

NBER WORKING PAPER SERIES

DO PATENTS MATTER?:
EMPIRICAL EVIDENCE AFTER GATT

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Working Paper 7495
<http://www.nber.org/papers/w7495>

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
January 2000

We are grateful to the many people, listed at the close of the paper, who contributed their time to this research project, as well as participants in the 1999 NBER 'Patents and Innovation' Conference. Richard Manning and Morris Friedman were particularly instrumental in arranging interviews with Pfizer and Merck Corporations. We also thank Susan Erickson and Stephen Gellerson of the NIH for providing budget information, and Ron Simmer of the UBC PATSCAN office for technical assistance. Karen Jensen provided excellent research assistance. Financial support was generously provided by the Alfred P. Sloan Foundation. The views expressed herein are those of the author and not necessarily those of the National Bureau of Economic Research.

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NBER Working Paper No. 7495
January 2000
JEL No. D21, I18, O34

ABSTRACT

Since the late 1980s the global intellectual property rights (IPR) system has been strengthening dramatically as much of the developing world introduces patent protection for new drug products. This may lead to more research on drugs to address developing country needs. As there are identifiable differences in the drug demands of these countries as compared to those already offering such protection the situation offers a unique opportunity to examine the incentive role of patent protection. We use new survey data from India, the results of interviews with industry, government and multinational institutions, and measures of R&D activity constructed from a variety of statistical sources to determine trends in the allocation of research to products specific to developing country markets. There is some, although limited, evidence of an increase in the mid- to late 1980s which appears to have leveled off in the 1990s. In interpreting the trends we examine factors that might enhance, or dampen, a firm's responsiveness to the availability of product patents. The picture presented here provides a 'baseline' against which future research activity can be compared once the new global patent regime is fully established and uncertainty about its implementation is resolved.

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I. Introduction

The first half of the nineties saw the beginnings of a remarkably dramatic reform of the global patent system. As of the end of the eighties, at least forty developing countries (including the most populous) did not grant patents for pharmaceutical product innovations (Siebeck, 1990). Most of these also did not grant process patents. As a result of the intellectual property component of the GATT agreement, and U.S. bilateral pressure since the mid-eighties, most countries have either implemented or are committed to implementing new legislation that allows for twenty-year protection for all pharmaceutical innovations. That is, they are moving, in one step and together, from zero to twenty years of protection. We propose to use this event to examine the importance of patent protection in stimulating innovation.

It has been argued that the patent system is no longer an important mechanism to encourage innovation. Product cycles have speeded up making patents, granted only after two or more years, irrelevant. Even more extreme, it is argued that litigation, and defensive behavior to avoid litigation, may have made patents positively counter-productive. Multi-country theoretical models have also pointed to the possibility that the incremental incentive provided by additional countries granting protection may not stimulate much additional R&D investment (Deardorff, 1992; Chin and Grossman, 1990). On the other hand, the pharmaceutical industry is commonly viewed as one where patent protection is crucial to investment in research. This is certainly the position of the industry itself (see the *PhRMA Annual Report, 1997*). Consistent with this view, during the TRIPs negotiations the industry argued that the developing countries would, contrary to their perceptions, actually *benefit* from accepting the proposed introduction of product patents, one reason being the encouragement it would give to private R&D investment in drugs for tropical diseases (a point formalized in Diwan and Rodrik, 1991).¹

For many reasons the current situation provides a unique opportunity to examine the R&D stimulus provided by patents. The policy reform represents an unusually *large* change, affecting the bulk of the world's population and a sizable and growing pharmaceutical market. More importantly, and unlike previous introductions of pharmaceutical product patents,² the

¹ Increased research on tropical diseases is not the only potential benefit and in interviews firm executives expressed their belief that it is likely to be a small part of the picture - the major benefit coming in the form of faster introductions of new products and greater investments by firms in marketing and in educating the local medical community about new therapies.

² For example: Germany, 1968; Japan, 1976; Switzerland, 1977; Italy, Holland and Sweden, 1978; Canada

group of countries now introducing protection have identifiably different drug demands than the countries preceding them. Their demands are different in two senses. First, although they already share diseases important in the developed countries there remains a set of diseases whose sufferers are found almost exclusively in less developed countries (LDCs). Second, certain drug therapies might be particularly relevant to LDCs in their tradeoff between cost and effectiveness or other characteristics, such as stability in the face of adverse storage conditions. As a result of these differences in their demands for drug therapies, one might expect changes in the *pattern* of research expenditures as a result of the strengthening of the patent system, which would be easier to detect and ascribe to the policy reform than would be changes in overall *levels* of investment. Finally, a useful feature of the current policy reform from the point of view of analysis is that it can only be viewed as exogenous to the affected countries. They fought the TRIPs agreement as a group and were put under intense pressure to accede to it.³

The paper has two goals. The first is to both identify and create data sources which can be used to establish empirically whether there has been (or will be) any shift in R&D investment and product development towards LDC markets or tropical diseases in response to this substantial strengthening of the global patent system. The second is to understand why, if anticipated changes are not observed, firm responses might be muted. What needs to go with patent laws to create sufficient incentives for investment?

Knowing the answers to these questions would be useful in pinning down the role of the patent system in encouraging innovation. This in turn would help in policy-making in the sphere of intellectual property rights (IPRs). For example, a better understanding of patent-generated incentives could lead to better responses to industry's pressure to strengthen its patent position (via patent extension acts, research exemptions, Bolar exemptions--which determine when generic producers can begin production--and so on). It would also be useful in designing combinations of policies that might be more effective than patent protection alone. An example is the 1983 U.S. orphan drug legislation which provided firms with multiple incentives -- in addition to exclusive marketing -- to develop treatments for diseases with small patient populations. International organizations, in partnership with firms and governments, are currently trying to devise effective packages--of R&D subsidies, guaranteed markets, plus patents--to encourage private investment in vaccine development.

and Denmark, 1983; Austria, 1987; and Spain, Portugal, Greece and Norway, 1992. (Santoro, 1995).

³ The threats were credible. As discussed below, in the late eighties the U.S. actually implemented tariffs on trade with Brazil because of dissatisfaction with its treatment of intellectual property--and removed

Finally, establishing the empirical facts has potential value for future policy debates specific to this context. Patent protection is a tradeoff: the profits generated create the incentives necessary for firms to make the investments in R&D which lead to new drugs and better health, but it is at the cost of higher prices to consumers. It is relatively straightforward to obtain information on drug prices. In India, for example, there have been many inflammatory articles about drug prices in the popular press over the past decade, both because of the GATT negotiations and in response to changes in their price control system. It is far more difficult to measure the *positive* effect of patents on innovation. As a result, in the absence of any offsetting information, the public in the affected countries will be left with the impression that having been 'forced' to have drug patents will greatly lower their welfare.

This impression matters--because putting in place new patent laws does not automatically create an effective intellectual property regime. In recognition of this, the intellectual property component of the GATT agreement specifies internal enforcement procedures to an extent unprecedented in an international treaty. However, the best, and probably only, way to get effective enforcement of the new patent laws in the developing countries is to convince people in those countries that drug patents have benefits for them and not *only* costs. Thus, the imbalance between the ease of obtaining price information (the negative side) and the difficulty of measuring research and innovation (the positive side) could pose a very real obstacle to the acceptance and enforcement of pharmaceutical patents in the developing world. Objective evidence demonstrating the beginnings of new private research efforts would make it easier to argue that the developing countries benefit from granting patent protection to innovative companies, which would, in turn, encourage them to enforce the new laws with more enthusiasm.

We have taken a multi-faceted approach in trying to answer the questions posed, including gathering statistical data, fielding surveys and conducting interviews. In order to develop a 'baseline' picture of R&D investment in tropical diseases or in drug therapies targeted to LDC markets we have collected information on trends over time in various indicators. These include: worldwide patenting activity in relevant, very specific, technology classes by all inventors and overall pharmaceutical patenting by Indian inventors; scientific publications concerning tropical diseases; and US federal government support of biomedical research through the National Institutes of Health (NIH). Though these data are informative, the categories

them only when Brazil agreed to change its intellectual property laws.

available in these data do not capture precisely what we are after. In some cases they are too broad, for example 'tropical' may include TB which is an important emerging disease in the developed countries, and in other cases they are too narrow. In particular, none allow us to identify research done on therapies designed for LDC markets but for diseases common to the world. Thus, to supplement these data, we have surveyed the larger pharmaceutical firms operating in India, asking them to identify and quantify appropriate projects in their R&D portfolios. We are currently in the process of determining, through discussions with industry, how to approach fielding a similar survey of U.S. and European firms.

Finally, we have interviewed pharmaceutical and biotechnology firms in the US, Canada and India; PhRMA, the U.S. industry organization, and the corresponding Indian trade associations; as well as people involved in tropical disease issues at the NIH, the World Bank, and Yale and Harvard public health institutes. These interviews have been useful in designing the survey questions and strategy. For example, while it was clear from talking to executives that they were able to answer questions regarding current spending on relevant projects, the categories we are dealing with are not those which firms typically use when describing their R&D portfolios. This argues against a strategy of waiting five years and asking retrospective questions about research happening now, and in favor of repeated surveys focused on research ongoing at the time of questioning. The interviews together with the statistical data give us a picture of current research activity which will serve as a baseline against which we can track changes. The interviews also allowed us to identify factors that might interact with the change in patent laws and affect the appropriate interpretation of trends in the data. Finally, the discussions were used to try and understand the role of patents and other factors that determine where private firms decide to invest their R&D dollars.

The following section describes the recent history of international negotiations over pharmaceutical product patent rights. We discuss the timing of the 'event' of their introduction, noting that any observed incentive effects will depend not just on the timing of the 'event' and the characteristics of actual legal changes, but also on firms' information and beliefs about those changes. In Section III we specify in more detail how demand patterns for drugs may differ between the countries which have had product patents for some time and the group of countries newly introducing protection. Section IV provides the statistical and survey data, with a focus on trends over time. In Section V we discuss factors besides IPRs that might be encouraging more R&D expenditure on tropical diseases, affecting the interpretation of trends. In Section VI we consider factors that might contribute to a failure to see changes -- again, what needs to go

with patents to make them effective? Finally, Section VII concludes.

II. The 'Event'

The absence of patent protection in the developing world has seriously damaged the economic interests of research-oriented Western drug companies. Pharmaceutical products are typically quite straightforward to manufacture, and once a country has developed a domestic production capacity, new drugs can be quickly imitated and produced in bulk. Without patent protection, the innovator may struggle to make the profits which are its reward for incurring the substantial risk and expense of developing its product. The experience in India illustrates this situation well. There, an active domestic pharmaceutical industry has been quite successful over the past decades in rapidly copying new drugs: typically they have managed to introduce imitated products to the Indian market just four or five years after their appearance in the world market (Lanjouw, 1998). Indian executives indicated in interviews that they usually wait to see whether new products are successful on the international market before beginning development, so the reverse engineering process is clearly very rapid. Emphasizing this point in a discussion, the managing director of Glaxo (India) Ltd. explained that they had tried to be first in the Indian market with their anti-ulcer drug Zantac, but were met by seven local competitors on the launch day. At the time of its world launch of Viagra, Pfizer already faced Indian competition: three Indian firms were developing the active ingredient with five more expected to request marketing approval.⁴ CIPLA, one of the largest Indian firms, is exporting its version of Viagra elsewhere. Faced with this competition, Pfizer did not itself launch the drug locally (*The Wall Street Journal*, July, 1998). Without the protection of patent rights, with easy to copy products and firms waiting to do so, even lead time does not give the originator firm much scope for making profits.

