge in any serious way; but it was never intended to be. In a very real sense, from the viewpoint of the scientific community, it doesn't exist. Far from jettisoning 'idle curiosity' as an extravagant luxury, privatized clinical science treats all curiosity as antithetical to efficient research.

If modern clinical trials do not exist to produce scientific 'information' (with the obvious exception of successful trials slated for FDA examination), then what exactly are they for? This is where we discover the most pronounced feedback from means to ends. If privatized pharmaceutical

research in an IP regime is to produce a stream of copycat versions of successful drugs, then it follows that a major commercial motivation of clinical trials is for advertising, since the key to a successful copycat is marketing. By one 2000 estimate, the drug industry's 11 Fortune 500 companies devoted 30% of their revenue to marketing and administrative costs and only 12% of their revenue to research and development (Public Citizen Health Research Group, 2001: 20). Much of this promotion is buttressed by Phase IV clinical research performed by CROs to lend some veneer of justification for the assertions of the efficacy of these patented medicines (generics often don't merit advertising). Because this research is being tailored to the requirements of an advertising campaign, it is increasingly the case that the contracts for the clinical trials, the ghostwriters, and the rest are negotiated, not by the R&D arms, but by the marketing departments and advertising agencies of Big Pharma (Bogdanich & Petersen, 2002). While academics might cringe at the prospect, for a CRO this is just another ripe market opportunity. The line between science and advertising is consciously being blurred in pharmaceutical research, because the regime of privatized science makes it possible and profitable.[52] The CRO is an instrument that helps make this happen.

It gives one pause to observe the extent to which the outward trappings of science can so easily be turned into occasions for marketing. It has become standard practice to convene so-called all-expenses-paid 'medical conferences' in desirable tourist destinations, which turn out to be elaborate sales presentations for new products, all under the guise of the presentation of research papers (Tilney, 2003). Other more modest perks are free dinners and honoraria given in the guise of 'continuing medical education', liberally sprinkled with promotional presentations (Wazana, 2000; Angell & Relman, 2002; Siegel, 2002). An even more insidious practice is to subordinate the protocol of clinical research more directly to marketing imperatives in the form of seeding and switching trials (Smith, 2003: 1203). Here the companies simply conduct the trials in order to get the doctors to begin to prescribe their drugs. Non-academic physicians are recruited to take part in trials for which they possess little information or basis upon which to judge the research design; they are paid handsomely to participate; they are unsure of the identity of the ultimate sponsors (since funding is channeled through CROs); they never see the 'results' of their endeavors. These trials have no particular research objective, with no well-defined question or set of controls; primarily, the physicians are chosen by the CRO or other agency simply on the basis of their prescription histories. Since the trials go unregistered, no one can effectively ask questions about the validity of the protocols or the absence of subsequent publications.[53] The objective is simply to get physicians accustomed to prescribing the proprietary and often costly drug.

Suppose that through the efforts of researchers like those cited throughout this paper, the extent of the transformations of pharmaceutical science become much more widely known. It would not be unusual if such

familiarity were to breed contempt for most of the claims of clinical medical research: not just the advertisements and the dubious presentations at scientific 'meetings' by academics under contract, but also for the medical journals themselves, and the assertions made by medical researchers when they speak publicly on behalf of the community of scientists. Observers might come to regard all scientific clinical data as corrupt, and not out of ignorance or irrationality, but rather with some justification. Whereas the prime objective of AHCs was to make patients better, the prime directive of CROs is to shape the research to the short-term demands of the client. Because the pattern of bias and silence runs so deep, simple measures to ensure or restore 'objectivity' and confidence could not begin to rectify the situation. And when it comes to medical wisdom, the average member of the public will never feel confident about exercising their purchase options in the 'marketplace of ideas'. When knowledge becomes an expensive luxury and a mere byproduct of clinical research, then cynicism about science is sure to follow.

Conclusion

The CRO sector represents a major test-bed for the implementation of a thorough-going commercialization of scientific research. Because the Mertonian Tories and Economic Whigs have neglected this phenomenon, they have missed one of the purest formats of commercialized science, as well as one of the prime conduits of the diffusion of commercialized practices into the university sector. This helps explain why the Tories have been boxed into the role of Cassandra, for they witness their citadels of ideal scientific community inundated by a new approach to scientific research ever more removed from the Mertonian ideal, without really understanding where the innovations are coming from. The Whigs, equally focused upon the university, have attempted to counter the sometimes appalling anecdotes related by the Tories by treating them as isolated aberrations, and, by means of market models, to rationalize the 'efficient' commercialization of research in academia. Both positions erroneously view the university as the prime locus where the new model of conduct of scientific research has been forged, overlooking the fact that the transmutations in the organization of science in AHC are largely symptomatic of re-engineered science in the pharmaceuticals and the CRO industry.

This paper advocates a third approach to the commercialization of science, which we (perhaps unwisely) call 'Triggish'. Trigs don't believe that the process of scientific research has any 'natural' baseline; they remain provisionally agnostic on whether we inhabit a Golden Age of Science, or conversely, an Age of Dross. We believe that close attention paid to the hopes and fears of the participants tend to be the best indicators of where significant social innovations in the processes of scientific research are taking place; it told us that the CRO is one of the prime locations of action in the globalized privatization of modern science.

The job of the Triggish science studies scholar is to document those changes, and then subject them to causal analysis.

The alterations in the character of research and the nature of results that we have identified in the CRO sector have a range of implications for social policy, most of which we have restrained ourselves from discussing in this paper due to length constraints. For instance, one tends to approach with a newly jaundiced eye the rather common assertion in the USA that citizens must not seek to lower the price of new drugs retailed by Big Pharma (through importation from abroad, government negotiated price discounts, reassertion of government IP ownership, and so on), since such efforts would strangle the quest for new drugs and technologies in the most dynamic, high-tech research sector in the world. It also tends to inoculate many of us against the paeans to the virtues of market incentives emanating from many neoclassical economists and their philosophical fellow-travelers. However, as we intimated in the first section (p. 6), this would only really follow upon more Triggish research into the extent of the five classes of transformation identified in the third section (p. 11). Their prevalence and extent in pharmaceutical research are one research task high on the agenda, but not the only item we should like to put there.

