The New York Review of Books

VOLUME 52, NUMBER 15 · OCTOBER 6, 2005

Review

The Body Hunters

By Marcia Angell

The Constant Gardener
a film directed by Fernando Meirelles, based on the novel by John le Carré

Shortly before I started work on my book *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*,[1] a friend gave me John le Carré's newly published novel, *The Constant Gardener*, and urged me to read it right away. I did as I was told, and found the tale apposite, to put it mildly.

The villain is a global pharmaceutical company called Karel Vita Hudson (KVH). The heroine, Tessa Quayle, is the wife of a low-level British diplomat stationed in Nairobi, Kenya. She stumbles across evidence that KVH is testing a dangerous tuberculosis drug, called Dypraxa, on powerless and unsuspecting poor Africans, and not reporting the resulting deaths. When she threatens to expose the company, she is brutally murdered, and the British government colludes in the cover-up. Her husband, Justin Quayle, a seemingly docile civil servant at first, becomes obsessed with finding out why his wife was murdered and by whom. He finally does, and at the end of the book, he too is murdered. In between the deaths, we follow Justin's gradual awakening to the ruthless activities of a corporation too powerful to be accountable to anyone.

Now *The Constant Gardener* has been released as a film, starring Ralph Fiennes and Rachel Weisz and directed by Fernando Meirelles. It is both better and worse than the book. Visually, it is stunning. The many aerial shots of Kenya show the stark beauty and sweep of the African countryside, and the film also conveys in its urban scenes the miserable overcrowd-ing and hopeless poverty in Nairobi, something the book only suggests.

Where the film most improves on the book is in its treatment of the main characters. Fiennes and Weisz portray the relationship between Tessa and Justin as touching and believable, something the book fails to do. Le Carré presents Justin as self-contained to the point of inertness and seemingly with no serious interests beyond his garden. It hardly seems plausible that such a man would throw over his career, and risk his life, to investigate the death of his wife. In this film, Justin is revealed as not so much passive and narrow as controlled and quietly determined. And Weisz portrays Tessa, a passionately uninhibited champion of the poor and downtrodden, as a shrewder and more perceptive woman than the one we find in le Carré's book; she does not share her discoveries about the drug companies with her husband for fear of compromising him. As in the book, Tessa's murder takes place at the beginning, and we come to know her through flashbacks. But Fiennes's face at hearing of her death, controlled and virtually immobile, somehow manages to convey the enormity of his loss as well as his determination to find out the truth about her death.

The film falls far short of the book, however, in telling us what KVH (for some reason renamed KDH in the film) was up to; it never explains why every institution that might have interfered with the company, including the British government, was colluding with it. We only get hints. We are told in passing that KDH and the people it controlled coerced poor Africans into acting as guinea pigs by denying them

medical care unless they took part in company experiments; but we learn little about the rules which prevent that sort of coercion in prosperous countries but not in poor ones. We're told that deaths were covered up—literally; bodies were thrown into a lime pit and their existence denied. But we learn little about why that was done, or why companies conduct clinical trials (that is, tests on human beings) in the first place, and why they find it advantageous to do so in Africa.

Since the film tells us very little about the motives of the drug company, we are left with a story that has plenty of passion and intrigue but is played out in something of a historical vacuum. In fact, most viewers would probably conclude that insofar as we do learn anything about KDH, its deadly practices are wildly implausible, in no way representative of real drug company behavior. After all, in the real world, we don't hear of pharmaceutical whistle-blowers being murdered, and there have been several whistle-blowers recently.

But le Carré himself cautions us against drawing any such conclusions. In an author's note at the end of the book he makes a grudging disclaimer to the effect that no person or organization in the book is based on an actual person or organization. He also makes it clear, however, that he is obliged to say this "in these dog days when lawyers rule the universe." He adds, "But I can tell you this. As my journey through the pharmaceutical jungle progressed, I came to realize that, by comparison with reality, my story was as tame as a holiday postcard."

Quite so. Le Carré obviously did careful research, and the book is rich in details about ordinary drug company practices. Without being pedantic, he has his characters explain how drug companies distort research to make their drugs look safer and more effective than they are; how they can get away with this more easily in poor regions of the world; and how they use their vast wealth to influence governments and the medical profession and any other institutions that might interfere with their single-minded pursuit of profits. On the basis of the research I did for my book I believe that most of the background facts about drug company behavior in *The Constant Gardener*, however hard to believe, are correct.