Seeing markets lost to successful imitators, U.S. industry, with the aid of the U.S. government, in the early 1980s began to make energetic efforts to strengthen patent regimes in the developing world. With the support of other industries, representatives from pharmaceutical firms and trade associations argued that intellectual property should be included in the Uruguay round of the GATT negotiations. In alliance with their counterparts in Europe and Japan, they were successful in getting 'TRIPs', the trade-related aspects of intellectual property, onto the

⁴ Because it was patented elsewhere before the GATT agreement went into effect, Viagra is not eligible

agenda in the late 1980s.

Meanwhile, the U.S. was also pursuing its agenda in aggressive bilateral negotiations. In 1984, Congress passed a revision of the Trade and Tariff Act, which authorized the U.S. government to take retaliatory action against countries failing to give adequate protection to intellectual property (Section 301). This was strengthened in 1988 with legislation mandating that each year the U.S. Trade Representative identify countries without adequate protection. In 1989, for example, Brazil, India, Mexico, China, Korea, Saudi Arabia, Taiwan and Thailand were put on the "Special 301" Priority Watch List. The resulting pressure was successful in convincing several countries to change their patent laws regarding pharmaceutical protection as part of larger reforms to their intellectual property rights systems. Korea introduced protection in 1986, and Mexico passed new laws in 1991. Brazil showed more reluctance, so, in 1989, the U.S. levied 100% tariffs on \$39 million of imports from Brazil in retaliation for its copying of patented drugs. In the early 1990's Brazil backed down and in 1996 passed legislation creating pharmaceutical product patents. The U.S. applied similar pressure to Thailand, withdrawing its GSP trade benefits in 1990 because of dissatisfaction with its lack of protection for pharmaceuticals (Santoro, 1995).

With its demonstrated ability to apply bilateral pressure in the background, the U.S. government obtained a TRIPs agreement which satisfied most of the interests of industry, including the requirement that signatory countries protect both pharmaceutical process and product innovations. The treaty was signed in April, 1994, and came into effect in January, 1995. In other multilateral negotiations, the 1993 North American Free Trade Agreement (NAFTA) also included an agreement to grant full protection to pharmaceutical product innovations.

In addition to the fact that bilateral pressure convinced some developing countries to agree to grant product patents in advance of the GATT treaty, two other considerations affect the timing of the availability of legal protection for pharmaceutical innovations. The first is the extent to which new patent legislation includes so-called 'pipeline' protection. Pipeline protection stipulates that during the phase-in period of a new product patent regime, innovations which have not been marketed in the country are eligible for protection even if they have been patented, and sometimes even marketed, elsewhere. (That is, they are exempt from the usual novelty bar.) Countries instituting patent protection early and under pressure have typically

for protection in India.

offered this protection, so the effect of the change is felt more immediately. It was also part of NAFTA. Pipeline protection is not, however, required under the TRIPs agreement, and many countries, such as India, will not grant pipeline protection. In these countries, only innovations which *followed* the treaty agreement are eligible for protection.

The second feature of the TRIPs agreement that affects timing is that developing country signatories have been allowed a ten-year grace period for adjustment and are not required to grant product patents until January, 2005. However, they must accept applications (the 'mailbox' provision) and, beginning in 2000, they must offer 'exclusive marketing rights' (EMR) to any inventor with a patent in a WTO member country and marketing approval for the new drug in his home market. EMR are very similar to patents in offering monopoly marketing rights to the inventor so, effectively, protection for product innovations will be available in all member countries at the end of 1999.

The 'event' which really matters from the point of view of our investigation is not the actual implementation of legal changes, but rather firms' beliefs about them: whether they will occur, when they will occur, and how effective the new systems will be. Thus, one influence on timing is the extent to which the new regime was anticipated. For example although the new laws in Brazil went into effect only in 1997, already by 1993 a patent bill was in the Senate (Rozek and Berkowitz, 1998). Similarly, although the GATT treaty was signed only in April of 1994, it was clear years before, once TRIPS was officially on the agenda, that some form of strengthened protection for pharmaceutical innovations would be included.

There remains the question of whether firms believe that countries joining the WTO will honor their commitments--both explicitly, with timely implementing legislation and restricted compulsory licensing, and implicitly, with effective enforcement.

It now appears likely that signatory countries will comply with the terms of the TRIPs agreement. As the country most outspoken in its criticism of the TRIPs component of the GATT, events in India are, again, perhaps illustrative. The first implementing legislation failed to gain approval in 1995 in the upper house of Parliament. In 1996 the U.S. requested the establishment of a disputes panel at the WTO, arguing that India did not have a formally recognized process for the acceptance of pharmaceutical product patent applications, and that administrative procedures alone were insufficient.⁵ From interviews and a reading of the popular press during that period one was left with the impression that India might well pull back

⁵ The panel ruled in favor of the U.S. and did not overturn its opinion on appeal.

from its agreement, if not in the letter, at least in the spirit.

However, in the course of interviews a year later with executives at several Indian and MNC subsidiary firms and the two industry associations, it became clear that the terms of the debate within the country had shifted. No one any longer expressed doubt the India would, in fact, be in compliance with WTO intellectual property requirements when deadlines were reached, and this despite the election of a new, and more outspokenly nationalistic, government in the meantime. As evidence of the government's intentions, a professor at one of the country's top business schools noted that he had recently attended an introductory course on intellectual property sponsored by the government. Business schools are being encouraged to introduce courses on intellectual property to increase awareness within the business community. (Several interviewees were curious about how the Chinese were dealing with the practical problem of introducing a new system of patents.) Interestingly, these recent interviews indicated that there was an entirely new debate underway in the country over whether India should voluntarily skip the end of the grace period under EMR and go straight to the granting of product patents in 1999. They were echoed in a September 7th article in the *Observer of Business and Politics* (1998) which led with the statement that "India will allow product patents in pharmaceuticals ahead of its international obligation if the current view in the industry ministry prevails".

That said, one of our interviewees at a U.S. firm stated quite firmly his belief that India had "no intention of implementing the legislation".

Even given timely legislation, there remains a concern about whether the developing countries will effectively enforce their new laws. The TRIPs agreement spells out specific procedures and legal remedies to be used in defending patent rights. Sherwood (1997) summarizes these, in part, as follows: "Civil and administrative procedures and remedies are delineated ... They include the assurance that confidential information will be protected during and after proceedings authority to discover evidence solely in the hands of another party is to be provided, The conditions under which precautionary measures, such as injunctions, are to be made available are stipulated.... articles recite the approach to damages, to other remedies, to compelling information regarding other infringers and indemnification of defendants...Member countries [must] provide authority for a party to lodge a request with customs officials to block the importation of infringing goods....Finally, Article 61 specifies various criminal procedures which countries are to make available to prevent infringements." Of course, in countries with limited judicial capacity such directives will be of limited use. It will also take time before uncertainty about the effectiveness of enforcement procedures is resolved. However, ultimately,

if enforcement is less than satisfactory, the "pro-patent" countries may be able to obtain redress by exerting the same pressure that led to adoption of the TRIPs agreement in the first place.

Although industry expresses some doubt about implementation, their actions suggest that they view the commitments made as credible. Patent applications made to the Indian PTO for pharmaceutical innovations show a doubling in 1995 over previous levels--and most of the increase was to foreign inventors. Applications for *product* innovations were about 57% of total applications in 1995 (CDRI, 1996; and authors' calculations). These are incremental since such protection was not available in earlier years. Of these incremental patents, 86% were to inventors with a non-Indian address. This is far higher than the representation of foreign patentees taking advantage of the process patent regime: among patents recently granted (and therefore restricted to process innovations) foreigners received 61% in 1995, 53% in 1996 and 45% in 1997 (IDMA 1996-98).

Given the progress of both bilateral and multilateral negotiations and, importantly, the U.S. government's demonstrated willingness to make intellectual property an issue high on the agenda in its discussions with developing countries, by the end of the 1980s pharmaceutical companies could have been reasonably confident that most of the developing world would be protecting inventors rights within the coming decade. While doubts continue to remain about the quality of those rights, it does not appear likely that much backsliding will be allowed, or even attempted. Given the long lags associated with the research and development of new products, we believe these expectations could have been sufficient to encourage some response from firms starting at the end of the 1980s or beginning of the 1990s.

III. The Differences

As discussed in the introduction, a crucial feature of the current policy reform for the empirical analysis is that the disease patterns and drug demands of the group of countries introducing patent protection differ in an identifiable way from those of the countries which have had such protection for some time. One difference, due to the substantially lower incomes and difficult climates of these countries, is in the optimal characteristics of therapies. For example, Indian R&D directors pointed out that an important part of their development work when adapting Western drugs to the Indian market involves improving products' stability characteristics so that they can maintain their efficacy longer on pharmacy shelves, and survive rougher transport conditions and extended periods of time out of cold storage. There will be a

stronger preference for low-cost therapies, too. For example, recently a rotavirus vaccine was developed which could prevent the diarrheal disease responsible for about a million deaths annually in developing countries. However, it was marketed at \$114 for a three dose series: cost effective for the developed country market at this price, but far out of reach of most LDC consumers. And there is an alternative. Keusch and Cash (1997) note that "...oral rehydration therapy is an inexpensive and effective treatment for serious, dehydrating rotavirus diarrhea". The marginal increase in effectiveness and convenience might be worth the higher cost of treatment in a rich country, but not in a poor one.

The second difference between the two groups of countries is in their disease patterns. Table 1 lists all of the diseases for which 99% or more of the global burden was in low- and medium-income countries in 1990. The global burden of a disease is based on the disability adjusted life years, or DALYs, lost to the disease. DALYs capture both the impact of long-term disability and premature death (WHO, 1996). Note that this is not a ranking of the most important diseases in the LDCs. It is rather those which are *specific* to developing countries - which is the distinction we are after in trying to pick up effects of changes in patent rights in those countries. A few cases make the distinction less than perfectly clean. For example, leishmania/HIV co-infection is considered to be an emerging disease, especially in Southern Europe, where 1.5-9.5% of AIDs patients suffer from visceral leishmaniasis, the most serious form (WHO, 1998a). However, even then one would be hard pressed to think of any other change in patent laws where differentiated markets could be defined so precisely across those affected.

IV. Recent Trends

In this section we examine trends in various statistical sources and establish baseline survey results.

Worldwide Patenting of Therapeutics for Tropical Diseases

Patent applications serve as a useful indicator of early stage research in pharmaceuticals. Innovative activity in this industry is conventionally divided into two phases: "discovery" wherein new candidate molecules are identified, and "development" wherein the chemistry of promising candidates is refined, and drug candidates are put through clinical trials and regulatory testing. Competitive pressures and novelty requirements in patent law lead pharmaceutical

companies to patent promptly and prolifically, making patent applications a good measure of inventive activity in the discovery phase. We therefore expect trends in patent applications for compounds to treat tropical diseases to provide an early indicator of increased research activity in these areas -- with the caveat that, to the extent that some inventive activity is directed at "platform" technologies with a wider application beyond tropical medicine, counts of patents on therapeutics for tropical diseases are likely to understate the level of R&D activity induced by the TRIPs agreement.

