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Chapter 05: Therapeutic areas: strategically important diseases of the future

Diverging views of society & industry
There are a few especially important diseases and therapeutic areas from the viewpoint of society, as well as from the viewpoint of the industry. These are especially important because these diseases affect a very large number of patients, have high prevalence, and thus, they affect the economic output of society and the distribution of expenditures within healthcare and, in a broader sense, within the whole society.

Some of these diseases are able to disrupt the workings of our society. Most countries recognize that epidemics are politically and legally highly destabilizing and cause huge economic losses. Even before modern globalization brought enormous and rapid flows of goods and people from all corners of the world together, epidemics of the plague, cholera, polio, and so forth showed the difficulties in isolating microbes, stopping outbreaks, and halting the spread of disease. Recently avian influenza (bird flu), severe acute respiratory syndrome (SARS), and the fights to restrict methicillin-resistant Staphylococcus aureus, and multidrug-resistant tuberculosis (MDR-TB), have confirmed modern vulnerability to outbreaks. The response to microbial epidemics needs to transcend national borders and ignore differences in the payer systems of national healthcare. This is clearly recognized, with the cooperation within the World Health Organization, with the setting up and use of the Global Fund, but it is not sufficient just to share diagnostics and epidemiological data: we need vaccines and drugs developed for the whole world. Even with multinational cooperation, friendly countries such as the UK and the United States can be enveloped in arguments about delivery of paid-for flu vaccines.

76 The Global Fund to Fight AIDS, Tuberculosis, and Malaria.
Two large epidemics are slowly encompassing the whole world, not only Africa: obesity/type 2 diabetes and Alzheimer’s disease (AD). These epidemics threaten abrupt and almost unstoppable reorganization of the economy and societal structures unless we bring them under medical and pharmacological control. The obesity/diabetes epidemic is going to affect countries like China and India dramatically, while countries with an aging population like Japan, Germany, and the UK will be hit by the consequences of AD the hardest. Models of the consequences show that up to 15% of the work force will be involved in the 24/7 care of AD patients. These trends should be shaking governments into action.

The health economics that deal with the economic effects of disease burden and the effects of healthcare cost in society is, together with the study of public health, becoming increasingly important in political discourse in all countries; there are superb books on the topic from different political viewpoints. We will only deal with aspects of these important branches of the economy and of medicine that affect the choices of pharmaceutical companies.

Companies try to look forward 10-12 years and to foresee not only the biology and epidemiology, but also the economic and political landscape at the time when any new drug would enter clinical practice, would be paid for, and should start to produce revenue.

The development of drugs to prevent, or at least to treat, these strategically important diseases constitutes from society’s view the most important task for the industry, yet today in all countries’ pharmaceutical industry even vaccine production is in strictly private hands and the decisions are privately made. Governmental organizations weigh in on the safety of what is produced and, in cases of vaccines (and insulin and antipsychotics), about who should pay for the goods if proven safe and effective. Governments, by recognizing the societal importance of vaccine development and vaccination programs, have also influenced outcomes by limiting the liabilities of the private vaccine producers. Active involvement of nongovernmental organizations (NGOs) and governments
in what drugs to develop is restricted to the trickle of funds devoted as charity to organizations working on diseases predominantly afflicting poor populations, such as malaria, leishmaniasis, sleeping sickness, and MDR-TB, which is now shared by all of Asia and prevalent in countries like Russia, China, and India.

The drugs that will treat these large diseases also potentially represent the largest incomes. Yet, because some of the diseases represent large drug development risks, even over the unusually high risk the whole industry carries, the big companies are abandoning work in some of these disease areas. The declining interest in AD and pain are examples. This does not bode well for our society.

The understanding and willingness of governments to step in as a partner and financier or limiter of liabilities is not apparent when it comes to the several large and potentially very profitable diseases we are discussing. Governments have always been involved as regulators and distributors, and have previously been involved in the development of some pediatric vaccines and drugs, for example, to control outbreaks or treat epidemics of infectious diseases. These increasingly neglected diseases are just as important for our society as are the infectious diseases.

The human & economic cost of major diseases

Among these large strategically important therapeutic areas/diseases that affect very large numbers of patients and have large human and economic costs are the following:

1. New antibiotics, especially for treatment-resistant *Pseudomonas*, *Staphylococcus*, and tuberculosis
2. AD
3. Obesity and type 2 diabetes, and associated kidney and retinal complications
4. Neuropathic pain
5. Schizophrenia
6. Ovarian, prostate, lung, and gastric cancer, and glioblastoma
7. Hundreds of neurological diseases that collectively affect approximately 10 million patients, that are chronic, and where the scientific understanding of the pathophysiology is good but the market size is judged by the industry’s present standards as too small.