CROs are not a natural, parochial phenomenon, but a manufactured, and therefore exportable phenomenon. Consequently, we see the possibility of commercialization spillover. Some of the research problems now endemic to the biopharmaceutical sector are not peculiar to that sector, and likely have begun to spread to other sectors. One might identify trouble with human subjects in areas like environmental services or psychological experimentation, problems of confidentiality and disclosure in the commercialized defense industry, the need to control 'research tools' in chemical or software industries, the spread of ghost authorship to information technologies and social policy[54], and the need to provide marketing innovations for IP in an entire range of wholesale and retail settings. Once the CRO becomes solidly identified with successful institutional innovation in the control of research, we see no special reason why it might not pop up wherever corporate research capacity needs to be outsourced and re-engineered, albeit modified to better conform to local concerns.

Thus, it seems a safe prediction that the commercialization of scientific research will continue to occur – stemming from structural changes wrought by CRO-like entities and other devices goading academia to continue to re-engineer its own scientific organization. Consequently, the new phenomena of research we have identified in the pharmaceutical sector may also become more prevalent elsewhere. Unless the structural changes taking place in the corporate sector receive comprehensive attention, the denizens of the university will never come to understand the future implications of the commercialization of scientific research. Thus, the CRO sector needs to be brought to the forefront of science policy debate, not just to rectify biomedical problems or mitigate debilitating conflicts of interest, but also to understand further the social structures of research and thereby better protect its integrity.

Notes

We would like to thank Tom Uebel, Nicholas Rasmussen, Sergio Sismondo, the referees, and the participants of seminars at the University of Hertfordshire and Universidad de la Republica Uruguay for their comments.

1. Some other examples of this position would be Press & Washburn (2000), Croissant & Restivo (2001), Newfield (2003), and Krimsky (2003).
2. For similar assessments: the 'growing commercial engagement has not, thus far, altered the research culture of universities, so as to privilege applied orientations at the expense of basic science' (Owen-Smith & Powell, 2003: 1696); 'Science today is only a short way down the path to becoming a toady of corporate power' (Greenberg, 2001: 3); do we see 'universities compromising their core values [?] . . . at least at the major research universities, their revenue-enhancing activities have not seriously distorted such values' (Baltimore, 2003: 1050); 'There is evidence to suggest that university licensing facilitates technology transfer with minimal effects on the research environment' (Thursby & Thursby, 2003: 1052). Other exemplars of Whiggism might be Nowotny et al. (2001), Feldman et al. (2002), David & Dasgupta (1994), Etzkowitz (2002), and Leonard (2004).
3. These themes are explained in greater detail in the Introduction to Mirowski & Sent (2002), which argues that using market models of generic commodities tends to distract attention from the more important aspects of the scientific enterprise. A Whiggish disagreement by a Science Warrior with this assessment is Leonard (2004).
4. See, for instance, Eisenberg (2001), Magnus et al. (2002), and McSherry (2001). Ryan (1998: 27) reports that the pharmaceutical industry was awarded the most US patents per year.
5. Of the four largest pharmaceutical CROs, Quintiles Transnational was incorporated in 1982, and Parexel International was founded in 1983. Covance was formed in 1987, as a unit of Corning. On these and other firms, see Rettig (2000). CROs differ profoundly from earlier for-profit toxicology, bioassay, and pharmaceutical testing firms, which they have tended to drive out of business.
6. Differences between these estimates can be attributed to differing definitions of the base, namely, the total amounts spent by pharmaceutical firms for drug R&D. The definitions are confounded by extramural/intramural distinctions, international accounting, indistinct separation of clinical from basic categories, and so on.
7. Here, we presume that CROs and AHCs are discrete mutually exclusive categories. The evidence presented in this paper raises a disturbing possibility that, as they are rendered more similar, they also are becoming less distinct as separate entities.
8. The pre-eminent advocate of this position is Nicholas Rasmussen. See, in particular, Rasmussen, 2002, 2004, 2005. Another representative would be Harry Marks, who nevertheless has pointed out (1997: 234) that up until our modern period, those whom he calls 'therapeutic reformers' stigmatized 'those who operate in profit-making institutions . . . as operating on the edges of, if not outside, the boundaries of science.'
9. Nick Rasmussen asked us in private communication: 'Why regard the decade or two of post-Kefauver vigilance, ending with Reagan in 1980, as representing the baseline natural relationship between drug companies, academia and regulators? What if one chose to regard the mid-60s through 1970s as aberrant, and the preceding two decades as the natural baseline . . . ?' The short answer is that we just don't know, and cannot begin to address that argument here. These are precisely the kinds of questions that are undreamt of in the philosophies of both the Whigs and Tories, questions the Trigs want to provoke. Trigs don't believe Science has any 'natural' or persistent baseline.
10. See note 9. We have been continually frustrated to find that, within the growing mass of literature on technology transfer and the economics of science, such histories are notably absent. One of us (P.M.) suspects this is due to the pernicious influence of crude metaphors of 'marketplace of ideas', and the Whig projection on to science of the neoclassical economic distinction between the public and private good.