One major problem with using patent data for this purpose is that it can be very difficult to consistently identify the disease to which the invention is applicable. The classification schemes applied by the U.S. patent office (USPTO) and other patent-granting bodies are oriented largely towards chemical structure, and are relatively unhelpful for identifying narrow disease-specific applications. Our primary method for identifying patent applications relevant to a particular disease was, therefore, searching the text of patent abstracts for keywords. For example, for malaria-related inventions we searched for MALARIA, MALARIAL, PLASMODIUM, etc. To be exhaustive, keyword searches require both adequate knowledge of the disease and related science, and considerable skill in formulating database queries. Given the relatively small numbers of patents involved (as few as five per decade in some cases) it would be very easy to make significant errors in assessing inventive activity, so we therefore supplemented keyword searches with searches based on the proprietary coding of patents into detailed therapeutic classes found in Derwent Inc's *World Patent Index*. This classification scheme is based on close reading of the patent's claims and disclosure by individuals with advanced scientific training, giving us confidence that the disease application is correctly identified.

A second issue is international coverage. Not all pharmaceutical innovations lead to US patent applications, and we therefore use data sources such as INPADOC, which, like the Derwent *WPI*, are built by collecting and collating information on patent applications and grants from all the major patent offices in the world. Patents filed in different jurisdictions that cover the same invention are organized into "families". In this context, a family can be thought of as the collection of all worldwide patents claiming a particular "molecule". Counts of these families thus capture patenting activity in any of the jurisdictions covered by the database --- which are all major patent-granting countries. Note however that though incoming data are processed relatively promptly, families come into being only when patent applications are laid open (typically 18 months after the filing date) and therefore there is at least an 18-month delay in

establishing a reliable count. After adding several months for processing time it is clear that reliable data are only available at this point for 1996 and earlier.

Table 2 gives the results of compiling counts of patent families using different search criteria. Counts are by the first worldwide priority date found in the applications making up the family, which places the timing of the invention quite close to the research activity which generates it.⁶ Because gaps in scientific knowledge or the absence of useful treatments also affect research priorities (see discussion in Section V), in consultation with public health experts we have broken down the diseases in Table 1 into two groups: those for which there is a reasonably good, low cost, treatment or vaccine available today, and those for which further progress is needed. The first three columns in Table 2 give counts of patented innovations related to the group of diseases 'with treatments' and its two main components, schistosomiasis and trachoma. The next column gives counts of patents related to diseases 'needing treatments'. Here, and below, we have included tuberculosis in this group.⁷ In the final columns we give counts for the specific diseases malaria, leishmaniasis, Chagas' disease and leprosy.

Although the raw numbers give some insight into the relative level of research activity across the diseases, it is important to normalize the series when interpreting their trends. There has been a steep upward trend in the series of overall patenting in pharmaceuticals reflecting the remarkable expansion of the industry over the past three decades, and intensification of research activity within it. The number of families falling into Derwent's class B "Pharmaceutical Preparations" increased by 168% from 1975 to 1996. Thus, in Figures 1a-f we display the trends over time in worldwide patenting related to tropical diseases as percentages of total pharmaceutical patenting.

The first two figures give trends for the two disease groups. The numbers we are dealing with are small – never is patenting related to tropical diseases more than about half of a percent of overall pharmaceutical patenting – so the series are not very smooth. Nevertheless, two points are apparent. First, there is clearly a difference between these two groups, with greater patenting, and growth in patenting, related to diseases still needing good treatments. Second, in both series there appears to have been a notable increase in patenting beginning in the mid-1980s followed by a leveling off in the 1990s. For the group of diseases needing treatments, this was preceded by a more gradual increase in patenting from the mid-1970s.

⁶ The priority date is established by the first application made in any country (the 'priority patent').

⁷ Today 99% of the disease burden due to TB is in the developing world. It was slightly below this level in 1990, the year considered when constructing Table 1. See the notes to Table 2 for the full list of diseases

This overall trend in patent for the group needing treatments conceals interesting differences in the trends in patenting for specific diseases, however. Malaria, for example, experienced a marked surge in patenting, but somewhat earlier – beginning in the early 1980's. Further, patenting actually fell off substantially in the 1990's. Patenting related to leishmaniasis and Chagas' disease followed more or less the pattern described for the group, but that related to leprosy was flat, and low, over the entire period.

Pharmaceutical Patenting by Indian Inventors

We have also collected information on all pharmaceutical patenting by Indian inventors in the U.S. and at the European Patent Office (EPO). Unlike the data just discussed, these patents are not specifically for tropical disease therapies. Since Indian inventors have always had the ability to patent in the U.S. and in Europe, and to access the global market, the prospect of new patent-generated profits in LDC markets would present only a small marginal increase in their incentive to invest in R&D directed at global products. However, we hypothesize that inventors in developing countries have a comparative advantage in research on tropical diseases such that profits in LDC markets might induce a greater than marginal increase in their overall research efforts. Assuming that the more important discoveries would also be patented abroad, we would then expect to see increased pharmaceutical patenting by LDC inventors in the U.S. and in Europe.

Table 3 displays changes over time in pharmaceutical patenting by Indian inventors. A 'pharmaceutical' patent is defined as one falling in the International Patent Classification categories A61K or A01N; an 'Indian' is identified by the address of the first inventor or, in the case of U.S. patents, also by the country of priority being India; and the 'year' corresponds to that in which the application was made. The first column in the table is numbers of U.S. pharmaceutical patents granted to Indians and column 2 gives these relative to all patenting by Indian inventors. The third column gives number of applications made for pharmaceutical patents at the EPO by Indian inventors. This is compared to all pharmaceutical applications received by the EPO in column 4. Because of lags in application and granting, there is truncation in the last numbers of the series so the percentages are more informative.

The numbers of patents presented in Table 3 are increasing but small so one should not read too much into the trends. However, they are suggestive that pharmaceutical research by

included in each group.

Indians is becoming more significant. It appears to be growing in importance relative to their activity in other technology areas. Over the 1980s, pharmaceutical innovations accounted for about 15% of total U.S. patents to Indian inventors. In 1990 this rose to something on the order of 25%, with a large jump in 1997. The data also suggest that Indian inventors are becoming increasingly active as participants in world pharmaceutical innovation. Relative to the 1980s there has been a noticeable increase in their representation among pharmaceutical patentees, particularly in the most recent years.

Bibliometric Data

Another avenue for picking up changes in research investment in tropical diseases is through publications in the scientific literature. We extracted data on publications from the online PubMed database of bibliographic information which is drawn primarily from MEDLINE, PREMEDLINE and molecular biology databases. These databases include citations from approximately 3,900 current biomedical journals published in the US and 70 foreign countries. Although we cannot distinguish in these data between publications by private researchers and those by public or academic researchers, the industry is increasingly closely linked to academic researchers through collaborative research (Cockburn and Henderson, 1998). These linkages are likely to influence academic research programs so an increasing interest in tropical diseases on the part of industry is likely to influence research publications more broadly.

We collected data on all citations using search words for target diseases and for the subset associated with drug therapies or vaccines. These data were collected for each year 1980 through June of 1999. We are primarily interested in examining trends and these are presented in Figures 2a-f. In the figures the counts are normalized by the number of all citations so as to avoid any biases in the trends caused by the introduction of new journals over time.

Our focus categories represent a very small percentage of total biomedical research as evidenced by the presence of these keywords in journal articles, although larger than their representation in the pharmaceutical patenting. Those with the word 'malaria*' were just 0.30 percent of the total in 1998, while those with one of the other keywords represent only an additional 1.06 percent. Thus, taken together references to the set of tropical diseases were found in about one and a half percent of all citations.

Figures 2a and 2b again display the trends in citations related to a group of diseases having a good treatment and a group still in need of one (these are somewhat broader than the corresponding groups for the patent series. See the notes to Table 4 for details). Even more than

in the patent series there is a very clear difference across the two groups. Biomedical citations to diseases which have good treatments, if anything, declined somewhat over the period. On the other hand in the early 1980s there was a 10-15% rise in the percentage of articles with citations to diseases needing treatments. This was followed by an even greater increase beginning in the late 1980s and continuing on into the early 1990s. As in the patent series, there are differences across specific diseases. Both citations to malaria and leishmaniasis have trend patterns similar to the group as a whole. However citations to Chagas' disease show no change over the twenty-year period and citation to leprosy plummets.

Although one might expect that an increase in the potential profitability of drugs for tropical diseases would lead to more research in the science base associated with those diseases, the more direct affect might be a shift within those categories towards more applied research on products - either drug therapies or vaccines. Thus, Table 4 gives the percentage of the citations to each of the two disease groups, and malaria, which also mention these product types. Here we see, yet again, that there is a difference between the two groups, with a larger percentage of the journal articles related to diseases needing treatments also being concerned with a drug product. However there appears to be little change in these percentages over time. At most one might say that product citations became somewhat more frequent in the malaria literature between the 1980s and the 1990s.

National Institutes of Health - Grant Awards

The NIH is a public institution and therefore one might suppose that its decisions would not be influenced by changes in the patent regime. However, interviews at NIH suggested that a change in the diseases of interest to private firms could well affect the direction of NIH grant funding in three ways. The first is direct -- some grants are the result of CRADA or SBIR submissions by private firms.⁸ The second is that company representatives sit on NIH advisory councils and Ad Hoc working group panels. If firms would like to see more basic research done on malaria host immune responses, for example, then they can press for this in these fora. In response, NIH might put out a corresponding Request for Application (RFA) in which the specific interest is specified. RFA's represent only 10 percent of extramural grants, however, so this route is limited. The third route is through the growing industry/academic collaborative research links discussed above. These are likely to influence the direction of academic research,

⁸ Cooperative Research and Development Agreements (CRADAs) and related contracts were created in the

and hence the characteristics of the remaining 90% of extramural grant proposals submitted to NIH by from academics: the 'researcher initiated,' or R01, grants.

NIH maintains a comprehensive database of federally funded research grants made by the U.S. Public Health Service, known as CRISP. The bulk of these are awards made through and administered by the NIH itself, with a small number originating with the Centers of Disease Control, the FDA and other government agencies. The majority of these grants support research conducted at universities, hospitals and research institutes, with smaller numbers of awards received by private sector organizations, either directly through the granting process or under CRADAs or the SBIR program. Intramural NIH research projects are reported, but not the amount of the award. Projects include clinical research as well as basic science, and awards for training and infrastructure development. The database contains descriptions of research projects, the amount of funds awarded, and information about the investigator and institution performing the research, plus subject indexing terms.

As in the analysis of worldwide patenting and citation trends, we focus on research grants directed at (or at least mentioning) malaria. Table 5 shows the total number of "malaria" projects identified in the CRISP file and their total funding, in current dollars for fiscal years 1972-1997. A "malaria" project is one found by searching project titles and descriptions for a list of relevant keywords: malaria, malarious, plasmodium, falciparum, vivax etc. Not all of the research projects selected by this search strategy are exclusively focused on malaria, and some may just be trying to maximize support for their proposal by listing as many applications of the research as possible, but we have no basis to believe that these sources of bias change systematically over time. To normalize these figures we use the total number of awards and the overall budget of the NIAID (National Institute of Allergy and Infectious Diseases) which is the originator of the great majority of federally funded grants for tropical disease research.