Data are available in widespread sources for the estimated economic costs of these diseases. For example, the American Diabetes Association published these data in 2008:

*The total estimated cost of diabetes in 2007 is $174 billion, including $116 billion in excess medical expenditures and $58 billion in reduced national productivity. Medical costs attributed to diabetes include $27 billion for care to directly treat diabetes, $58 billion to treat the portion of diabetes-related chronic complications that are attributed to diabetes, and $31 billion in excess general medical costs.*

Table 4.1 and Figure 4.3 describe the gap between the number of pharma-supported projects and the existing medical need. The list above is just a summary of the position in 2012. Most diseases are under-researched. Even though research is broad for many, it is just that it is not proportional to the need.

Of the diseases listed, only type 2 diabetes is being adequately addressed by resources of the industry. For the rest, we are not doing very well. While progress in the treatment of cancers, especially leukemias and breast cancer and in the past 2 years melanoma and non-small cell lung cancer, has been substantial, it is thanks to government-funded basic research since the 1960s. Because of this large long-term investment, scientists are aware of many drug targets and thus the industry, which largely dropped its own basic research by the end of the 1990s, makes steady progress.

77 American Diabetes Association (2008) Economic costs of diabetes in the U.S. in 2007. *Diabetes Care.* Mar; 31(3):596-615.
78 See Figure 4.2.
Each of these areas will be discussed in purely economic terms because, along with having disease-specific aspects, they also provide some very general points of view about the development of pharmaceuticals, about the interplay between government and private industry, and about the importance of government investment in basic research when industry does not want to or cannot anymore afford it.

**AD: the most loomingly threatening disease**
The most important example is AD. This neurodegenerative disease, which leads to cognitive decline, loss of memory, and inability to recognize faces or names, is, in short, one of the most horrible diseases in many senses. Many argue that all our humanity depends on our memories, and our memories determine who we are. When we lose these we are losing ourselves.

Although Alois Alzheimer diagnosed the first patient more than 100 years ago, AD has not been an important issue of research or of healthcare discussions, and certainly was not discussed in terms of a major threat to society as it is recognized today. The reason for this is that the major risk factor for AD is age. When the average life span of the population was 50-60 years, the frequency of AD was relatively low. Since definitive diagnosis still requires postmortem neuropathological examination of the brain, not many cases were identified. In contrast, the prediction for the United States is that in 2030 every second person aged 80 or above will have AD. The proportion of these people in Japan and the whole Western world is rapidly increasing.

What it really means is that up to 10% or more of the 2030 population in Japan, North America, and Europe may suffer from AD, and this is now being modeled by think tanks and insurers everywhere. Taking care of an Alzheimer patient, if they are taken care of individually, requires three full-time working persons each working 8 hours per day. This translates to a very large proportion of the productive labor force being devoted to taking care of patients with advanced AD, who cannot themselves be relied upon for the most elementary of functions. This is only the economic
The societal implication is huge; there is currently a shortage of caregivers.\textsuperscript{79} The 2011 estimate is that $600 billion is being spent on taking care of AD patients. Yet there is no drug available that prevents or cures the disease, or even significantly modifies the rate of progression of the disease. The only drugs today approved are giving a relatively small—although in large trials statistically significant—slowing of the loss of cognitive function in mild to moderate AD and in one case are approved to treat moderate to severe AD. Memantine (Namenda from Forest Laboratories) is a 30-year-old German drug (from Merz) originally used for neuropathic pain treatment. It produces very small changes in the rate of decline in already seriously demented patients. It is liked because of its relative safety, not its efficacy. The total number of approved, available drugs is five and none of them can be used to prevent, cure, or even significantly slow the progression of this disease.

The number of diagnosed Alzheimer patients in 2011 in the United States was 5.3 million, and a similar number applies to Western Europe, but, including the nondiagnosed patients, the total is estimated at some 30\% higher. Where do we stand with the development of drugs to be used in the therapy of AD patients? The scientific background is such that in this disease there are both sporadic forms, accounting for 99.8\% of cases, and clear familial (or inherited) forms, which is to say, cases that have an early onset of disease at about 40 to 45 years based on a genetic predisposition; these account for 0.2\% of cases. There are several other genetic vulnerabilities identified. A very frequently occurring vulnerability is being a carrier of a protein isoform called ApoE4. One can carry two of these gene copies when one is homozygotic. One can carry one ApoE4 and one ApoE3, which is more common in the population, when one is heterozygotic. But, the vulnerability for AD is significantly higher in the ApoE4 homozygotes, who make up 2\% of the U.S. population.\textsuperscript{80}

\textsuperscript{79} See also Chapter 11.