11. An insightful comparison of the US and German experience (the German pharmaceutical industry briefly predated the US one) can be found in Daemmrich (2004). The pivotal role of the FDA standards in the global drug industry is attested in interview excerpts in Getz & de Bruin (2000: 732).
12. However, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use has sought to reduce these requirements. See Abraham & Smith (2003: 88–90).
13. All US patients must sign an informed-consent form, detailing potential benefits and risks. Not infrequently the form can be more than 30 pages long.
14. The 'FY [Fiscal Year] 2003 President's Budget' confirms Abraham's calculation, and it estimates that approximately 17% of the 2003 FDA budget will comprise expeditionary fees or user fees (Abraham, 2002: 1499).
15. See, in particular, Rettig (2000), Pichaud (2002), Davies (2001), Gelijns & Their (2002), and Azoulay (2002).
16. 'For such drugs as antibiotics for acute infections, large populations and long timelines are seldom needed to establish efficacy and safety. With the new emphasis on prevention and treatment of chronic diseases, however, clinical drug research has changed. Many people take antihypertensive drugs and lipid-lowering drugs for many years in order to prevent relatively few undesired clinical endpoints' (Bodenheimer, 2000: 1539).
17. Since its origins in the early 1980s, the biotechnology industry has burgeoned into a multibillion-dollar global industry. The first successful biotech, Genentech, went public in 1980 – it received an unrivaled Wall Street reception – beginning the International Public Offering (IPO) phenomenon. This heralded the 80 plus biotech firms that surfaced in 1981 (Hope, 2003). Thereafter, the industry grew exponentially.
18. See 'Pharmacogenomics' Reality Check' at < www.windhover.com > .
19. One recent exception we shall discuss is Krimsky (2003), which, however, does not cover CROs. One of our intentions is to fortify Krimsky's anecdotes with some more substantive Trig theoretical underpinnings.
20. See, for instance, Stephens (2000), Lemonick & Goldstein (2000), and Shah (2003).
21. 'The varieties of roles that bioethicists inhabit . . . complicates the question of corruption, because it is not clear what duties and loyalties are expected of them . . . . Until recently, students studying the ethics of stem cell research would not have suspected that their teacher was a consultant for Geron; scholars criticizing industry-sponsored clinical trials would not have imagined the editor evaluating their manuscript was working for Eli Lilly; newspaper readers would not have thought that the ethicist commenting on genetic engineering was drawing a pay cheque from Celera' (Elliott, 2002: 36). See also the papers by Foster and Corrigan in Abraham & Smith (2003).
22. This issue received wide publicity with the death in 1999 of Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania. James Wilson, the principal investigator in the study, held a 30% stake in Genovo, which owned the rights to the drug Wilson was testing. Investigations into patient deaths in clinical trials in other cities also raised the issue of whether experimental subjects realized that they were risking their lives, given the confidentiality arrangements imposed by the commercial ties of their physicians (see Wilson & Heath, 2001).
23. See Stephens (2000), Shah (2003), Flaherty et al. (2000), DuBois (2003), Stone (2003), and Breitstein (2001).
24. The cases of China and India are discussed in Shah (2003). Forster (2002: 520) discusses the phenomenon of IRB shopping in the Third World. Roman (2002) provides a general overview of regulatory avoidance.
25. 'Academic medical centers have a bad reputation in the industry because many overpromise and underdeliver' (Greg Fromell of Covance, quoted in Bodenheimer, 2000: 1540).
26. See Olivieri (2003) and S. Hughes (2002). For further discussion, see Krimsky (2003). When academic researchers found that Remune, an anti-AIDS therapy, was ineffective,

their sponsor Immune Research Corporation sued the scientists in 2001 for US$10 million damages (Newman, 2002).

27. The variables that regularly enter into the 'auxiliary hypotheses' in drug trials are discussed in Bero & Rennie (1996) and Morgan et al. (2000). Those familiar with the philosophy of science literature will recognize the general problems with falsifications discussed under the rubric of 'Duhem's Thesis'.
28. See Kjaergard & Als-Nielsen (2002) and Davidson (1986).
29. See Davidoff et al. (2001) and <www.icmje.org> for the actual guidelines. A reflection on their motivation is Frank Davidoff, 'Between the Lines', <www.healthyskepticism.org>. These incidents are also described by Krimsky (2003).
30. The impression that the FDA stands as the final bulwark against such pervasive bias is equally naive. Just as with the academic journals, its drug approval advisory committees are equally rife with conflicts of interest (Goliszek, 2003). Few realize the extent of government–Big Pharma ties. For instance, it is emblematic that Donald Rumsfeld was Chief Executive Officer (CEO) of Searle before he became the ultimate Defense Department insider.
31. There is a small literature in the philosophy of science that attempts to assert that marketplace models of science can demonstrate that self-interested biases need not or will not impugn the quality and integrity of the knowledge produced under such circumstances. Undoubtedly this literature has been prompted by phenomena such as described in this section. Some of these arguments may be sampled in Mirowski & Sent (2002); this literature is criticized in Mirowski (2004b).
32. Some of the more important sources are Campbell et al. (2002), Dreyfuss et al. (2001), Lessig (2001), McSherry (2001), Mirowski (2001), Boyle (2003), and Sell (2003).
33. The 1980 Supreme Court decision (447 US 202) *Diamond v. Chakrabarty* is discussed in detail in Kevles (1994, 1998).
34. That is the reason why this paper is not confined to narrowly defined clinical research. Indeed, CROs have recently moved upstream into 'recycling' studies (Pollack, 2004).
35. Some of these technical changes are discussed in the *Report of the NIH Working Group on Research Tools* (<www.nih.gov/news/researchtools/index.htm>) and explained at an elementary level by John C. Brown, *What the Heck is a Receptor?* (<http://people.ku.edu/~jbrown/receptor>).
36. The problems with portrayal of non-market formations as gift economies are discussed in Mirowski (2004a).
37. An anonymous referee reminded us that some of the early products that were patented included recombinant insulin, human growth hormone, and cytokine. Further, receptors were not patentable per se, although the specification of a generic application such as 'diagnostic' did present de facto IP barriers.
38. See Eisenberg (2001: 229) for a description of various attempts by the National Institutes of Health panel in 1998 to define the meaning of a 'research tool'. As she points out, each player was 'eager to establish that the term "research tools" means something other than their own institution's crown jewels.'
39. As described by Azoulay (2003), curiosity leading to appropriable IP is engineered out of the system. This was put in a colorful fashion by a financial officer of a pharmaceutical firm:

> Our purchasing department uses a matrix where relationships can be described anywhere from a continuum that goes from 'used-car salesman' to 'We're married' kind of thing. For the used-car salesmen, we try to squeeze whatever we can out of the price, and we don't care if they go out of business, we do not care if they lose money, we are just trying to get the best deal we can .... And we are more on the used-car salesman end of the spectrum. I think that's the case for most sponsors. I think that Merck and Pfizer are even tougher with the CROs than we are. (2003: 16)

40. A notorious example of a reach-through patent claim is the University of Rochester's patent on the cyclooxygenase (COX)-2 enzyme, which claims IP on the target and any compound that acts on it to produce the desired effect, without describing the nature of the compounds. A different and more egregious example is the patent issued to the Massachusetts Institute of Technology in June 2002 for the nuclear factor kappa B (NF-κB) cell-signaling pathway. It was licensed to Ariad Pharmaceuticals, which turned around and filed suit against Eli Lilly for patent infringement. Ariad's lawsuit reveals the pathologies of reach-through, 'because they had really not made any effort to do research on that pathway itself, [Arti] Rai says. This is a case of a very broad patent on a fundamental technology being asserted against companies that actually developed the technology and produced a product without the benefit of a patent' (in Agres, 2003).
41. The control of research tools as a departure from prior practices is discussed in Eisenberg (2001) and Walsh et al. (2003).
42. A term of abuse used to refer to CRO clinical trial monitors; see Azoulay (2003).
43. Again the lone exception has been (Krimsky, 2003). For instance, in chapter 10, 'The Scientific Journals', Krimsky describes the conflict of interest in scientific publications and in policies and procedures of journal editors. The reconfiguration of the scientific author has drawn the attention of some students of science studies (Mirowski, 2001; Biagioli & Galison, 2003). One major attempt to widen the discussion to include the general public has been by Johnson (2003).
44. The chronology of events can be found at < www.CouncilScienceEditors.org > . For further chronological developments see < www.icmje.org/sponsor.htm > .
45. Perhaps the first revelations of medical ghostwriters surfaced in court cases related to the diet drug 'fen-phen' (actually a combination of fenfluramine, dexfenfluramine, and phentermine). Company documents subpoenaed from the producer Wyeth-Ayerst Laboratories revealed that it had commissioned Exerpta Medica, Inc. to write 10 papers concerning the drug, two of which were subsequently published in refereed medical journals under the names of prominent researchers, one of whom claimed in testimony he had no idea that Wyeth had commissioned the paper (Zuckerman, 2002).
46. One potentially important historical finding is that an indeterminate amount of corporate ghostwriting in pharmaceuticals may date back as far as the 1930s. See Rasmussen (2004, 2005).
47. CROs openly advertise these services on their websites. See, for instance, the site of Parexel at < www.parexel.com/products_and_services > , where it is stated 'PAREXEL medical writers provide ghost writing services both as stand-alone projects and as part of a larger scope of PAREXEL services.'
48. This point has been made with perspicuity by Mario Biagioli in Biagioli & Galison (2003: 253–279).
49. Itself a rather awkward notion broached in an ineffectual manner by Michael Polanyi; for more on this, and its role in the Cold War era, see Mirowski (2004a).
50. See, for instance, Bok (2002) and Nowotny et al. (2001).
51. Since this paper was written, there have been a number of attempts to claim that such a registry will be created or already does exist (Meier, 2004), but at this writing, the situation is still in flux.
52. Again, Rasmussen (2004, 2005) suggests an indeterminate amount of this disguised advertising in the form of 'seeding trials' has occurred for more than a century. Our Triggish point is simply that the CRO facilitates and stabilizes a practice that might be more difficult to prosecute on an industrial scale in AHCs.
53. We think it worthwhile to point out that the paucity of critical scrutiny of the practices described in this section is linked to the heavy dependence of newspapers, broadcast media, and even medical journals (Smith, 2003) upon pharmaceutical advertising revenue, and in the case of the broadcast news media, even pharmaceutical marketing departments for those 'medical news' segments, which themselves are often thinly veiled advertising. Hence we have been driven to the expedient of citing public television reports such as Bogdanich & Petersen (2002) and Johnson (2003) for evidence.

54. See, for instance, the website of History Associates Incorporated at: <www.historyassociates.com/services>.

References

Abraham, John (2002) 'The Pharmaceutical Industry as a Political Player', *Lancet* 360(9344): 1498–502.

Abraham, John & Helen Smith (eds) (2003) *Regulation of the Pharmaceutical Industry* (London: Palgrave).

Agres, Ted (2003) 'The Cost of Commercializing Academic Research', *The Scientist* 17: 58–59.

Angell, Marcia & Arnold Relman (2002) 'Patents, Profits and American Medicine', *Daedalus* (Spring): 102–11.

Azoulay, Pierre (2002) 'Acquiring Knowledge Within and Across Firm Boundaries', Columbia University School of Business, Working Paper.

Azoulay, Pierre (2003) 'Agents of Embeddedness', Columbia University School of Business, Working Paper.

Baltimore, David (2003) 'On Over-Weighting the Bottom Line', *Science* 301: 1050–51.

Bekelman, Justin, Yan Li & Cary Gross (2003) 'Scope and Impact of Financial Conflicts of Interest in Biomedical Research', *Journal of the American Medical Association* 284: 454–65.

Berenson, Alex (2004) 'An Industry in Poor Health', *New York Times* (18 December): A1.

Bero, Lisa & D. Rennie (1996) 'Influences on the Quality of Public Drug Studies', *International Journal of Technological Assessment in Health Care* 12(2): 209–37.