The first three columns of Table 5 give total funds awarded and the number of grants by fiscal year. The slightly more than sevenfold increase in the number of awards between 1972 and 1996 is echoed by the increase in total funding in real terms of 663%, much of which has occurred since 1986.⁹ Normalizing by the total NIAID budget (given in columns 4 and 5) or the total number of NIAID administered grants gives similar results: between 1972 and 1984 malaria grants accounted for less than 2% of total NIAID grant dollars, rising sharply after 1985 to the

mid-1980s to encourage joint public/private research efforts.

⁹ Current dollars are converted to 1997 dollars using the BEA's Biomedical Research and Development Price Index.

more current level of 3.7%. A similar increase is apparent in the share of malaria grants in the total number of projects funded through NIAID, which rises from under 3% prior to 1984 to more than 6% in the late 1990s.

Unlike our previous data series, here we can disaggregate by public and private sector activity. The breakdown of the malaria grant data by type of institution reveals some interesting trends. In the 1970s 90% or more of total awards went to projects conducted at universities. But by the mid-1980s about 15% of funds went to other types of "not-for-profit" institutions such as research institutes and clinics. After 1985 a small but growing fraction was awarded to for-profit organizations: in 1995 more than 5% of total NIH extramural grant dollars went to research projects conducted in the private-sector. These figures point to a growing interest in malaria by profit-oriented researchers, though they may also be driven by the changing institutional and legislative environment.¹⁰

Surveys

We have completed the first round of what will be a repeated survey of Indian firms designed to capture more precisely changes that might arise as a result of the new patent laws. The survey results will complement the longer time trends available in the statistical data sources already discussed.

The two basic questions are:

Thinking about your current research projects underway at a pre-clinical stage,

1) *For how many of them is it the case that more than one-half of sales revenue is expected to come from developing country markets and what annual dollar amount do these projects represent?*

2) *How many of them are directed at one or more of the following diseases [LIST- Table 1] and what annual dollar amount does this set of projects represent?*

These questions capture the two dimensions of demand differences: different priorities regarding the cost/effectiveness tradeoff or other characteristics and different disease patterns.

We surveyed the largest pharmaceutical firms operating in India, both Indian-owned firms and multinational subsidiaries. The population of firms includes all members of the

¹⁰ For example, passage of the Bayh-Dole Act which allows the patenting of some government-funded

Organization of Pharmaceutical Producers of India (OPPI) and two non-members identified in industry interviews as also being active in R&D. In total, the survey was sent to some 65 chairmen or managing directors.

The survey instrument is attached as Appendix I. In addition to the questions above it includes further questions regarding development research. The reason for including these questions even though one would expect patent protection to be a more important stimulus to innovative research is twofold. First, we do not expect to see real growth in new therapies coming from this quarter. From discussions with many firms based in India it is clear that, faced with the introduction of patent protection, few are planning large increases in spending on discovery research directed at novel compounds. The substantial investment in personnel and infrastructure required to do this successfully is prohibitive for most. Of those that are following this strategy, interviews suggest that the targeted markets are large and global: cancer, diabetes, and so on. On the other hand, many executives in India suggested that subcontracted development work -- both by multinational subsidiaries for their home offices and by India firms for non-affiliates -- is undertaken by a much larger group of firms and is of growing importance. Since a Western firm with a new potential drug therapy appropriate to an LDC market might well consider engaging an Indian firm to work on its development, repeated surveys should not only track research within India but should also pick up changes in activity by Western firms in this area.

We received 20 completed questionnaires, of which five were multinational subsidiaries. The total R&D expenditure of these firms together is 1,647 million Rs (about 43 million dollars). The OPPI reported total R&D for their membership (which, again, includes most research firms) as 1,850 million Rs in 1996-97. Thus, our respondents represent about ninety percent of all R&D investment in India. Of these, nine report that they do not have any research or development projects on tropical diseases or targeted at LDC markets. The eleven who do report having such projects have allocated 261.9 million Rs (about 6.9 million dollars) to them. Thus, about 16% of R&D expenditure among our 18 respondents is directed towards the specified types of projects. As expected, only 51.5 million Rs, or 19.7%, of that expenditure is discovery research as opposed to development research, so just measuring the former would, indeed, have missed much of the action. Interestingly, 120.9 million Rs of the 261.9, or 46.2%, are on products targeted at developing country markets but which are not for diseases on the list of

research outputs.

Table 1. That is, they are for diseases found globally but for products with characteristics suited to the LDC environment. It is this part of the stimulus to innovation created by the new patent protection which would be missed by only tracking changes in research on tropical disease therapies. Since the latter is all that is possible using standard statistical data sources, the fact that almost half of Indian research is of this second type demonstrates the importance of trying to create a series of survey data to complement the statistical databases.¹¹

Summary

Taken as a whole these various data sources point to an increase in inventive activity on at least some LDC-specific pharmaceutical products. There are a number of difficulties with interpreting these data, in particular with establishing the precise timing of activity, and in some instances the time series may be too short to draw meaningful conclusions about trends. Nonetheless some interesting provisional conclusions can be drawn.

The comparisons across diseases of patenting and citations strongly support the importance of market considerations in general in directing the allocation of pharmaceutical research effort. We see that diseases for which there is a good low cost therapy available are much less interesting to the research community than those for which a treatment is still needed. Further, within the latter group there is considerable variation, with malaria consistently a focus of attention but leprosy attracting very little. It is possible that the sustained research on malaria is driven by public sector initiatives. This cannot be discounted and is probably part of the story (see section V). However, there are also clear differences across diseases in patient populations and therefore in expected market size which, in turn, affect the profitability of finding treatments. An analysis of the size of the Indian market in each therapeutic category by McKinsey, India, had leprosy at the bottom of the list but placed malaria in the middle as it cuts across the income spectrum (a rich man's tropical disease). This was also noted in interviews with Indian firms: the medical director at Lupin stated that leprosy had a smaller estimated market (130 million dollars) than the cost of developing a drug and was therefore not an interesting prospect for a private firm without public subsidies. At the same time, the managing director of CIPLA stated his belief that a company could make a profit from malaria treatments.

It is in the trends in the patent, citation and NIH grant series that we must look for direct evidence of changes in research patterns due to the wider availability of patent protection. The

¹¹ We are currently discussing with the industry how to extend our survey to U.S. and European firms.

trends in biomedical citations and in NIH grant funding should be most directly linked to research inputs related to tropical diseases. In both of these data we find that, where growth occurs, it tends to start or pick up in mid-1980. In the case of citations there is then a leveling off in the 1990s. The patent series reflect the output of this research in the form of potential products. Where there is growth in patenting, it too is strongest in the late 1980s, and tends to level off or decline in the 1990s. These patterns would be consistent with the view that firms anticipated a more favorable market environment once TRIPs was under discussion and the western governments were clearly behind it, that this led the firms to take more interest in tropical disease research, but that later events made them more hesitant, perhaps wanting to see how the legislation is actually implemented in the developing world. In the following section we consider this, and other, potential factors influencing the trends.

The data on patenting by Indian inventors in the U.S. and Europe, together with the insights from interviews with Indian executives and the firm survey, are again suggestive, rather than conclusive, but do raise some interesting issues. Most notably, it is clear that the impact of the TRIPs agreement on incentives for the research-intensive companies based in the OECD is only part of the picture: strengthened IPRs appear also to be stimulating *domestic* R&D in countries which have not previously emphasized them. We hypothesized above that this might be research most relevant to their own markets, where they might be thought to have a comparative advantage. But company executives made plain the contrary: that any discovery research is and would be on global diseases and on products for the worldwide market. Interestingly, the survey results suggest that, while this may be true, Indian firms are nevertheless allocating a non-negligible portion of their R&D budgets to tropical disease research and LDC products, and that the fraction of this going towards the discovery of new products, rather than development, may well be increasing.

V. Confounding Factors

In this section we examine a range of possible confounding factors which might affect trends in the data presented in the previous section.

Increase in Public Concern

They are, however, reluctant to divulge their level of investment in these activities.

Since WWII, infectious disease has largely been viewed as a receding threat in the developed world. However, the emergence in the 1980s and 90s of HIV/AIDs and drug resistant organisms for other once easily treated diseases has changed perceptions and led to an "intense public interest in 'emerging and re-emerging' diseases." (WHO, 1996). Two particular reasons for concern are the increase in drug resistance and demographic change -- particularly urbanization, more extensive land use and greater travel. For example, multiple-drug resistant strains of tuberculosis have been emerging around the world. These are very expensive to treat: in NYC, where there has been an epidemic, it costs \$250,000 per case to treat versus a previous \$2,000. According to the Centers for Disease Control, about 19,000 new cases of TB were diagnosed in the U.S. in 1997. Perhaps as a result, rifapentine, the first new TB drug in 25 years, was approved for marketing by the FDA this year. (*Washington Post*, June 24, 1998).

This public concern is one of themes of a report published by the U.S. Institute of Medicine entitled "America's Vital Interest in Global Health" (1997). They sound the warning that, "Even though the majority of people affected by infectious diseases are in the developing world, all nations, even the richest, are susceptible to the scourges of infection...diseases -- including tuberculosis, dengue, malaria and cholera -- that had been partially controlled are resurging ... exacerbated in some cases by the spread of drug-resistant strains. The emergence and reemergence of infectious diseases in the United States and abroad pose serious challenges to our detection and surveillance systems."

The recent increased public interest in these diseases could be having a direct effect on the data sources we have examined. Public and academic researchers would be encouraged to do more in these areas, publishing more articles, patenting more innovations, and obtaining more grants. Although it may be moderate, public interest may also have some effect on private firm research investments. Certainly international organizations, foundations and governments have been *trying* to influence firms. The most obvious example is malaria. An article entitled 'Bank Gears Up to Fight Malaria,' announced a new effort at the World Bank to coordinate research on malaria. One of the three main goals outlined was to "...enlist the drug companies." and it claimed that "...a breakthrough was made to persuade the biggest multinational giants together to adopt 'orphan diseases', with malaria top of the list.'" (*Bank's World*, July 21, 1997). In October, 1998, the Director-General of the WHO, Dr. Gro Harlem Brundtland, announced the launch of the 'Roll Back Malaria' project, a joint effort with the UNDP, UNICEF and the World Bank. Again, one stated goal is to establish 'private-public partnerships with industry on *new* malaria products' (emphasis ours. WHO, 1998b).

Another initiative, the 'Medicines for Malaria Venture', began the end of 1999. First suggested by the WHO as a non-profit venture to be supported by private firms to develop new treatments, the 180 million dollar project was viewed as too costly and competitive with individual firm efforts to be acceptable. However, support has now come from public sources and it will begin operation along the lines of a venture capital fund for a single product. Grantees will take potential products to the point of phase I clinical trials or an Investigational New Drug application and then pass the reins over to private drug companies for development and marketing. (Kaiser, 1998). Interviews at NIAID indicated that this strategy is also followed by the NIH. After they discover a potential new drug in one of their laboratories, they attempt to license it to industry as early as possible in the development process (often via a CRADA contract). This is usually before phase II clinical trials although they have to go further, sometimes through phase III, for tropical disease therapies in order to interest industry.

A much publicized initiative has been the establishment of the Global Fund for Children's Vaccines by the Bill and Melinda Gates Foundation, with 50 million dollars allocated to identifying promising malaria vaccine candidates and 750 million to purchase existing new vaccines. Looking to the future, Jeffery Sachs is leading efforts to establish a "Millennium Fund" – a commitment on the part of donors to purchase future new vaccines for tropical diseases at a prices which would cover research costs (*The Economist*, August 14, 1999).