\textsuperscript{80} See also Chapter 09.
Incidentally, in 2007-2008, the first two full-genome sequences of notable individuals were published: those of Craig Venter,81 who published “The Sequence of the Human Genome”82 coincidently with the Human Genome Project’s parallel study,83 and Jim Watson,84 the co-discoverer of double helix.85 In the first case, Venter’s sequence showed increased risk of AD86 and in the second case the ApoE3/4 encoding sequence was omitted from Watson’s data at the specific request of Dr. Watson. He did not want to know if he were susceptible to an incurable disease to which a grandmother had succumbed.87 Interestingly, the cost of the Human Genome Project was $3 billion over 13 years, Venter’s sequence cost some $100 million, and Watson’s was variously reported at $1-2 million in 2-4 months.88 The costs are dropping in a dramatic manner: Complete Genomics, Life Technologies, and Illumina have disclosed that from January 2012 they will provide a full genome sequence for anyone for $1,000. We have yet to start a discussion about what cognitively happens to individuals carrying both the ApoE3 and ApoE4 genes—one from each parent—as their age increases.

There are more serious, but luckily less frequent, genetic causes of AD, such as the “Swedish” and “Dutch” mutations in the amyloid precursor protein. These mutations and mutations in another associated protein, presenilin, and a combination of these mutations lead, in a small group of people, to very early onset (about 40 years of age) rapid progression AD. These patients, who will have “familial forms of AD,” make up a small

81 Levy S et al. (2007) The diploid genome sequence of an individual human. PLoS Biol. Sep 4; 5(10):e254.
82 Venter JC et al. (2001) The sequence of the human genome. Science. Feb 16; 291(5507):1304-1351.
83 International Human Genome Sequencing Consortium; Lander, ES et al. (2001) Initial sequencing and analysis of the human genome. Nature. Feb 15; 409(6822):860-921.
84 Wheeler DA et al. (2008) The complete genome of an individual by massively parallel DNA sequencing. Nature. Apr 17; 452(7189):872-876.
85 Watson JD and Crick FHC (1953) A structure for deoxyribose nucleic acid. Nature. Apr 25; 171, 737-738.
86 In addition to antisocial behavior, cardiovascular disease, and wet ear wax (see http://en.wikipedia.org/wiki/Craig_Venter).
87 See http://www.nature.com/news/2007/070528/full/news070528-10.html
88 See http://www.nature.com/news/2008/080416/full/452788b.html
portion, 0.1–0.2%, of all AD patients. Most of the AD patients endure the sporadic form, yet the discovery of patients with familial AD suggests the possibility of highly focused trials for AD preventive medicines in a group whose risk is very high. Almost 100% will develop the disease unless we succeed in finding a preventive therapy.

It is worth explaining that in diseases where there is a large sporadic group of patients yet a small “familial group” or “genetically determined group” the understanding of the familial forms had great importance, in almost all cases, for finding treatments for the sporadic cases. This is because when people with familial disease are treated, we are fairly sure of the causative mechanism. It may be compared to the increasing introduction of companion diagnostics in oncology: treating those who have a genetic cause of the tumor improves responder rates from 5% to over 60%. Yet we have great difficulties in finding any (preventive AD) trials involving family members of patients who have or have died from familial AD. The patient associations that “organize” these individuals have good lists of who would be eligible, but basic research and pharma have failed these people and missed this opportunity for two reasons. One is pure greed: “Why wait 4–5 years to show in familial cases that a therapy works, and then do another 4-5-year study in the real market representing sporadic patients?” goes the argument. It is added that “it is hard to recruit for familial case clinical trial,” which does not seem to be true, or it has to do with the second factor: the drugs we so far have put into trial are associated with such bad side effects that it is hard to convince people presently fully healthy, even if they know that they are likely to have early AD, to endure the side effects for an uncertain delay of the onset or for the prevention of the disease. We need to improve science and pharmacy, and we need governments, not NGOs, to pay for the more focused trials.90

89 See Chapter 08.
90 See also Chapter 11, where we may reveal that our argument is vindicated: one trial, designed in the way we recommend, is now being conducted. For those readers who wish to “fast forward” you should look, for example, at http://www.multivu.com/mnr/56128-banner-alzheimer-s-institute-genentech-nih-prevention-trial-genetics
It is important that in the new healthcare legislation in the United States, upheld by the Supreme Court in June 2012, one cannot be excluded or penalized for a pre-existing condition or a genetic predisposition. This will become more and more important, especially as genome sequences are becoming affordable as part of diagnostics, not just as a research tool.