Bhopal, R., J. Rankin, E. McColl, L. Thomas, E. Kaner et al. (1997) 'The Vexed Question of Authorship', *British Medical Journal* 314: 1009–12.

Biagioli, Mario & Peter Galison (eds) (2003) *Scientific Authorship: Credit and Intellectual Property in Science* (New York: Routledge).

Blumenthal, D., E. Campbell, N. Causino & K. Seashore Lewis (1996) 'Participation of Life-Science Faculty in Research Relationships with Industry', *New England Journal of Medicine* 335: 1734–39.

Bodenheimer, Thomas (2000) 'Uneasy Alliance – Clinical Investigators and the Pharmaceutical Industry', *New England Journal of Medicine* 342: 1539–44.

Bogdanich, Walt & Melody Petersen (2002) 'Science for Sale – Ad Agencies and Drug Companies Hand in Hand?', *Bill Moyers Now* available at <www.pbs.org/now/transcript/transcript144_full.html> (accessed 18 March 2005).

Bok, Derek (2002) *Universities in the Marketplace: The Commercialization of Higher Education* (Princeton, NJ: Princeton University Press).

Boyd, Elizabeth, Mildred Cho & Lisa Bero (2003) 'Financial Conflict-of-Interest Policies in Clinical Research: Issues for Clinical Investigators', *Academic Medicine* 78: 769–74.

Boyle, James (ed.) (2003) 'The Public Domain', *Law and Contemporary Problems* 66(1/2).

Breitstein, Joanna (2001) 'World Watch: Protecting People Everywhere', *Pharmaceutical Executive* (December).

Brown, James Robert (2000) 'Privatizing the University', *Science* 290: 1701.

Business Wire (2002) 'PharmaLinkFHI to Present', 30 January.

Campbell, Eric, Brian R. Clarridge, Manjusha Gokhale, Lauren Birenbaum, Stephen Hilgartner et al. (2002) 'Data Withholding in Academic Genetics: Evidence from a National Survey', *Journal of the American Medical Association* 287: 473–80.

Campbell, Eric, Joel S. Weissman, Ernest Moy & David Blumenthal (2001) 'Status of Clinical Research in Academic Health Centers: Views from the Research Leadership', *Journal of the American Medical Association* 286: 800–06.

Cho, Mildred K., Roy Shohara, Anna Schissel & Drummond Rennie (2000) 'Policies on Faculty Conflict of Interest at US Universities', *Journal of the American Medical Association* 284: 2203–08.

Croissant, Jennifer & Sal Restivo (eds) (2001) *Degrees of Compromise: Industrial Interests and Academic Values* (Albany, NY: SUNY Press).

Daemmrich, Arthur (2004) *Pharmacopolitics: Drug Regulation in the United States and Germany* (Chapel Hill, NC: University of North Carolina Press).
Datta, P. (2003) 'Are We Ready for Drug Trials on a Large Scale?', *Financial Times* (24 September).
David, Paul & Partha Dasgupta (1994) 'Towards a New Economics of Science', *Research Policy* 23: 487–521.
Davidoff, Frank, C.D. DeAngelis, J.M. Drazen, J. Hoey, L. Hojgaard et al. (2001) 'Sponsorship, Authorship and Accountability', *New England Journal of Medicine* 345: 825–27.
Davidson, R.A. (1986) 'Source of Funding and the Outcome of Clinical Trials', *Journal of General Internal Medicine* 1: 155–58.
Davies, Helen (2001) 'The Role of the Private Sector in Protecting Human Research Subjects: A CRO perspective', talk delivered to the Institute of Medicine on 21 August. Available at <www.acrohealth.org/policy/pdfs/testimony_082101.pdf> (accessed 18 March 2005).
Davies, Helen (2002) 'Role of Contract Research Organizations (CRO) in Protecting Human Subjects', talk delivered at the DIA 2002 Annual Meeting. Available at <www.quintiles.com/NR/rdonlyres/eynjegbwzxe4gsp2huilgm5p7eym4zq3d7sknf7cpxr6g5c6zalzh65fgrxbpjdn7hoephi3vwkzon7e4tgupbas5a/Helen_Davies_DIA2002.pdf> (accessed 18 March 2005).
DeYoung, Karen & Deborah Nelson (2000) 'Latin America is Ripe for Trials, and Fraud', *Washington Post* (21 December) (fifth of six-part series).
Dickerstein, Kay & Drummond Rennie (2003) 'Registering Clinical Trials', *Journal of the American Medical Association* 290: 516–23.
Drahos, Peter & John Braithwaite (2002) *Information Feudalism* (New York: New Press).
Drennan, Katherine (2002) 'Patient Recruitment: The Costly and Growing Bottleneck in Drug Development', *Drug Discovery Today* 7(3): 167–70.
Dreyfuss, Rachel, Diane Zimmerman & H. First (eds) (2001) *Expanding the Boundaries of Intellectual Property* (New York: Oxford University Press).
DuBois, William (2003) 'New Drug Research, the Extraterritorial Application of FDA Regulations, and the Need for International Cooperation', *Vanderbilt Journal of Transnational Law* 36: 161–207.
Eisenberg, Rebecca (2001) 'Bargaining over the Transfer of Proprietary Research Tools', in R. Dreyfuss, D. Zimmerman & H. First (eds), *Expanding the Boundaries of Intellectual Property* (New York: Oxford University Press): 223–50.
Eisenberg, Rebecca & Arti Rai (2003) 'Bayh-Dole Reform and the Progress of Biomedicine', *Law and Contemporary Problems* 56: 289–314.
Elliott, Carl (2002) 'Diary', *London Review of Books* (28 November): 36–37.
Enserink, Martin (1999) 'NIH Proposes Rules for Materials Exchange', *Science* 284 (28 May): 1445.
Etzkowitz, Henry (2002) *MIT and the Rise of Entrepreneurial Science* (London: Routledge).
Feinstein, Alvan (2003) 'Scholars, Investigators and Entrepreneurs', *Perspectives in Biology and Medicine* 46: 234–53.
Feldman, Maryanne, Albert Link & Donald Siegel (2002) *The Economics of Science and Technology* (Kluwer, Norwell).
Fisher, Morris (2003) 'Physicians and the Pharmaceutical Industry', *Perspectives in Biology and Medicine* 46: 254–72.
Flaherty, Mary P., Deborah Nelson & Joe Stephan (2000) 'The Body Hunters', *Washington Post* (18 December): A1 (second of six-part series).
Flanagin, A., L. Carey, P. Fontanarosa, Stephanie G. Phillips, Brian P. Pace et al. (1998) 'Prevalence of Articles with Honorary Authors and Ghost Authors in Peer-Reviewed Medical Journals', *Journal of the American Medical Association* 280: 222–24.
Forster, David (2002) 'Independent Institutional Review Boards', *Seton Hall Law Review* 32: 513–23.