When it comes to encouraging firms to develop or donate existing products there have been some notable successes. These include:

Onchocerciasis: 1997 was the 10th anniversary of Merck's decision to donate ivermectin to treat onchocerciasis, or river blindness, as part of the WHO Onchocerciasis Control Programme, and the company signed a Declaration of Intent reaffirming its commitment to continue to donate the drug as long as it is needed to treat this disease (Merck, *Annual Report*, 1997). Ivermectin was developed in the 1970s to kill parasitic worms in livestock, and became one of the leading veterinary products. In the early 1980s, Merck tested it in humans, found it effective, and brought it thorough phase I trials. At that point they approached WHO, and received support for later trials and field testing in Africa (WHO, 1998c). 18 million people were treated in 1996.

Lymphatic Filariasis: WHO has enlisted SmithKline Beecham (SKB) in a campaign to eradicate lymphatic filariasis, a parasitic infection of the lymphatic system transmitted by mosquitoes. Recent research shows that SKB's drug albendazole, in combination with ivermectin or

diethylcarbamazine, is 99% effective in preventing transmission. SKB is donating the drug, and other support, to a program which will reach one billion people over twenty years - a donation with an expected cost of about a billion dollars to the firm. Merck has been approached to donate ivermectin to this program. (*Scrip*, no. 2305, January 30, 1998).

Other: Pfizer recently pledged \$60 million and four million Zithromax doses to combat trachoma, a major cause of blindness in poor countries (*The Wall Street Journal*, November 11, 1998). Pasteur Mérieux-Connaught have agreed to donate enough doses of Hib vaccine to cover needs of Gambia's immunization programme for five years (CVI, 1998). Novartis and Glaxo-Wellcome have also recently contributed to WHO projects for the treatment of fasciolosis and malaria. (WHO, 1998c).

Although these public/private collaborations are not research programs, their experience suggests that when the public sector does seek to encourage more private R&D on targeted diseases it may be successful in influencing private behavior.

The major new initiatives directed towards encouraging firm involvement in research on tropical diseases are, however, very recent and were largely unpredictable, and are thus unlikely to have influenced decisions relevant to the data series presented here. Further, it is also not clear that the concern about re-emerging diseases has led, as yet, to a substantial redirecting of *public* research funds in that direction. The NIH Revitalization Act of 1993 formally added 'tropical diseases' to NIAID's mission statement in recognition of NIAID's role as the primary source of funding for U.S. civilian investigators conducting research in areas of tropical medicine (NIAID, 1997). Thus, one would expect any change in public support to be seen there. Table 6 gives NIH budget figures for tropical disease research over the past decade. It is broken into two sub-periods because of change in the definition of 'tropical' in 1996.¹² In real terms, spending on tropical diseases increased only 8.7% from 1990 to 1995, and did not increase at all as a share of the total NIH budget. Between 1996 and 1999 real spending increased by 9.0% but *fell* as a share of all spending.

Increasing Incomes in LDCs

¹² The figures for each institute are compiled by their budget officers, who 'pro-rate' grants across disease categories. There may be some inconsistencies over time in decisions about double counting and the allocation of overhead expenses but we do not expect them to be substantial.

Although in the longer term one hopes that incomes will increase substantially in these countries, there is no particular reason to have expected a significant revision in expectations at just this time. It is also not obvious that the anticipation of increasing incomes in the longer run would raise expectations about the market size for our target diseases. The middle and upper classes in the developing countries have disease profiles which look more like those of residents in the developed world. Thus, rising incomes in the LDCs will not necessarily make the potential willingness to pay for drug therapies for these diseases larger – in fact it may have the opposite effect by making the disease incidence smaller!

Science Gets Easier

Some increase in R&D might be due to new technological opportunities. For example, in the early 1980s researchers learned how to grow a malaria parasite in vitro, which could explain the acceleration of activity that we see in the data series for that disease. Looking to the future, researchers at the Pasteur Institute in Paris and the Sanger Center near Cambridge, MA, have decoded the DNA sequence of the tuberculosis bacterium. “This advance is likely to open up new approaches for developing drugs and vaccines against the microbe, and to reinvigorate research efforts in a difficult and slow moving field.” (*International Herald Tribune*, June 12, 1998).

New technologies have the potential to provide very inexpensive equivalents to existing vaccines. DNA vaccines may be manufactured by relatively low cost large-scale chemical synthesis methods, avoiding expensive virus cultures, bioreactors, complex purification steps, and so on. They have the inherent advantage of stability without refrigeration or other special handling requirements. Thus this new technology may facilitate vaccine delivery to the developing world (Dunn, 1997). However, advances in biotechnology and genetic engineering are spurring investment in vaccines (and pharmaceuticals) more generally. Some 50 biotechnology companies have entered along with big investments by larger pharmaceutical companies, and about 75 new vaccines are in development. (*The Economist*, May 9, 1998). There is no obvious reason to think that current technological opportunities are concentrated in, or specific to, our focus areas.

An Increase in the Effectiveness of Other Mechanisms of Appropriation

New biotech drugs may be significantly harder to copy than the traditional “small molecule” drugs, so some part of change could be ascribed to new but alternative mechanisms of appropriation. According to one interviewee at a small biotechnology company, their technologies are sufficiently difficult to master that duplication by LDC firms is not a major threat, making existing protection at home sufficient to keep competitors away. This view was also voiced by experts in the Office of Technology Development at NIAID. It would suggest that changes in the patent regime are unnecessary to explain increases in R&D on drugs aimed at LDC markets.

VI. Understanding What Happens – or Doesn’t

Here we consider issues, many of them raised by industry, which might explain a muted response to strengthened IPRs in developing countries.

The Science is Really Hard

Referring to the scientific challenges posed by some of these diseases, one executive described malaria as a ‘big hairy mother’. Nevertheless, he did not view this as an important explanation for spending priorities. AIDs also presents enormous scientific challenges, yet it is seeing a great deal of investment. Furthermore the global budget for research on tropical diseases is so small that scientific obstacles cannot be much of the story. WHO (1996), for example, estimates that, in 1992, just \$2.4 billion, or 4.3% of global health-related R&D expenditure, was related to health problems of low and middle income countries.¹³ Just 0.2% was spent on pneumonia, diarrheal disease and TB, diseases which together account for 18 percent of the total global disease burden.

Good, Low-Cost, Therapies Already Exist

In some cases the products already on the market are so effective and inexpensive that further research is unlikely to yield much improvement. Examples would be measles and polio vaccines. But the head of research at Pfizer cautions against being complacent about this, noting

¹³ The data used includes all *public* health R&D (not necessarily drugs) in LDC countries, plus public expenditure in DCs on tropical or relevant vaccines, plus any R&D expenditure, public or private, in DCs which involved collaboration with an LDC institution or scientist. The breakdown of the \$2.4 billion is: 1,200 million from the LDC governments, 683 from developed country governments, 80 million from private foundations and other non-profit organizations, and 400 million from the pharmaceutical industry.

that while a treatment for trachoma, tetracycline, has been available for many decades, the course of treatment required to cure the disease with that drug may be as much as six months, compared to the single dose required of their drug Zithromax. This greater convenience could be quite valuable in environments where regular and repeated treatments are hard to guarantee.

While there are treatments for many LDC-specific diseases, it is hard to support the hypothesis that so many adequate therapies exist that there is no need for further research. Many diseases lack any effective treatment, in other cases, the treatment may be dangerous, expensive, or impossible to administer effectively in areas where the disease is endemic. Consider trypanosomiasis, or "sleeping sickness", which is an example of a disease that has a variety of treatments, but ones which are far from ideal. According to the WHO, the four drugs currently available have many drawbacks: none are available in an oral dose, three have significant adverse side-effects (up to 5% risk of death in one case), and two are effective only against regional sub-species of the parasite, and one can only be used in a hospital setting. Delays in treatment can have significant adverse consequences: if the parasites have not yet reached the brain, the disease can usually be treated successfully with a ten day course of pentamidine injections. Later stage treatment takes a months and requires injections of melarsoprol, a poison which is almost 20 percent arsenic and is able to melt plastic IV tubes. If it seeps out of a vein it can require the amputation of a limb (Zimmer, 1998).

Similar problems are apparent in the armamentarium for other major diseases. Only two of the four drugs currently available for treating onchocerciasis and lymphatic filariasis have been demonstrated to meet standards for human use. TB is treatable, but many strains have developed resistance to existing drugs, and may require lengthy courses of treatment with drugs with significant side effects. New TB drugs hold some promise: rifapentine requires fewer doses to cure the disease, making it more likely that patients complete the full course of treatment. (*Washington Post*, June 24, 1998), and according to a survey conducted by PhRMA, a treatment for TB under development would cut treatment time from 6 months to two weeks (PhRMA, 1998). Schistosomiasis treatment relies precariously on a single drug, praziquantel. Like TB, leprosy, though treatable, is showing signs of developing multiple drug resistance.

Internal Firm Decision-making

An interesting question that came out of discussions with firms is when, and how, new opportunities in the marketplace feed into their decisions about research priorities. It seems that this is often an informal process - there being a sense of what are 'big diseases' but not an

explicit ranking of priorities. If research were to throw up a possible tropical disease drug candidate, for example as an offshoot of research on another disease or because of related veterinary research on parasitic diseases in animals, then it would probably be investigated at some level. One interviewee indicated that considerations of intellectual property and the market size have, at least until now, only come into their formal decision-making after phase I and II clinical trials. However, the large-scale funding required for phase III clinical trials, or decisions to invest in targeted research on tropical diseases, would require positive signals from marketing. Here it seems that information is weak: one of the repeatedly expressed desires of industry in the international fora is that they be provided with better information about the expected size of markets in developing countries. Thus, it may take some considerable time for any increased attractiveness of developing country markets to seep through to the point of altering research decisions, at least in the larger firms.

Bad Attitude

In some countries a variety of deeply ingrained beliefs and attitudes, historical experience, or simply lack of reliable information about the efficacy of new products present a substantial barrier to marketing innovative drugs. These include such factors as antipathy to "Western" products or medical practice, unrealistic expectations about drug prices acquired during decades of price controls, or simply a more general lack of enthusiasm for the idea of paying a lot for innovative drugs. Several interviewees indicated that a significant investment in the education of target populations would be required before innovative drugs could be profitably sold in these countries.

Weak Enforcement of Intellectual Property Rights

As indicated above, despite some evidence to the contrary, firms remain skeptical about the prospects for effective enforcement of IPRs. Bad experiences dealing with patent infringement in developing countries have done nothing to dispel these beliefs, nor have highly publicized cases of governments demonstrating a reluctance to enforce other intellectual property, such as the persistent pirating of CDs in China.

Global/Political Issues

A consistent theme in our interviews has been that firms need to be able to effectively price discriminate when there are different markets for their products if they are to address the

medical needs of LDC populations. This may take the form of charging different prices for the same drug in different countries, or charging different prices for the same drug in different therapeutic applications. For example, consider pentamidine, a treatment for trypanosomiasis which cost \$10 per course of treatment until it found a "new" market in the treatment of infections prevalent in AIDs patients. At that point the price shot up to \$300, effectively denying treatment to sufferers from trypanosomiasis (Zimmer, 1998). Faced with the possibility of arbitrage across countries, manufacturers would only supply the drug to countries where trypanosomiasis is endemic if they were willing to forgo significant returns in their home markets.