Yet the story is based on the premise that a pharmaceutical company would be so threatened by disclosures of its activities that it would have someone killed. That is what is fantasy. In fact, many of the practices that so horrified le Carré's heroine are fairly standard and generally well known and accepted. They seldom provoke outrage, let alone murder. A company like KDH would not kill someone like Tessa even if it were willing to do so; it wouldn't have to. Her concerns would have seemed isolated and futile, and the companies would hardly have taken notice of them.

There is no question that the US and other rich countries have been conducting more and more clinical research in Africa and other parts of the third world. Although exact figures are hard to come by, it is likely that tens of thousands of studies sponsored by first-world drug companies and governments are now underway in Africa, parts of Latin America and Asia, and the former Soviet Union. Most of this research is intended to find new treatments for use in well-to-do countries. After all, that is where the paying customers are. In this sense, third-world countries are being used as laboratories for first-world needs. Relatively few studies are devoted to finding treatments for the diseases that plague poor countries, such as malaria, sleeping sickness, and schistosomiasis. The big companies are more interested in the usual first-world conditions, like high cholesterol, obesity, and arthritis.

The rapid movement of drug studies to third-world countries began in 1980, when the US Food and Drug Administration (FDA), in considering applications to approve new drugs, first agreed to accept foreign trials as evidence of safety and effectiveness. Before a company can sell a drug in the US (or market an old drug for a new use), it must get approval from the FDA, which means it must demonstrate in

clinical trials that the drug is reasonably safe and effective. Nearly every large drug company, wherever it is located, wants to get into the US market, because that is the major source of profit for pharmaceuticals.

Probably close to half of all clinical trials are now conducted in the third world, although there is no way to know for sure. The reasons are clear. It is cheaper and in many respects easier and faster to do them there. A huge new industry has arisen that conducts third-world research for drug companies (like le Carré's fictional research firm, ThreeBees). These companies, called contract research organizations, or CROs, hire local doctors to find people who will take part in clinical trials, and while the payments to the doctors per patient are lower than in first-world studies, by local standards they are munificent. Doctors can multiply their income tenfold or more. Patients, too, are readily enticed by small amounts of money and promises of free care. In fact, as in le Carré's story, enrolling in a trial may be the only way they can get any care at all.

This system makes a mockery of the notion of informed consent—the requirement that subjects be given full information about the nature of the research and have the right to refuse to participate, without penalty or consequences for their usual health care. That requirement is enforced in the US and other well-to-do countries, and partly for that reason, drug companies are having a hard time getting enough volunteers for the growing number of clinical trials. Not so in the third world, where authoritarian regimes and corrupt local government officials and health authorities are eager to be paid off by first-world organizations and to have good relations with them. They "encourage" entire villages or prov-inces to enroll in research programs, while local doctors enrich themselves by providing human subjects.

Perhaps the most important reason for conducting human research in Africa and other poor regions outside the US is that it is a way of circumventing FDA regulations. In the US, drug companies are required to file "investigational new drug applications" (INDs) with the FDA before they begin human testing of a drug they hope to get approved. The applications give detailed descriptions of the proposed research, including plans for obtaining informed consent and for monitoring the progress of the study. Companies must also provide evidence that ethics committees (called institutional review boards, or IRBs) have been set up to review each clinical trial. These committees are supposed to ensure that risks to human subjects are, in the words of the applicable federal regulations, "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result," and further, that all risks are "minimized." The FDA can deny approval of the IND or request changes in the proposed research. It may also conduct on-site inspections of the trials.

The requirements for foreign research are much looser. In fact, the FDA may not even know about such trials until after they are completed, when the company applies for final approval of a new drug. Only then—when there is no longer an opportunity to verify the information—does the company have to describe the way in which the research was conducted, or say whether there was ethics committee approval and informed consent. Furthermore, the FDA rarely conducts on-site inspections abroad. While it conducts very few in the US, there is always the possibility that it will decide to do so. For research done in the third world, the agency simply takes the word of the sponsors of the research.

When research does not require FDA approval, there may be no oversight at all. Companies can conduct preliminary studies of drugs in poor countries before formal testing even begins. Quite literally, the participants in their studies are used as guinea pigs, subjects of research that really should be done on experimental animals. That was the case in le Carré's fictional account. Although some research in the US and other wealthy countries also escapes formal oversight, there are generally more restrictions on what researchers can get away with.

Several real third-world clinical trials were described in detail in a six-part *Washington Post* series in 2000, called "The Body Hunters." One of them has parallels to le Carré's story. In 1996, Nigeria was in the grip of a widespread epidemic of bacterial meningitis, which eventually claimed over 15,000 lives. Pfizer,

the world's biggest drug company, was at that time conducting the largest research program it had ever undertaken to get FDA approval for a new antibiotic called Trovan. Eventually the drug was tested on 13,000 people in twenty-seven countries. When one of Pfizer's doctors heard about the epidemic in Nigeria, he immediately got approval from Nigerian authorities to bring a team to Kano, a city of two million people in northern Nigeria, to test Trovan in children with meningitis. The aim was to demonstrate that oral Trovan would work as well in these children as an established fast-acting intravenous antibiotic.