Friedberg, M., B. Saffran, T. Stinson, Wendy Nelson & Charles E. Bennett (1999) 'Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology', *Journal of the American Medical Association* 282: 1453–57.

FY 2003 President's Budget for Department of Health and Human Services (2002) <www.fda.gov/bbs/topics/ANWSERS/2002/ANS01135.html> (accessed 18 March 2005).

Gad, Shane C. (2003) *The Selection and Use of Contract Research Organizations* (London: Taylor & Francis).

Gelijns, Annetine & Samuel Their (2002) 'Medical Innovation and Institutional Interdependence', *Journal of the American Medical Association* 287: 72–78.

Getz, Kenneth & Annick de Bruin (2000) 'Breaking the Development Speed Barrier: Assessing Successful Practices of the Fastest Drug Development Companies', *Drug Information Journal* 34: 725–36.

Giombetti, Ric (2002) 'Suicide Science – Paxil's Friendly Ghostwriter?' (April 8). Available at <www.counterpunch.org> (accessed 18 March 2005).

Goliszek, Andrew (2003) *In the Name of Science* (New York: St Martin's).

Greenberg, Daniel (2001) *Science, Money and Politics* (Chicago, IL: University of Chicago Press).

Healy, David (2003) 'In the Grip of the Python: Conflicts at the University–Industry Interface', *Science and Engineering Ethics* 9: 59–71.

Healy, David & D. Cattell (2003) 'Interface between Authorship, Industry and Science in the Domain of Therapeutics', *British Journal of Psychiatry* 183: 22–27.

Hedgecoe, Adam & Paul Martin (2003) 'The Drugs Don't Work', *Social Studies of Science* 33(3): 327–64.

Heller, Michael & Rebecca Eisenberg (1998) 'Can Patents Deter Innovation? The Anticommons in Biomedical Research', *Science* 280: 698.

Hicks, Diana (1995) 'Published Papers, Tacit Competencies', *Industrial and Corporate Change* 4: 401–24.

Hope, Janet (2003) 'Intellectual Property and the Biotechnology Revolution', <http://rsss.anu.edu.au/~janeth/Law.html> (accessed 18 March 2005).

Horton, Richard (2002) 'The Hidden Research Paper', *Journal of the American Medical Association* 287: 2775–78.

Hughes, Graham (2002) 'Annual Review of Contract Research Organizations', *European Pharmaceutical Contractor* (Spring), available at <www.samedanltd.com/homepage/epc.htm> (accessed 18 March 2005).

Hughes, Sue (2002) 'Does the Pharmaceutical Industry Have Too Much Control Over Clinical Trials?', *Heartwire* (15 November).

Johnson, Erica (2003) 'Medical Ghostwriting', *CBC Marketplace* (Air Date 25 March). Available at <www.cbc.ca/consumers/market/files/health/ghostwriting>.

Kahin, Brian (2001) 'The Expansion of the Patent System: Politics and Political Economy', *First Monday* 6(1). Available at <http://firstmonday.org/issues/issue6_1/kahin>.

Kaitin, Kenneth & Joseph DiMasi (2000) 'Measuring the Pace of New Drug Development in the User Fee Era', *Drug Information Journal* 34: 673–80.

Kaitin, Kenneth & Elaine Healy (2000) 'The New Drug Approvals of 1996, 1997 and 1998', *Drug Information Journal* 34: 1–14.

Kessler, David (2001) *A Question of Intent* (New York: Public Affairs).

Kevles, Daniel (1994) 'Ananda Chakrabarty Wins a Patent', *Historical Studies in the Physical and Biological Sciences* 25: 111–36.

Kevles, Daniel (1998) 'Diamond v. Chakrabarty and Beyond: The Political Economy of Patenting Life', in Arnold Thackray (ed.), *Private Science: Biotechnology and the Rise of the Molecular Sciences* (Philadelphia, PA: University of Pennsylvania Press): 65–79.

Kjaergard, L. & B. Als-Nielsen (2002) 'Association between Competing Interests and Authors' Conclusion: Epidemiological Study of Randomized Clinical Trials in the BMJ', *British Medical Journal* 325: 249–52.

Krimsky, Sheldon (2003) *Science in the Private Interest* (Lanham, MD: Rowman & Littlefield).