Another disheartening example is that of the UNICEF vaccine programme. Prior to 1982, European and American manufacturers bid to supply UNICEF with vaccines for poor countries at low prices. "In congressional hearings in 1982 concerning federal and state expenditures for the purchase of children's vaccines, however, the U.S. vaccine industry was *savaged* for allegedly subsidizing vaccines for the poor children of the world by charging high costs to U.S. families and taxpayers." (IOM, 1997, emphasis ours). Not surprising, the U.S. industry withdrew from this market, leaving it to the European manufacturers.

An inability to limit arbitrage across political boundaries or resist domestic political pressure mean that firms are forced to address huge disparities in willingness to pay across markets by charging a single optimizing price which will overwhelmingly reflect demand conditions in their home markets.¹⁴ Absent some mechanism for controlling arbitrage or domestic political pressure, most LDC consumers will be priced out of the market. Segmenting markets is not impossible. Manufacturers of new Hib vaccine for *Haemophilus influenza* type *b* charge \$15-17 to the U.S. private sector, \$5-7 to the U.S. public sector and \$3 to developing countries (CVI, 1998). And organizations such as UNICEF or the WHO are eager to provide a framework for controlled, enforceable price discrimination. However, as long as this worry remains in the minds of industry, the development of products for LDC markets will be retarded.

Role of Investment Funding

One potentially important source of innovative drugs for tropical diseases is the biotech

¹⁴ According to a firm executive, "...the newer, more expensive, vaccine for Hepatitis B, which is still under patent protection and sells for approximately \$1.50 a dose, has not yet found a large and profitable market in developing countries. *Arbitrage across national boundaries, international political pressure* or genetic variation of the virus might prevent a manufacturer from selling the same product at a distinct profit maximizing price in each separate country...." (italics ours).

sector of the industry. These firms are largely engaged in very early stage research, and are less directly concerned with marketing questions. However, the strength of IPRs does affect research activity through the funding mechanism used by these firms. One interviewee cited the influence of having to continually "sell" the company to venture capitalists, or other investors, who "only like fat markets". In these circumstances, research targeted at LDC diseases goes "underground" or is simply not pursued. Conversely, a growing perception that these markets represent a significant commercial opportunity would result in an "avalanche of new money".

VII. Conclusion

Do patents matter? It may still be too early to tell in this case, where the economic impact of the TRIPs agreement is only just beginning to be felt. Developing new drugs takes significant amounts of time as well as money, and though strengthening IPRs makes developing country markets more attractive, these long lags mean that the "demand-pull" effect of the TRIPs agreement on pharmaceutical R&D may take many years to become fully visible. The picture is further blurred by the role of expectations: rather than being a "surprise" announcement in 1994, the movement to reform patent laws in LDCs gathered strength over a number of years.

Nonetheless we do identify some distinct signs of stirring activity: for example it appears that research related to the treatment of malaria increased markedly beginning in the mid-1980s. Since malaria is a disease specific to the countries introducing stronger patent protection, and there is no indication that the science somehow became "easier" in this period, it is hard to avoid the conclusion that the historical absence of IPRs played an important role in retarding the development of new treatments for this very important disease. However, we cannot yet place too much confidence in this result. The upward trend seems, in some of the data series, to have disappeared in the most recent years. Further, as discussed above, there are a number of potential confounding factors, primary among them the spate of new initiatives on the part of public sector institutions targeting malaria.

Set next to the activity in malaria, a second interesting finding is that there appears to be less new research activity directed towards other tropical diseases. As discussed in Section IV, one very plausible explanation for this finding is that the expected market sizes for different diseases are quite divergent. What we may be observing is attempts to find products for what is clearly one of the most valuable new LDC markets. Firms' interest in finding therapies for other

diseases may be hampered by markets which are simply economically or epidemiologically too small, in which case the availability of intellectual property rights will never be a sufficient incentive to invest. Another factor limiting investment may simply be a lack of information about these markets. Finally, firms may be 'testing the waters' with malaria, in which case they may follow in time with a broader research agenda if the implementation and enforcement of the new patent laws is satisfactory and there is a supportive attitude taken in the developing countries. If the latter two explanations are relevant, we should see a pick up in R&D investment in other tropical disease areas in the coming years.

The survey results from India underlined the importance of focusing not just on tropical diseases, but also on changes in R&D directed at products for LDC markets which are for diseases found globally. To the extent that that survey is representative, a significant part of the R&D induced by the new patent laws could be of the latter sort. This is problematic since no existing statistical sources categorize research inputs or outputs in this way. Hence, in order to get a complete accounting of the research benefits of the new patent laws it appears crucial to obtain cooperation from industry in extending the surveyed population to firms in the developed countries.

The fieldwork component of this study highlighted for us the importance of analyzing patents in a broader context. Interviewees frequently mentioned that IPRs are just one aspect of the commercial environment of "difficult" markets. Unmet medical needs in these countries are both a serious human problem, and a economic opportunity, but addressing them requires more than just a sustained increase in R&D to develop new treatments. Being able to deliver these treatments to those in need may also require substantial complementary investments in infrastructure for distributing and marketing pharmaceutical products, and in the education of consumers and health care providers. A commitment to respecting property rights more generally, for example by eschewing nationalization as an industrial policy or maintaining a workable system for enforcement of commercial contracts, may be required before "Big Pharma" is willing to make these unrecoverable ancillary investments.

Table 1
Diseases for Which 99% or More of the Global Burden
Falls on Low- and Middle-Income Countries in 1990

Disease	DALYs (Thousands, 1998)	Deaths per Year (Thousands, 1998)
Chagas Disease	588	17
Dengue	558	15
Ancylostomiasis and Necatoriasis	na	Na
Japanese Encephalitis	502	3
Lymphatic Filariasis	4,698	0
Malaria	39,267	1,110
Onchocerciasis-river blindness	1,069	0
Schistosomiasis	1,696	7
Tetanus	12,950	409
Trachoma	1,255	0
Trichuriasis	1,287	5
Trypanosomiasis	1,219	40
Leishmaniasis	1,707	42
Measles	30,067	882
Polio	213	2
Syphilis	4,957	159
Diphtheria	181	5
Leprosy	393	2
Pertussis	13,047	342
Diarrhoeal Diseases	72,742	2,212

Source: Global burden from World Health Organization (1996); Figures from WHO (1999). DALYs are estimates of years of life lost or lived with a disability, adjusted for its severity.

Table 2: Frequency of Patent Families by Disease Groups

Year ^a	Diseases with Treatments ^b	Of which: Schistosomiasis	Trachoma	Diseases with Treatments Needed ^d	Of which: Malaria	Leishmaniasis	Chagas	Leprosy
1975	1	1	0	14	1	0	0	0
1976	2	1	1	17	1	0	2	4
1977	6	4	1	23	7	0	4	1
1978	1	1	0	22	1	3	4	1
1979	2	0	2	18	5	1	3	0
1980	1	1	0	35 ¹	4	1	4	1
1981	2	0	2	31	5	3	3	0
1982	2	1	1	33	9	0	3	2
1983	2	1	1	31	16	0	2	2
1984	8	0	7	55	23	4	0	3
1985	4	2	2	59	28	3	5	0
1986	5	4	1	59	21	1	4	5
1987	4	1	3	91	39	5	10	6
1988	17	5	10	99	37	10	14	1
1989	7	3	4	105	33	3	12	3
1990	10	1	9	108	46	3	15	2
1991	7	1	5	82	36	3	7	2
1992	16	9	6	77	23	3	12	2
1993	13	3	8	119	35	7	11	4
1994	20	10	10	91	23	7	14	6
1995	9	3	5	118	22	7	21	3
1996	11	4	6	113	28	7	9	2

Notes: ^a Year of priority patent application.^b Includes patents related to at least one of: Ancylostomiasis, Trachoma, Schistosomiasis.^c Includes patents related to at least one of: Chagas, Leishmaniasis, Leprosy, Lymphatic Filariasis, Malaria, Tuberculosis.

Table 3
Trends in Pharmaceutical Patenting by Indian Inventors^a

Year	U.S. Patent Grants			EPO Patent Applications	
	Number	Pct. All Indian	Pct. All Pharma	Number	Pct. All Pharma
1980 - 84	12	14.5%	0.09%	3	0.03%
1985 - 89	23	16.7	0.13	3	0.02
1990	11	28.2	0.26	1	0.02
1991	14	37.8	0.35	0	0.00
1992	18	36.7	0.40	3	0.06
1993	11	16.9	0.22	2	0.04
1994	9	13.2	0.14	2	0.04
1995	17	21.8	0.19	6	0.15
1996	19	25.0	0.40	2	0.16
1997	18	75.0	0.55	-	-

Notes: ^a Pharmaceutical patents are those in IPC groups A61k or A01n. Indian are first inventors with an Indian address or Indian priority patent. Year is that of application. For U.S. patents the values are numbers granted as of July, 1999.

Table 4: Frequency of Citations to Disease Groups in the Biomedical Literature

Year	Diseases with Treatments^a		Diseases Needing Treatments^c		Malaria	
	Drug/Vaccine^b (%)	All	Drug/Vaccine (%)	All	Drug/Vaccine (%)	All
1980	0.20	161	0.24	2,288	0.22	427
1981	0.21	192	0.23	3,029	0.25	509
1982	0.27	182	0.23	3,529	0.29	634
1983	0.15	178	0.24	3,501	0.26	665
1984	0.23	193	0.24	3,514	0.27	736
1985	0.25	210	0.23	3,713	0.27	770
1986	0.19	180	0.23	3,850	0.24	768
1987	0.19	218	0.22	4,000	0.28	883
1988	0.23	180	0.24	4,140	0.30	913
1989	0.22	218	0.24	4,445	0.30	956
1990	0.24	264	0.24	4,773	0.31	1,091
1991	0.36	212	0.24	4,864	0.29	1,175
1992	0.17	264	0.24	4,858	0.30	1,200
1993	0.17	242	0.23	5,151	0.26	1,178
1994	0.17	215	0.24	5,272	0.29	1,249
1995	0.21	221	0.24	5,442	0.30	1,156
1996	0.21	192	0.25	5,576	0.31	1,217
1997	0.22	224	0.26	5,431	0.30	1,355
1998	0.23	228	0.25	5,673	0.29	1,281
1999 ^d	0.18	51	0.20	2,084	0.23	471

Notes: ^a Includes citations with at least one of: Ancylostomiasis, Necatoriasis, Onchocerciasis, Schistosomiasis, Trachoma.

^b Percent citations to the group in the online PubMed database with 'drug therapy' or vaccine in addition to the disease search words.

^c Includes citations with at least one of: Chagas, Japanese Encephalitis, Leishmaniasis, Leprosy, Lymphatic Filariasis, Malaria, Trypanosomiasis, Tuberculosis.

^d Citations through June, 1999.