In general, the presence of genetic forms of the disease accelerates the understanding of the disease and indirectly accelerates the development of drugs to treat the disease. This is also the case with AD. The early onset disease has been linked to mutations in the metabolism of the amyloid precursor protein leading to the appearance of amyloid plaques. These are amorphous aggregates formed from several proteins. The major component is a fragment of the amyloid precursor protein. Research directed toward the proteolytic enzymes that produce this fragment of amyloid protein, the amyloid beta (or Aβ or Abeta) peptide, led to an investigation to dismantle the plaques formed from this peptide. The last 15 years have seen a tremendous effort by the industry to develop inhibitors for the two major APP-hydrolyzing proteases. Beta-secretase and gamma-secretase produce the amyloidogenic Abeta 1-40 or 1-42 peptides, but, so far, no peptidase inhibitor has reached clinical use. A gamma-secretase inhibitor (semagacestat or LY450139) from Lilly came closest; it reached phase 3 trials and then was withdrawn in 2010 because of toxicities. This additionally shook the confidence of large pharma in Alzheimer therapies.91 It is worth examining which companies try to develop AD drugs, the intensity of their effort, and the major issues that affect the intellectual and economic investment in the development of Alzheimer drugs.

**Early diagnostic imperatives**

The start of each treatment is diagnosis of the disease. Today, AD diagnosis heavily relies on neuropsychology test batteries, which have

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91 Confidence has not been improved by the poor results from Lilly’s therapeutic antibody trial of solanezumab (see Chapter 06).
become better and better. They are now able to detect mild cognitive impairments and early AD. But nobody really knows how much damage has already occurred in the brain when cognitive impairment becomes obvious to relatives, friends, and colleagues. It is, therefore, very important that 2011 has seen the clinical entry of several imaging agents. When working well, these permit the visualization of amyloid plaques in the living brain, and might, therefore, be important in establishing whether a drug aimed at inhibiting the production of amyloid peptide is really successful in reducing the plaque load. It is, however, evident that nobody is bothered by carrying amyloid plaques. When it is conclusively shown that the amyloid plaque load predicts cognitive impairment, we will then be able to convince people who exhibit no cognitive evidence of AD to take drugs that prevent the formation of amyloid peptide and amyloid plaques. But then these drugs will have to be very, very “clean” with no or a very low incidence of serious side effects or even annoying side effects.

If we had succeeded in producing a drug candidate with a strong scientific rationale suggesting it would prevent AD, without major and minor side effects, then which people would be convinced to take it? Firstly, those with a very high risk of developing familial AD would take it, preferably before showing any symptoms. Later, those who, through aging and some first signs of mild cognitive impairment, appear to have the risk of developing AD in a few years would take it. Some of these candidates would have to be prepared to test this drug in trials that will take 3-5 years. The principle is very similar to the way we have convinced millions and millions of people to take the cholesterol-lowering statins. High cholesterol per se is not a disease, but it is a harbinger of many cardiovascular diseases. If amyloid peptide and amyloid plaques can be detected and shown more rigorously to be a harbinger of AD, then volunteers would be easier to find. But for this to happen one will need much cleaner and much safer Alzheimer drugs than those we presently have.

92 The approval for the imaging agent florbetapir (Amyvid) to image amyloid plaques from Avid-Lilly was, however, delayed over procedures of evaluation.
Based on earlier neuropsychological diagnosis, patients are selected for the clinical trials of proposed Alzheimer drugs. These trials are becoming longer and longer. The reason for this is that we are entering into these trials based on the success of neuropsychological assessment that now captures early Alzheimer patients, in ever milder forms of the disease.

The first Alzheimer drug clinical trials in moderate to severe patients could show that the first class of drugs, the acetylcholine esterase inhibitors (AChEIs), could slow the decline of cognitive abilities significantly after a 6-12 month treatment (trial) period. The latest trials with AChEIs have, however, taken 18 months to show a significant difference in cognitive decline between drug-treated and placebo patients. The milder, and earlier the AD cases enrolled into the trials, the longer we have to dose the drug to show a significant difference in the cognitive performance between drug-treated and placebo patients. This is a clear recognition by pharma that, in order to show efficacy, they will need longer trials. These are a major expenditure, but, more importantly, the results are further and further away from what affects the stock price in the 2-3-year period upon which present pharma executives focus or are obliged to focus.