Kunin, Stephen, Mark Nagumo, Brian Stanton, Linda S. Therkorn & Stephen Walsh (2002) 'Reach-through Claims in the Age of Biotechnology', *American University Law Journal* 51: 608–38.
Kupiec-Weglinski, J.W. (2003) 'Interactions between the Pharmaceutical Industry and Academia Revisited', *Transplantation Proceedings* 35: 1238–39.
Lemonick, Michael & Andrew Goldstein (2000) 'At Your Own Risk', *Time* (22 April): 46–56.
Leonard, Thomas C. (2004) 'Making Betty Crocker Assume the Position', *Journal of the History of Economic Thought* 26: 115–22.
Lessig, Larry (2001) *The Future of Ideas* (New York: Basic).
Lester, David & Jane Connor (2003) 'New Tools for Clinical Practice', *American Pharmaceutical Outsourcing* (May/June). Available at <www.americanpharmaceuticaloutsourcing.com/articles>.
Lexchin, Joel, Lisa Bero, Benjamin Djulbegovic & Otavio Clark (2003) 'Pharmaceutical Industry Sponsorship and Research Outcome and Quality', *British Medical Journal* 326: 1167–77.
McSherry, Corynne (2001) *Who Owns Academic Work?* (Cambridge, MA: Harvard University Press).
Magnus, David, Arthur Caplan & Glenn McGee (eds) (2002) *Who Owns Life?* (Amherst, MA: Prometheus).
Marks, Harry (1997) *The Progress of Experiment* (New York: Cambridge University Press).
Marshall, Elliot (1997) 'Need a Reagent? Just Sign Here . . . ', *Science* 278: 212–13.
Maurer, Stephen (2002) 'Promoting and Disseminating Knowledge: The Public/Private Interface', Paper presented to NRC Symposium on Information in the Public Domain. Washington (September).
Meier, Barry (2004) 'Group is Said to Seek Full Drug-Trial Disclosure', *New York Times* (June 14): A1.
Milne, C. & C. Paquette (2004) 'Meeting the Challenge of the Evolving R&D Paradigm: What Role for the CRO?', *American Pharmaceutical Outsourcing*. Available at <www.americanpharmaceuticaloutsourcing.com>.
Mirowski, Philip (2001) 'Re-engineering Scientific Credit in the Era of the Globalized Information Economy', *First Monday* (December), <www.firstmonday.dk/issues/issue6_12>.
Mirowski, Philip (2004a) *The Effortless Economy of Science?* (Durham, NC: Duke University Press).
Mirowski, Philip (2004b) 'The Scientific Dimensions of Social Knowledge', *Studies in the History and Philosophy of Science* 35: 283–326.
Mirowski, Philip & Esther-Mirjam Sent (eds) (2002) *Science Bought and Sold* (Chicago, IL: University of Chicago Press).
Morgan, Steve, Morris Barer & Roberts Evans (2000) 'Health Economics Meets the Fourth Tempter: Drug Dependency and Scientific Discourse', *Health Economics* 9: 659–67.
Mowatt, Graham, Liz Shirran, Jeremy M. Grimshaw, Drummond Rennie, Annette Flanagin et al. (2002) 'Prevalence of Honorary and Ghost Authorship in Cochrane Reviews', *Journal of the American Medical Association* 287: 2769–71.
Nelson, Richard (2001) 'Observations on the Post Bayh-Dole Rise of Patenting at American Universities', *Journal of Technology Transfer* 26: 13–19.
Newfield, Christopher (2003) *Ivy and Industry* (Durham, NC: Duke University Press).
Newman, Nathan (2002) 'Big Pharma, Bad Science', *Nation* (25 July), available at <www.thenation.com/doc.mhtml%3Fi=20020805&s=newman20020725> (accessed 18 March 2005).
Nightingale, Paul & Paul Martin (2004) 'The Myth of the Biotech Revolution', *Trends in Biotechnology* 22: 564–69.
Nowotny, Helga, Peter Scott & Michael Gibbons (2001) *Rethinking Science* (Cambridge: Polity Press).
Okie, Susan (2001) 'Missing Data on Celebrex: Full Study Altered Picture of Drug', *Washington Post* (5 August): A11.

Olivieri, Nancy (2003) 'Patients Health or Company Profits?', *Science and Engineering Ethics* 9: 29–41.
Owen-Smith, Jason & Walter Powell (2003) 'The Expanding Role of Patenting in the Life Sciences', *Research Policy* 32(9): 1695–711.
Parexel (2003) *Pharmaceutical R&D Statistical Sourcebook* (Waltham, MA: Parexel International).
Pear, Robert (2003) 'Congress Weighs Drug Comparisons', *New York Times* (24 August).
Pichaud, B.S. (2002) 'Outsourcing in the Pharmaceutical Manufacturing Process: an Examination of CRO Experience', *Technovation* 22: 81–90.
Pollack, Andrew (2002) 'Despite Billions for Discoveries, Pipeline of Drugs is Far from Full', *New York Times* (19 April).
Pollack, Andrew (2003) 'Three Universities Join Researcher to Develop Drugs', *New York Times* (31 July): C1.
Pollack, Andrew (2004) 'Is Biotechnology Losing its Nerve?', *New York Times* (February 27): Section 3: 1.
Pomfret, John & Deborah Nelson (2000) 'In Rural China, a Genetic Mother Lode', *Washington Post* (20 December) (fourth of six-part series).
Posner, Richard A. (2002) 'The Law & Economics of Intellectual Property', *Daedalus* (Spring): 5–12.
Press, Eyal & Jennifer Washburn (2000) 'The Kept University', *Atlantic Monthly* 285(3): 39–54.
Psaty, Bruce & Drummond Rennie (2003) 'Stopping Medical Research to Save Money', *Journal of the American Medical Association* 289: 2128–30.
Public Citizen Health Research Group (2001) 'Rx R&D Myths: The Case Against the Drug Industry's R&D "Scare Card"'. Available at < www.citizen.org/hrg > (accessed 18 March 2005).
Rasmussen, Nicolas (2002) 'Of Small Men, Big Science, and Bigger Business: The Second World War and Biomedical Research in the US', *Minerva* 40: 115–46.
Rasmussen, Nicolas (2004) 'The Moral Economy of the Drug Company–Medical Scientist Collaboration in Interwar America', *Social Studies of Science* 34(2): 161–86.
Rasmussen, Nicolas (2005) 'The Commercial Clinical Trial in Interwar America: Three Types of Physician Collaborator', *Bulletin for the History of Medicine* (In the Press).
Reimers, Niels (1998) 'Stanford's Office of Technology Licensing and the Cohen/Boyer Cloning Patents', Oral History (Bancroft Library), Berkeley, CA.
Rennie, Drummond, Annette Flanagin & Veronica Yank (2000) 'The Contributions of Authors', *Journal of the American Medical Association* 284: 89–91.
Rettig, Richard (2000) 'Drug Research and Development: The Industrialization of Clinical Research', *Health Affairs* 19: 129–46.
Rochon, P., J.H. Gurwitz, R.W. Simms, P.R Fortin, D.T. Felson et al. (1994) 'A Study of Manufacturer-Supported Trials of Non-Steroidal Anti-Inflammatory Drugs in the Treatment of Arthritis', *Archives of Internal Medicine* 154: 157–63.
Roman, Joanne (2002) 'U.S. Medical Research in the Developing World: Ignoring Nuremberg', *Cornell Journal of Law and Public Policy* 11: 441–60.
Roses, Allen D. (2001) 'Pharmacogenetics', *Human Molecular Genetics* 10(20): 2261–67.
Ryan, Michael (1998) *Knowledge Diplomacy* (Washington, DC: Brookings).
Scherer, F.M. (2002) 'The Economics of Human Gene Patents', *Academic Medicine* 77: 1348–67.
Schulman, Kevin, D.M. Seils, J.W. Timbie, J. Sugarman, L.A. Dame et al. (2002) 'A National Survey of Provisions in Clinical-Trial Agreements between Medical Schools and Industry Sponsors', *New England Journal of Medicine* 347: 1335–41.
Sell, Susan (2003) *Private Power, Public Law: The Globalization of Intellectual Property Rights* (New York: Cambridge University Press).
Shah, Sonia (2003) 'Globalization of Clinical Research by the Pharmaceutical Industry', *International Journal of Health Services* 33: 29–36.
Shapin, Steven (2003) 'Ivory Trade', *London Review of Books* (11 September): 15–19.