Table 5
National Institutes of Health Grant Allocations
(Thousands of Dollars)

Fiscal Year ^a	Malaria projects			NIAID total			Malaria as pct NIAID	
	Total funding	1997 dollars	grants	Research	1997 dollars	grants	Funding	grants
1972	\$1,567	\$6,697	31	\$109,044	\$466,000	1493	1.44	2.08
1973	1,123	4,584	29	103,025	420,510	1485	1.09	1.95
1974	1,930	7,395	41	120,822	462,920	1539	1.60	2.66
1975	2,355	8,149	47	119,417	413,208	1753	1.97	2.68
1976	6,540	21,097	90	125,563	405,042	1615	5.21	5.57
1977	3,730	11,134	45	140,382	419,051	1428	2.66	3.15
1978	3,425	9,514	44	161,814	449,483	1512	2.12	2.91
1979	5,418	13,892	64	191,119	490,049	1806	2.83	3.54
1980	5,445	12,722	71	214,657	501,535	1940	2.54	3.66
1981	4,402	9,326	62	232,028	491,585	2099	1.90	2.95
1982	5,198	10,133	62	235,835	459,717	2139	2.20	2.90
1983	5,496	10,084	65	278,939	511,815	2288	1.97	2.84
1984	7,110	12,322	81	319,593	553,887	2379	2.22	3.40
1985	9,590	15,721	87	370,047	606,634	2529	2.59	3.44
1986	12,863	20,257	105	367,142	578,176	2416	3.50	4.35
1987	14,668	21,925	122	545,433	815,296	2718	2.69	4.49
1988	22,159	31,566	145	638,521	909,574	2911	3.47	4.98
1989	23,373	31,628	148	740,239	1,001,677	3084	3.16	4.80
1990	27,973	35,863	164	831,181	1,065,617	3370	3.37	4.87
1991	22,147	27,075	172	906,003	1,107,583	3568	2.44	4.82
1992	25,878	30,302	149	960,082	1,124,218	3477	2.70	4.29
1993	28,983	32,823	178	984,114	1,114,512	3629	2.95	4.90
1994	39,448	43,019	227	1,063,696	1,159,974	3756	3.71	6.04
1995	45,663	48,117	242	1,092,507	1,151,219	3716	4.18	6.51
1996	43,216	44,415	223	1,171,160	1,203,659	3824	3.69	5.83
1997	N/A	N/A	221	1,257,793	1,257,793	4177	N/A	5.29

Note: ^a FY is the fiscal year which runs to September.

Table 6
Budget Allocations to Tropical Disease Research at the National Institutes of Health
(Millions of Dollars)

Year	NIAID Tropical	Other Institutes ^a Tropical	Total Tropical in 1997 dollars	Pct Growth in Total over previous year	Share of Total Tropical in Total NIH	Pct Growth in Share of Tropical
1990	\$38.4	\$6.5	\$57.6	-	0.0053	
1991	39.5	7.8	57.8	0.4%	0.0051	(3.8)%
1992	43.6	8.4	60.9	5.3	0.0052	1.2
1993	36.9	10.1	53.2	(12.6)	0.0046	(12.6)
1994	41.3	12.2	58.3	9.6	0.0049	7.7
1995	44.2	15.2	62.6	7.3	0.0052	6.8
1996b	\$90.4	\$18.1	\$111.5	-	0.0091	-
1997	97.2	16.9	114.1	2.3%	0.0089	(2.2)%
1998	104.0	17.9	118.0	3.4	0.0089	1.2
1999 ^c	112.9	19.2	124.2	5.3	0.0084	(5.7)

Notes: ^a Other Institutes with spending on tropical diseases are: NCI, NIDR, NINDS, NICHD, NEI, NIEHS, NCRR, FIC.

^b The definitions of 'Tropical' changed in 1996 so the periods must be considered separately.

^c Estimated values.

Figure 1: Patents Related to Tropical Diseases as a Percentage of All Pharmaceuticals

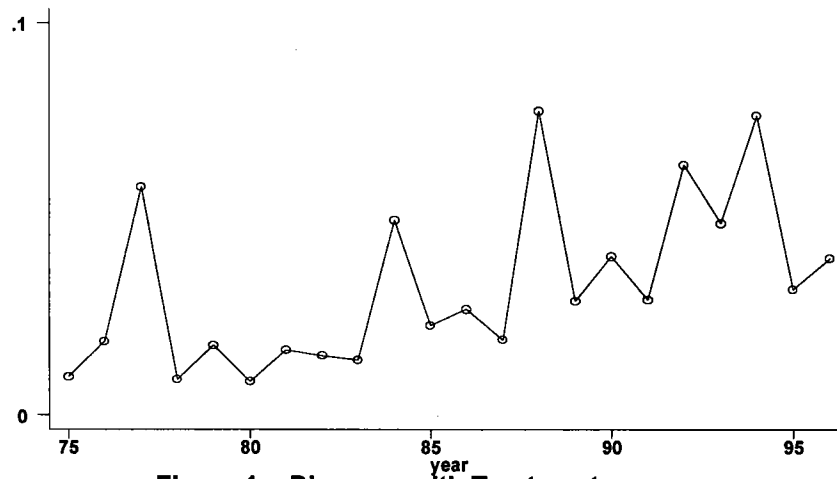


Figure 1a: Diseases with Treatments

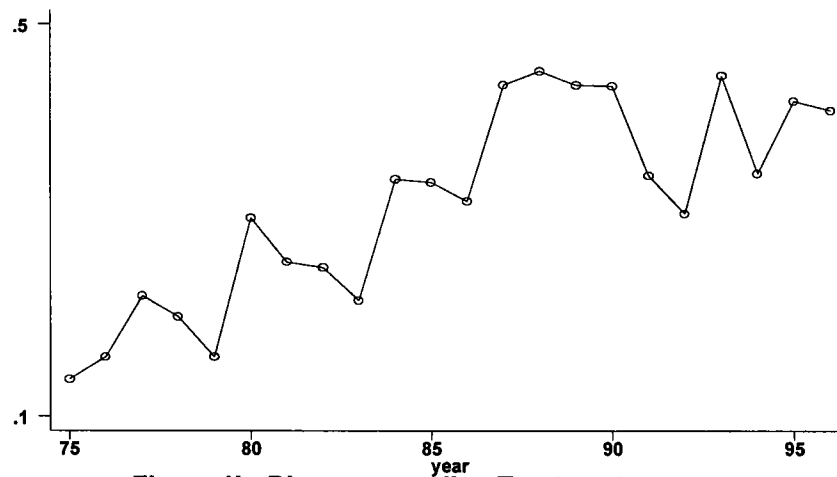


Figure 1b: Diseases needing Treatments

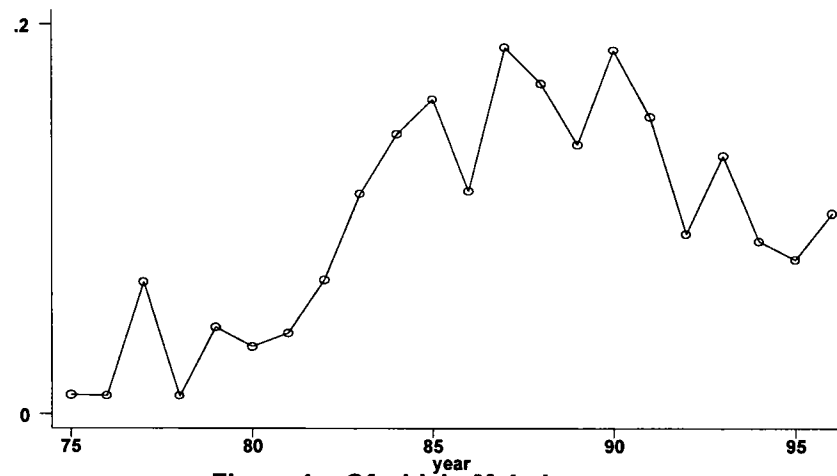


Figure 1c: Of which: Malaria

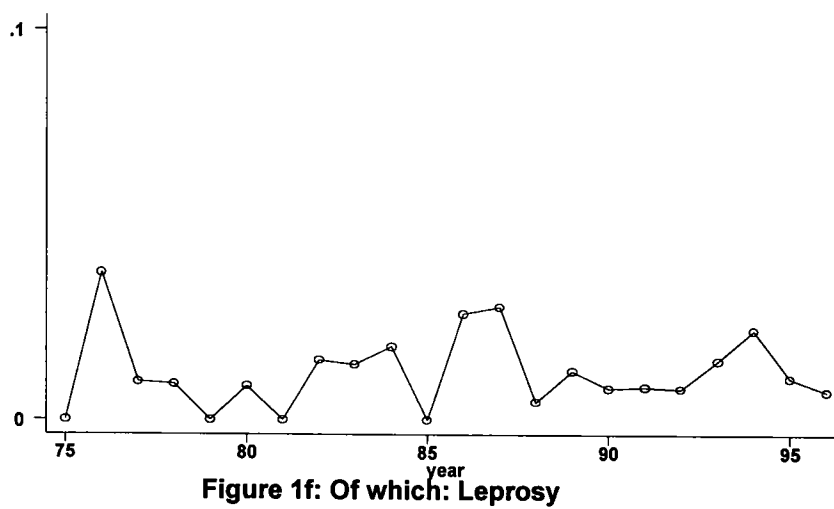
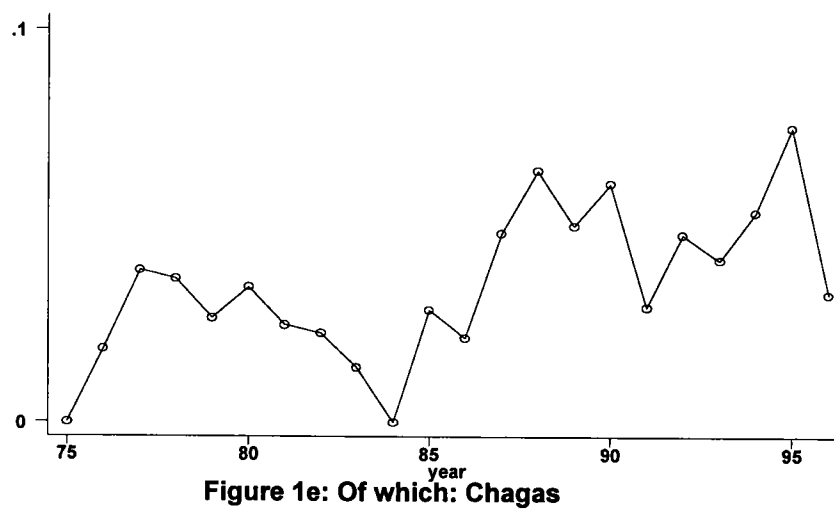
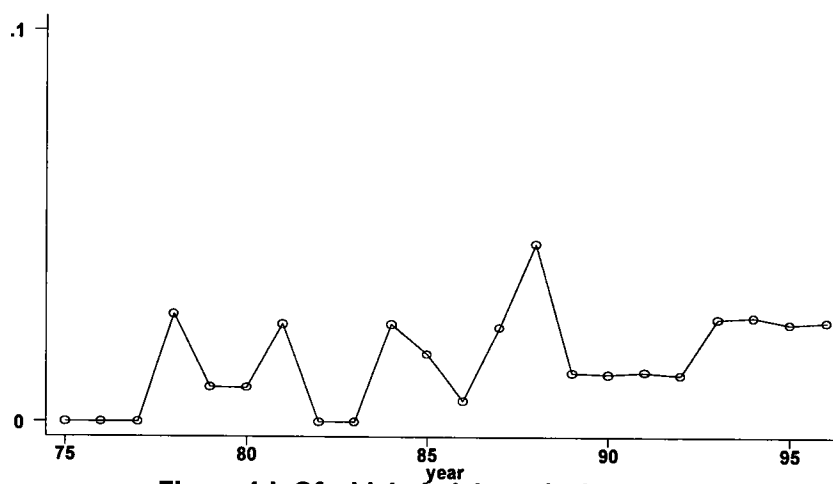