Another issue regarding Alzheimer patients and clinical trials is that the average age of these persons is above 65 and they suffer from a great number of other diseases, for which they are also being treated. This means that the drugs to be used in Alzheimer therapy have to be devoid of interactions with a very, very large number of drugs. It also means that because of age and other diseases, a relatively large number of these people will drop out of the trial or may die during the 18- or 24-month length of the trial. This means that these trials, at least at phase 3, will have to be very long and very large. The industry has conducted such long and large trials in cardiovascular disease and in type 2 diabetes. However, most large and long trials—usually post marketing, i.e., post approval, phase 4 trials—are carried out by governmental agencies in the UK, United States, and so forth. But the repeated failure of Alzheimer drugs over the last 10 years is making more and more companies silently withdraw from
the effort to develop therapeutic agents for the treatment of AD, which would slow disease progression, prevent the disease, or cure the disease. This is understandable from the point of view of profit within organizations, but it is not acceptable for our society. As we recognize AD as a serious risk for our society, we cannot afford to give up trying to make drugs that achieve effective treatment. Today, there are no seriously capable organizations except the pharma industry to develop such a drug. So, when they withdraw, openly or silently, and are permitted so to do, we will end up with the horrific prospect of every second over 80-year-old citizen suffering from AD, but not being offered any kind of treatment that would help the patient, the family, and society as a whole.

Translational research
When we say that the only seriously capable complex, sophisticated large organizations to develop therapeutics are the pharmaceutical companies, we are not disregarding the expensive efforts government-supported institutions, such as the National Institutes of Health (NIH) and corresponding European institutions, put into what they call translational research, that is, research that is directed toward affecting medical practice.

Translational research, which is the modern equivalent of applied research, is an increasingly important part of their task. However, in retrospect, one can today clearly state that these organizations have not discovered any major drugs in the past 40 years. They have, during these last 40 years, been the major contributors to the basic science breakthroughs that are the scientific basis of drug development in the world’s private pharmaceutical companies, which all abandoned in-house basic research from 1980 to 2000. The government-sponsored research institutions, together with some major NGO-sponsored research entities (e.g., the Wellcome Trust, the Howard Hughes Medical Institute, and the Bill and Melinda Gates Foundation), have introduced a multitude of extremely important tools to preclinical and clinical research. These permit the regulatory agencies and the industry to measure and improve
the success of drug discovery, drug development, and the drug approval processes. Starting in 2012 the NIH collaborated officially with the Food and Drug Administration (FDA); in principle they are both government sponsored. This will assist the FDA, which has so far relied on ad hoc panels of academics for scientific advice, to lean more on scientists in government pay. NIH scientists have a much stronger set of rules to keep them from receiving payments from the industries that apply for drug approval. This will help dilute the requirement of Congressional Committees periodically to uncover high-profile examples of the FDA receiving advice from academics with a conflict of interest. Conflict of interest is a serious matter that can undermine all public trust in the impartiality of FDA decisions regarding drug approvals, no matter if the decision itself was impartial.

Thus, the recent, long-awaited official agreement, pushed by the Obama Administration, to improve the quality and image of FDA decisions by having two U.S. tax-payer financed organizations, the NIH and the FDA, sharing scientific competence, bodes well. The NIH is the world’s powerhouse for preclinical discoveries through its intramural and extramural programs, and it is important in academic medicine in small proof-of-concept trials; however, as a clinical research organization, it is small to medium sized. The roughly $5 billion spent by the NIH on clinical projects and the $700 million proposed for translational research in 2011-2012 is dwarfed by the estimated $92 billion research budgets of major pharma and major biotech spent in the same year on R&D, over 85% of which is translational research (see Tables 5.1 and 5.2). The effort is also dwarfed by the collective experience that exists in these companies in the development and testing of clinically useful drugs.

It is clear that the NIH and its international counterparts bear huge responsibility for the “real” science in AD. When one compares funds poured into HIV/AIDS and cancer research to those put into AD, one is shocked. It is clear that funding initiatives can bring large numbers of scientists to work on a problem, and that it is what we badly need. Instead, AD research is conducted by a small club; this we cannot afford.
Therefore, it is not a promising route to let private industry back out of trying to develop Alzheimer drugs, saying: “it’s too hard; it’s too risky; it’s too slow; it’s too expensive,” and assume that governments will step in to the vacancy. There has to be a serious effort to find a formula by which governments, gently or not so gently, force the industry to continue its effort in developing Alzheimer drugs. Intervention can come from tax breaks or other incentives, as well as somewhat punitive legislation for pharma to release data from programs they have dropped, in order to support this highly risky activity because it is so important. We have seen how U.S. and other governments can enhance and semi-force the development and production of antidotes

Table 5.1: Top 15 R&D budgets of the major pharma companies in 2009

| No. | Company                | Budget   |
|-----|------------------------|----------|
| 1   | Roche                  | $8.7B    |
| 2   | Pfizer                 | $7.40B   |
| 3   | Novartis               | $7.06B   |
| 4   | Johnson & Johnson (J&J)| $6.66B   |
| 5   | Sanofi-Aventis         | $6.25B   |
| 6   | GlaxoSmithKline (GSK)  | $5.59B   |
| 7   | Merck                  | $5.58B   |
| 8   | Takeda Pharmaceuticals  | $4.64B   |
| 9   | AstraZeneca            | $4.23B   |
| 10  | Eli Lilly              | $4.13B   |
| 11  | Bristol-Myers Squibb (BMS) | $3.48B |
| 12  | Boehringer Ingelheim   | $3.03B   |
| 13  | Abbott Laboratories    | $2.61B   |
| 14  | Daiichi Sankyo         | $1.89B   |
| 15  | Astellas Pharma        | $1.63B   |

Total $72.88B

1 See also Figures 4.2 and 7.1.
Therapeutic areas: strategically important diseases of the future

to biological weapons, and how it can incentivize and encourage the production of vaccines.