Sharma, B.L. (2003) 'Indian Drug Institute Uses Computers to Reduce Animal Testing', *Associated Press Worldstream* (25 July). Available at < www.siliconvalley.com/mld/siliconvalley/6389346.htm?template = contentModules/printstory.jsp > (accessed 18 March 2005).

Siegel, Marc (2002) 'The Hungry Physician', *Nation* (30 December). Available at < www.thenation.com.doc.mhtml?I = 20021230&s = siegal > .

Smith, Richard (2003) 'Medical Journals and Pharmaceutical Companies: Uneasy Bedfellows', *British Medical Journal* 326: 1202–05.

Stelfox, H., G. Chua, K. O'Rourke & A.S. Detsky (1998) 'Conflict of Interest in the Debate over Calcium-Channel Antagonists', *New England Journal of Medicine* 338: 101–06.

Stephens, Joseph (2000) 'As Drug Testing Spreads, Profits and Lives Hang in Balance' (first of six-part series), *Washington Post* (17 December).

Stone, T. Howard (2003) 'The Invisible Vulnerable: Economically and Educationally Disadvantaged Subjects of Clinical Research', *Currents in Contemporary Ethics* 31(1): 149–53.

Streitz, Wendy D., Isabelle de Bear, Caroline S. Calmettes & Fred Reinhart (2003) 'Material Transfer Agreements: A Win-Win for Academia and Industry' (Power Point presentation), < www.autm.net > .

Thursby, Jerry & M. Thursby (2003) 'University Licensing and the Bayh-Dole Act', *Science* 301: 1052.

Tilney, N.L. (2003) 'The Commercialization of Transplantation', *Transplantation Proceedings* 35: 1235–37.

Walsh, John, Ashish Arora & Wesley Cohen (2003) 'Research Tool Patenting and Licensing and Biomedical Innovation', in W. Cohen & S. Merrill (eds), *Patents in the Knowledge-Based Economy* (Washington, DC: National Academies Press): 285–340.

Wazana, Ashley (2000) 'Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?', *Journal of the American Medical Association* 283: 373.

Wilson, Duff & David Heath (2001) 'The Hutch Zealously Guards its Secrets', *Seattle Times*, < http://seattletimes.nwsource.com/uninformed_consent > (accessed 18 March 2005).

Yank, Veronica & Drummond Rennie (1999) 'Disclosure of Researcher Contributions', *Annals of Internal Medicine* 130: 661–70.

Zuckerman, Diana (2002) 'Hype in Health Reporting: Checkbook Science Buys Distortion of Medical News', *Extra!* (September/October).

Philip Mirowski is Carl Koch Chair of Economics and the History and Philosophy of Science, and Fellow of the Reilly Center, University of Notre Dame. He is author of, among others, *Machine Dreams* (Cambridge University Press, 2002), *The Effortless Economy of Science?* (Duke University Press, 2004), *More Heat than Light* (Cambridge University Press, 1989), and the forthcoming *ScienceMart*™: *A Primer on the New Economics of Science*. His recent paper in *Studies in the History and Philosophy of Science* (2004) attempts to revive interest in the ways in which philosophies of science are linked to the political economies of their respective eras. Outside of the commercialization of science, he is collaborating with Wade Hands on a history of the theory of demand in the 20th century, and with Dieter Plehwe on the history of the rise of neoliberal doctrines in the postwar era.

Address: 400 Decio Hall, University of Notre Dame, Notre Dame, IN 46556, USA; fax: +1 574 631 8209; email: Mirowski.1@nd.edu

Robert Van Horn is a PhD candidate in economics at the University of Notre Dame. He is working on a thesis on the rise of the Chicago School of

Economics and its relationship to the stabilization of the field of law and economics.

Address: 400 Decio Hall, University of Notre Dame, Notre Dame, IN 46556, USA; email: rvanhorn@nd.edu