Within six weeks, the Pfizer team had set up its program in the squalid Kano Infectious Diseases Hospital at the center of the epidemic. A local doctor was named as principal investigator, and the team rapidly enrolled two hundred children for the study. Half were given Trovan, many of them in pill or drink form. The other half were given injections of ceftriaxone, an antibiotic known to be effective against epidemic meningitis. Two weeks later, at the end of the trial, an equal number of children had died in both groups. The new drug was apparently just as effective as the old one, and it could be given in oral form. On that basis, Pfizer applied to the FDA for approval to market oral Trovan for use in children with meningitis.

Those are the bare outlines of what happened. But critics such as Médecins Sans Frontières, the Nobel Prize– winning international medical relief organization, charge that this was exactly the sort of study that would not have been permitted in the Uni-ted States. To these critics, it was unethical to test an experimental drug orally in the midst of an epidemic. The usual treatment for meningitis in such urgent conditions would be intravenous antibiotics. In fact, the Pfizer doctor who organized the study told *The Washington Post* that antibiotics "would never be used like that in the United States. The standard is IV therapy." It was also charged that there had not been adequate preliminary research into how Trovan is absorbed and metabolized by children or how effective it is against meningitis.

Furthermore, to lessen the pain of injections, the dose of intravenous ceftriaxone given for comparison was much smaller than originally planned. But if the dose of the comparison drug were inadequate, that would make Trovan look better than if it were compared with a full dose of ceftriaxone. Pfizer maintained that the smaller dose was still more than sufficient, but the medical director of Hoffmann-La Roche, the manufacturer of ceftriaxone, was quoted as saying, "A high dose is essential."

Questions were also raised about whether the subjects had given informed consent and whether an ethics committee had approved the trial. The families did not sign informed consent documents, but the company maintained they had consented orally. However, some doctors and family members disputed this. A laboratory technician in Kano said, "The patients did not know if it was research or not. They just knew they were sick."

Even more troubling was the issue of ethics committee approval. A Pfizer spokeswoman told *The Washington Post* that the research had been approved by a Nigerian ethics board. But a month later, the *Post* found that the lead Nigerian researcher admitted to creating and backdating the approval document. According to the *Post*, the document was typed on the letterhead of the Aminu Kano Teaching Hospital and dated March 28, 1996 (six days before the trial began), but the researcher said that he actually wrote it about a year later. Pfizer reportedly gave the document to the FDA in 1997 during an audit of records supporting its application for approval of Trovan. The hospital's medical director told the *Post* the document was "a lie." In fact, he said, the hospital didn't even have an ethics board at the time the trial was done.

In 1997, Trovan was approved by the FDA to treat certain infections, but not for children and not for epidemic meningi-tis. The FDA found dozens of discrepancies in the documents from Nigeria. Trovan quickly became a highly profitable antibiotic widely used against a variety of infections. However, after less than two years on the market, there were over a hundred reports that the drug produced liver toxicity, causing several deaths, and it is no longer sold.

In 2001, the families of thirty Nigerian children who either died or suffered serious injury in the Kano trial filed suit against Pfizer in a New York federal district court. They alleged that the company increased the risk of death and injury by failing to provide a treatment of proven efficacy for children who did not respond to Trovan and by giving the patients used for comparison a weakened version of ceftriaxone. They also complained that they had not given informed consent. According to the complaint,

> Pfizer took the opportunity presented by the chaos caused by the civil and medical crises in Kano to accomplish what the company could not do elsewhere—to quickly conduct on young children a test of a potentially dangerous antibiotic.

During the following four years, Pfizer argued that the case should not be heard in a US court at all. In August of this year, Southern District of New York Judge William H. Pauley III agreed, ruling that Nigeria, not the US, was the proper place to try a lawsuit over Pfizer's conduct of the Trovan trial. The families plan to appeal.

Drug companies are not the only sponsors of research in the third world that wouldn't be allowed at home. In the 1990s, two government agencies, the National Institutes of Health (NIH) and the Centers for Disease Control (CDC), sponsored some nine clinical trials in the third world in which thousands of HIV-infected pregnant women under study were given a placebo (or sugar pill) instead of the drug AZT, even though the latter had been shown to cut by 70 percent the risk of transmission of HIV/AIDS from mother to infant. The aim of the studies was to see whether a shorter, simpler course of treatment might be as effective. The standard course required taking oral AZT for the last trimester of pregnancy, an intravenous infusion of the drug during labor and delivery, and oral treatment of the newborn for six weeks. There was preliminary evidence that oral treatment limited to the last few weeks of pregnancy and the first few days of the newborn's life might also be effective.