AD is not as acute as bird flu or the risk of a bioterrorist attack, but it is as, or more, threatening for the individual and for our society.

Obesity & type 2 diabetes
The first biological to be used on a large scale was insulin, albeit preceded by some vaccines and antidotes to snake toxins, and so forth. The first clinical trial of insulin involved one patient: a child. We often forget this. As discussed earlier, production of insulin is now made with recombinant technology in bacteria or yeast. The three major producers, Novo Nordisk, Lilly, and Sanofi-Aventis, are producing both acutely active and delayed, slowly, or long-acting depot or retard insulin preparations.

One may think that insulin-dependent diabetes is, therefore, a well-treated disease and needs no further diagnostic and drug development efforts. This could not be further from the truth: up to 30% of patients are resistant to the most widely prescribed diabetes drug, metformin

| Rank | Company             | Budget  |
|------|---------------------|---------|
| 1    | Amgen               | $2.72B  |
| 2    | Biogen Idec        | $1.2B   |
| 3    | Gilead Sciences     | $849M   |
| 4    | Genzyme             | $805M   |
| 5    | Celgene             | $745M   |
| 6    | Kyowa Hakko Kirin  | $478M   |
| 7    | Vertex Pharmaceuticals | $454M | |
| 8    | Life Technologies  | $320M   |
| 9    | CSL                 | $267M   |
| 10   | Amylin Pharmaceuticals | $172M |
| 11   | Genmab              | $123M   |
| 12   | Cubist Pharmaceuticals | $119M |
| 13   | Merial Animal Health | $115M |
| 14   | MannKind            | $109M   |
| 15   | Abraxis Biosciences | $107M   |
|      | Total               | $8.58B  |

Table 5.2: Top 15 R&D budgets of the major biotech companies in 2009
Around 80-90% of biotech budgets ($6.9B from the above) is allocated to translational research.

1 Originally Commonwealth Serum Laboratories.
(see below); most patients are becoming increasingly resistant to insulin; and we have ongoing exacerbations with the patients who are not becoming resistant to either of these two drugs.

Even with well-controlled diabetic patients who, by judicious use of insulin, do not let their blood glucose rise, the development of renal illness, blindness resulting from retinal vascularization problems, diabetes-induced neuropathies, and pain in the extremities is very high. On top of this comes the world’s increasing obesity, the most obvious risk factor for type 2 diabetes. Thanks to a rising standard of living and global flows of food staples, fewer and fewer people in the world are starving, or, rather, more and more people are not starving. Obesity growth is linked with the change of diet in Asia. In India and China, where more bountiful food, coupled with wealth, is added to some genetic predisposition in these two huge countries, there has been a dramatic increase in obesity and in type 2 diabetes. It should be noted that not all obese people will develop type 2 diabetes, only about 20% do, but the cost of treatment for these people and the cost of treatment of the complications from diabetes is staggering and comparable to that of AD.

It is clear that it is in the interest of patients, society, and the pharmaceutical industry to find drugs that prevent the rapid increase in the number of obese people and, therefore, reduce the risk that 20% of these will develop type 2 diabetes. It is also clear that we have to develop better treatments for this very large group, which is estimated to include close to 300 million people by 2030, all of whom will have type 2 diabetes. Unfortunately, it is very difficult to develop safe drugs that prevent or cure obesity when the patients are unwilling or unable to switch diet and to exercise. Diet control and exercise are both becoming increasingly difficult in the stressful world of rising standards and rising expectations of work and other achievements.

The pharmaceutical industry has seen some spectacular successes in this area. Unfortunately, these then turned into spectacular failures, sometimes taking with them the entire company, no matter how big it was. Most in the industry clearly remember the successful development
of Fen-Phen (fenfluramine + phentermine), a very active (amphetamine-like) mixture of appetite control drugs that has shown clearly visible, tangible results of large rapid weight loss. The beauty of trials on obesity drugs is that the patients can, by checking their waistlines or stepping on to a balance, see for themselves whether the drug is efficacious. The fallacies of these trials are many, however. While it is relatively easy to achieve a 5-10% weight loss in the first 6-8 weeks, it is very hard to keep it over 12 months. This is why the FDA now insists that drugs that might be approved achieve and maintain a 5% or higher weight loss over a 12-month treatment because less than that is not clinically meaningful. Also, drug treatment is not comparable to other ways of achieving dramatic weight loss such as bariatric surgery, itself not without dangers. Surgery is, however, very expensive and not acceptable or appropriate for every patient, but bariatric surgery can produce a 30% or higher weight loss that remains after 12 months.