Figure 2: Citations to Tropical Diseases as a Percentage of All Citations

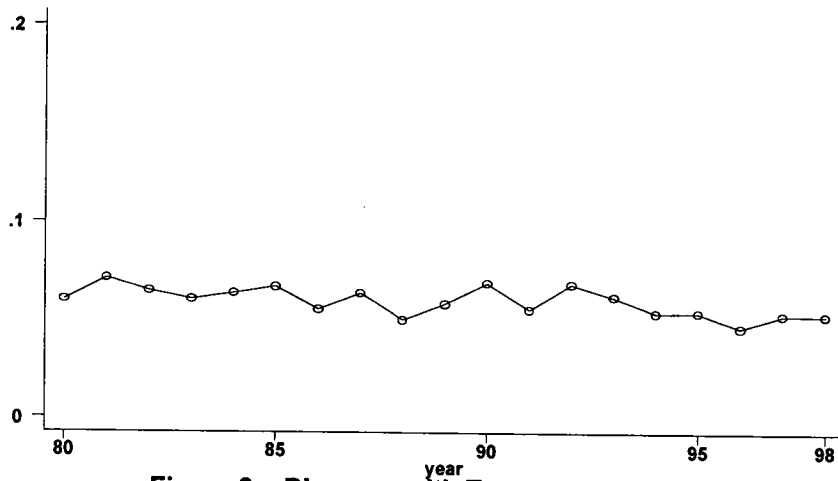


Figure 2a: Diseases with Treatments

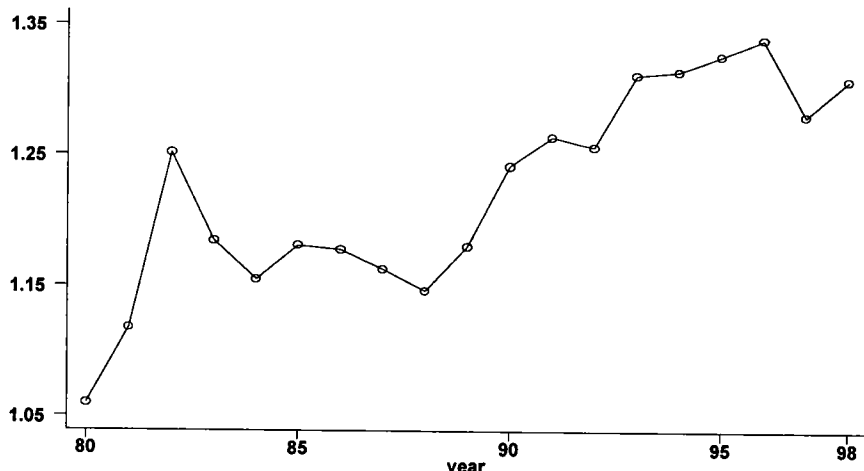


Figure 2b: Diseases needing Treatments

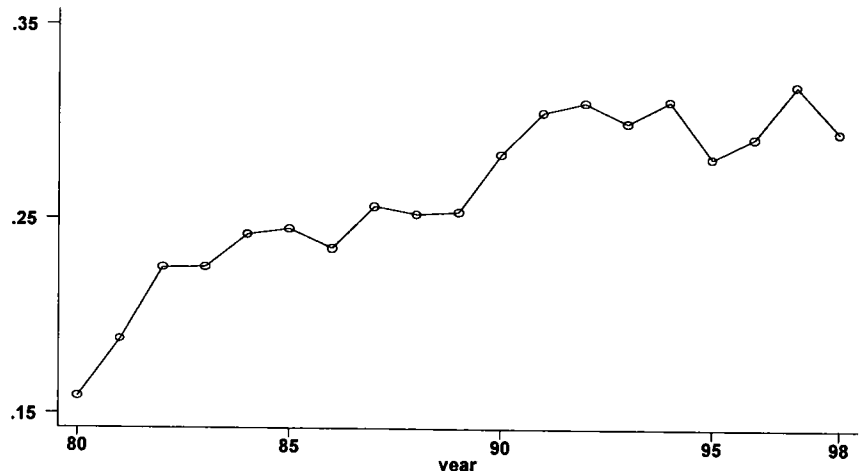
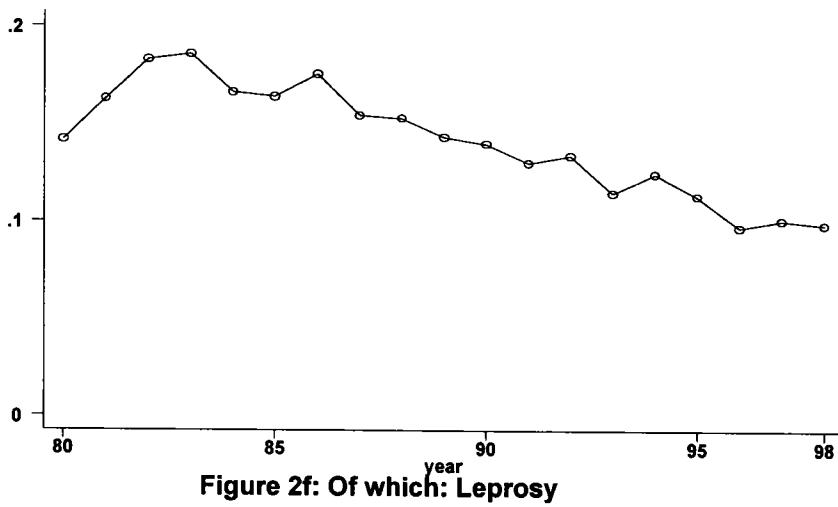
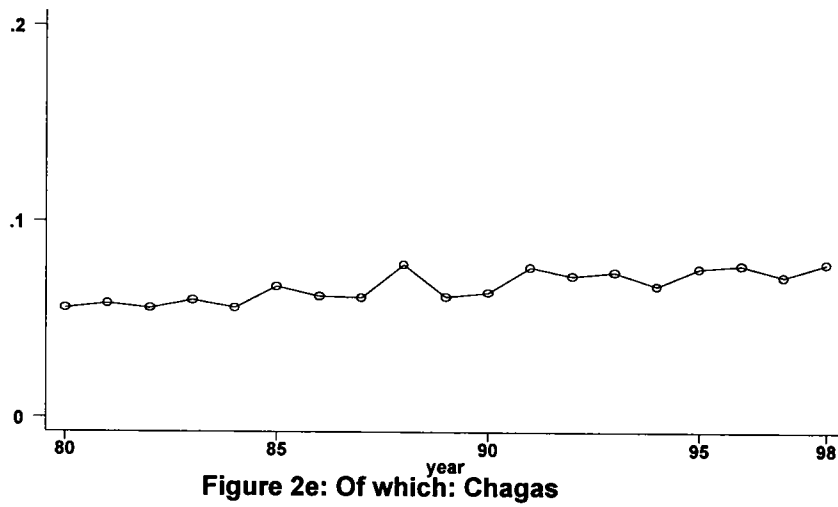
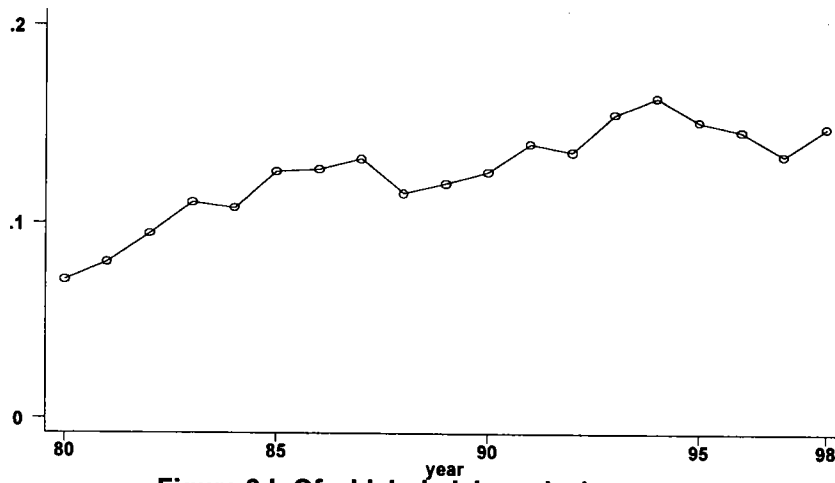


Figure 2c: Of which: Malaria



Appendix 1

Yale University R&D Questionnaire 1998

Company Name _____
 Current Annual R&D Expenditure _____ Rs

1. Thinking of all of the research projects that you have underway *at this time*, including joint ventures and contract research, do you have any projects which are:

A) discovery research directed at finding new pharmaceutical products for diseases on the attached list? (circle one)

Yes _____ (number) / No

If yes, what percentage of your total current annual R&D expenditure do these projects represent?

_____ %

B) directed at the development of new products, or new indications, for diseases on the attached list? (circle one)

Yes _____ (number) / No

If yes, what percentage of your total current annual R&D expenditure do these projects represent?

_____ %

2. Again thinking of all of the research projects that you have underway *at this time*, do you have any projects which are:

A) discovery research directed at finding new pharmaceutical products for *any* disease and for which you expect more than 50% of sales revenue to come from markets OUTSIDE the U.S., Europe and Japan? In other words, the main markets are expected to be India, other Asian or African countries, and so on. These projects may overlap with the projects in question (1a) above. (circle one)

Yes _____ (number) / No

If yes, what percentage of your total current annual R&D expenditure do these projects represent?

_____ %

B) directed at the development of new products, or new indications, for *any* disease and for which you expect more than 50% of sales revenue to come from markets OUTSIDE the U.S., Europe and Japan? In other words, the main markets are expected to be India, other Asian or African countries, and so on. These projects may overlap with the projects in question (1b) above. (circle one)

Yes _____ (number) / No

If yes, what percentage of your total current annual R&D expenditure do these projects represent?

_____ %

3. Thinking of those projects led to a 'Yes' response anywhere above, what percentage of your total current annual R&D expenditure does this group of projects represent taken together?
 (Please indicate zero if you responded 'No' everywhere above.)

_____ %

(please turn over page)

4. Thinking about the type of research projects that you expect to have underway *in five years*, including joint ventures and contract research, do you expect to have any projects which are:

A) **discovery** research directed at finding new pharmaceutical products for diseases on the attached list? (circle one)

Yes _____(number) / No

B) directed at the **development** of new products, or new indications, for diseases on the attached list? (circle one)

Yes _____(number) / No

5. Again thinking of the type of research projects that you expect to have underway *in five years*, do you expect to have any projects which are:

A) **discovery** research directed at finding new pharmaceutical products for *any* disease and for which you expect more than 50% of sales revenue to come from markets OUTSIDE the U.S., Europe and Japan? In other words, the main markets are expected to be India, other Asian or African countries, and so on. These projects may overlap with the projects in question (1a) above. (circle one)

Yes _____(number) / No

B) directed at the **development** of new products, or new indications, for *any* disease and for which you expect more than 50% of sales revenue to come from markets OUTSIDE the U.S., Europe and Japan? In other words, the main markets are expected to be India, other Asian or African countries, and so on. These projects may overlap with the projects in question (1b) above. (circle one)

Yes _____(number) / No

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Interviews

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