But instead of comparing the transmission rate in women who received an experimental short course of treatment with that in women receiving the standard course, the researchers compared it with the transmission rate in women who received only a placebo—thus consigning many babies in their care to be born with HIV/AIDS that could have been prevented. This was justified as being the fastest way to show whether a short course was reasonably effective, but designing the trials in that way certainly wasn't scientifically necessary, and, in any case, it would never have been permitted in the US.

In 1997, in an article in *The New England Journal of Medicine*, Peter Lurie and Sidney M. Wolfe of Public Citizen's Health Research Group protested that the trials should have compared short courses of treatment with the standard long one, not a placebo.[2] As executive editor of the *Journal*, I wrote an accompanying editorial in support of their view ("The Ethics of Clinical Research in the Third World"). The public reaction was intense. Many in the US research establishment, including the directors of the NIH and CDC, vigorously defended the trials, pointing out that the women denied AZT probably wouldn't have been able to obtain it where they lived anyway. But that argument, which was meant to mitigate criticism of the trials, simply underscored the fact that the NIH and CDC were willing to take advantage of the women's poverty and vulnerability. The researchers could easily have supplied the drug to all the women they enrolled (and for whom they thereby assumed responsibility), even if it wasn't widely available in the region.[3]

Some writers who comment on medical ethics are not so much concerned with the design and conduct of particular trials in the third world as with the legitimacy of carrying on research there in the first place. They believe it is virtually impossible to conduct medical research ethically in poor countries, because it is inherently exploitative. Although this seems to me too broad a judgment, I believe the amount of research sponsored by the first world in the third world should be sharply curtailed. It is driven too much by the search for profits. It offers quick answers precisely because it is so easy to cut corners.

Before a study is exported to the third world, two important questions should be asked. First, would it be possible to do the research in the first world? And second, why is it being diverted to poor countries? It is sometimes claimed that research should be done where health needs are greatest—and that is certainly the case in the third world. But this view confuses research with treatment. There is a great need to apply the *results* of research, wherever it is conducted, to the treatment of people in the third world. Unfortunately, that is not what happens. Research findings are applied predominantly in well-to-do countries even when the research is done in poor ones. The only clinical research that clearly needs to be conducted in the third world is research on third-world diseases. Such work is amply justified, and far more of it is needed. Unfortunately, it is not a high priority either for the pharmaceutical industry or the National Institutes of Health.

In my view, research should not be done in the third world unless it concerns diseases that are virtually confined to those regions. And regulations governing research in poor countries should be every bit as stringent—and enforced just as vigilantly—as in well-to-do countries. There is no justification for the present situation in which the standards are looser precisely where human subjects are most vulnerable.

Before research on human subjects is undertaken anywhere in the world, there should be adequate animal studies and preliminary tests on normal subjects to eliminate all unnecessary risks. Consent should be truly informed, and there should be no penalties for refusing to participate or undue inducements to do so. It is not enough to claim that informed consent was oral. It should be documented. If there is any doubt about whether the information given to subjects was understood, subjects should be asked to repeat their understanding of the research. To be on the safe side, that conversation and their consent could be videotaped. Companies should no longer be allowed to conduct research in the third world that they would not be permitted to do at home.

Le Carré seems bleak about the chances of any such reform. At the end of the novel, both Quayles are dead, no one is called to account, and KVH and all the people who serve its interests in and out of government presumably continue undeterred. The film, however, adds a Hollywood-style hint of justice to come. At Justin's funeral in London, Tessa's cousin, in whom she had confided, reveals in a eulogy for the couple just why they were killed. Reporters scribble in their notebooks and race for phones, while Sir Bernard Pellegrin, the unctuous and complicit director of affairs for Africa of the British Foreign Office, looks increasingly uneasy and finally flees in consternation. In adding this unlikely scene, the film writers did a disservice to le Carré's book, but that is a small fault. The larger one is in not making it clear, as le Carré did so well, exactly what Tessa Quayle was unhappy about.

Notes

[1] Random House, 2004; see also my essay "The Truth About the Drug Companies," *The New York Review*, July 15, 2004.

[2] "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *The New England Journal of Medicine*, September 18, 1997.

[3] This controversy was discussed in detail in David Rothman's "The Shame of Medical Research," *The New York Review*, November 30, 2000.