Fen-Phen had been a spectacular success for the company American Home Products until it turned out that a large number of patients develop valvulopathy—changes in the heart valve—as a result of taking this drug. As this is an irreversible disease state leading to death in many cases, the subsequent lawsuits brought down this very large pharmaceutical conglomerate. History should record that Fen-Phen as a combined drug was never approved by the FDA and was the result of an off-label development at some U.S. academic institutions.

Similar amphetamine-based weight loss drugs by Servier were questioned and were recently withdrawn in France. Other weight-loss drugs have fallen on other safety issues. Some of the few approved and “safe” ones have very unpleasant side effects. For example, orlistat (Xenical) blocks uptake of fat by the intestine, which causes hard to control diarrhea with almost inevitable soiling. Despite this, GlaxoSmithKline entered the generic drug market with orlistat (Alli) as its first generic (see Chapter 04).

The development of weight loss drugs is very attractive but very difficult; the last 3 years have seen the industry bringing forward compounds or combinations of compounds that showed efficacy of 6-
10% weight loss over 12 months, but which contributed to an increase in social isolation, suicidal ideation, and suicides. It forced the FDA to demand that companies specifically examine these side effects, and it finally asked its outside academic-clinical experts whether obesity is such a life-threatening condition that we should permit the taking of drugs that might significantly increase suicidality. The answer was no; we have to be able to find drugs that achieve the same weight loss without these serious side effects.

Other weight loss drugs have shown large increases in blood pressure and heart rate, and were deemed not safe. Presently, the industry is wondering if it is possible to make a truly safe obesity drug, while several biotechs are hampered by their financial inability to afford the long cardiovascular safety study rightly requested by the FDA.

But, unlike in the case of AD, the industry is not abandoning the area because it seems that the development of these drugs is easier in the sense that the scientific basis to fight obesity is better understood, and that the chance of proving that one has an efficacious safe drug is better than achieving the same in AD. In particular, the efficacy of the drug is shown and seen by the patients themselves within weeks. The other problem is maintaining this efficacy. It is so clear that there is a great desire in our world to achieve the ideal body weight determined by fashion and by health advisories of a body mass index (BMI) around 22–24. Despite a period of 3 years of efficacious drugs not being approved because they were not safe enough, it is less likely that the industry will abandon its search for obesity drugs.

When it comes to diabetes drugs, we start to recognize that the control of blood glucose can be further improved. The biggest contribution to improved control is not by drugs, but by continuous, daily, or repeated daily self-diagnosis of high blood glucose levels. These levels can be measured at home using the glucose meters developed in the last 30 years, which have become so cheap and reliable that all patients can use them. This so-called point of care device, of which we will see many in other indications, enables patients to control their own therapy, which
in this case is of great importance. The first glucose meter developed by Boehringer Mannheim was as big as a refrigerator and required 2-4 ml blood. Today’s machines use just a drop of blood, are pocket-sized, and, in most countries, given free of charge. This locks the patients into buying the measuring strips, much like Kodak practically gave away the instamatic camera so you would buy its film. That this marketing works shows how widespread self-monitoring of blood glucose has become.

Secondly, we realize that there are drugs like the GLP-1 (glucagon-like peptide-1) analogs and inhibitors of the GLP-1 degrading enzyme DPP-4 (dipeptidyl peptidase-4), which can fine-tune glucose control and will postpone some of the diabetic complications.

The problem for those who are developing diabetes drugs is that we have a very large number of relatively efficacious, cheap, generic drugs such as metformin, which have side effects but work quite well. For the largest number of patients these drugs will remain the mainstay of their diabetes treatment because they are well known and because they are cheap. The new drugs have to demonstrate significant improvements over the presently available insulin releasers, insulin sensitizers, and so on. In this quest for better control of blood glucose, we have also learned metabolic disease patients are accepting of injection, not only of insulin but also of other drugs. This opens the route for the use of biologicals in an area where this was not widely foreseen. Today, the GLP-1 analog exenatide (Amylin/Lilly’s Byetta—a synthetic version of exendin-4) and its competitor liraglutide (Novo Nordisk’s Victoza) are injectable biologicals generating revenues of more than a billion dollars each per annum. Together with insulin, we have now accepted in clinical practice other injectables to control blood glucose. In contrast, the inhibitors of DPP-4 are oral drugs: sitagliptin (Merck’s Januvia) and saxagliptin (BMS’s Onglyza).

93 Metformin has had a long history. First synthesized in 1920, then trialled by a French physician in 1957, it was introduced in the UK in 1958 but not until 1995 in the United States. In 2010, 48 million generic prescriptions were filled. See http://en.wikipedia.org/wiki/Metformin.
In summary, it has to be said that the impact of the fight against obesity as a major risk factor for type 2 diabetes cannot be overstated. The problems of finding efficacious and safe obesity drugs are great, both practically and theoretically, because eating is so deeply and intricately programmed in our brain. So many processes of mental well-being are controlled by parts of the neuronal circuits that control repeated, pleasurable activities such as eating. Nevertheless, it is clear that here the industry continues to stand at the gates of the FDA with new drugs and drug combinations that can achieve significant weight loss.

Surgical versus drug interventions
A comparison of surgical procedures such as bariatric surgery to drug treatment is an important one. Those who work for insurance companies and major health plans calculate the risk–benefit ratios of major surgeries. One often finds that bariatric surgery is only recommended for those who are relatively young and who are enormously difficult to treat with drugs, diet, and exercise. Whether this will change with improvements in surgical procedures or not is hard to foresee. But it is clear that many patients will prefer any available oral or injectable drug if it comes close to the efficacy of the weight loss produced by a surgery where today mortality is over 1%.

Neuropathic pain
Morphine is one of our oldest drugs. The ancient Egyptians called it “God’s own medicine.” This was not because of its marvelous pain-killing properties, but because it effectively stops diarrhea, which is one of the great killers in the world. The existence and knowledge of how to dose morphine and other opiates has been the basis for the effective treatment of pain for a long time. Many thought that opiates could be useful in the treatment of all pain states. Neither the patients nor the anesthesiologists held this view and it is manifestly not the case. There is a very large group of pain syndromes—neuropathic pain resulting from
neuronal injury and cancer pain—which are often not responsive to opiate painkillers. On top of this, opiates have huge safety problems that include constipation, alcohol interaction, and so forth, as well as their well-documented addiction potential. Relieving pain is one of the great dreams and aspirations of mankind. Yet the introduction of new efficacious pain medications is very, very slow. The inadequacy of all pain treatments is best illustrated by the following:

Most clinical trials for pain killers evaluate the efficacy of the medication using a visual analog scale. Patients judge for themselves the intensity of the pain on a linear analogue scale from “0” = no pain to “10” = excruciating pain. The gold standard of non-opiate, non-morphine-type pain drugs is gabapentin. Gabapentin is a more than $2 billion-selling drug that in its clinical trial reduced pain from an average of somewhat above “7” to an average of “4,” not to zero. The FDA suggests that patients may be recruited for pain trials if they assess their own pain to be above “4.” This means that even after having taken the best available drug many patients would still be eligible to enroll in a new trial for a painkiller.

Current practical treatment of pain may use multiple drugs. Physicians and patients learn to use several drugs to achieve some pain relief. The biggest problem is not that our basic pain research is lacking in effort, but that the animal models, in which we try to assess the efficacy of new pain medications, are not very reliable. Therefore, many clinical trials that were initiated after successful animal experiments have failed. There are additional big problems with developing new pain medications. This includes the potential for misuse of painkillers. People take them recreationally rather than because they have pain. Often these drugs, which were made for oral use, are being ground up and injected intravenously when their effect is much faster and much more robust in the brain, sometimes causing deadly accidents. So, whoever tries to introduce a novel serious painkiller has to prove or has to safeguard against abuse potential. This is difficult.
Painkillers are also the most often overdosed drugs. Patients in pain start taking the recommended dose then readily take more or more often when the pain does not abate. Therefore, these drugs have to be very safe even at 5 to 10 times the recommended dose. Another problem of many painkillers is their interaction with alcohol.

Despite these inherent difficulties, we cannot stop trying. In many ways painkiller development is ideal for the pharma companies as the trials are short: dental pain, 72 hours; postoperative pain, 3-7 days; and post-herpetic neuralgic pain, 7-14 days. It is just that what works in all the animal models consistently fails in patients, explaining why the industry has openly stopped trying in some very notable cases. Some of the largest pharmaceutical companies, such as Roche—the most profitable pharma company today—Novartis, Astra-Zeneca, and others, have openly closed their pain research units, saying that it is too difficult. This leaves the field to small companies or to companies such as Merck and Pfizer (previously active in COX-2 inhibitors, see Chapter 03) that are mostly only interested in one type of pain, inflammatory pain, for which we already have relatively good medication, as everybody who has been given ibuprofen by the dentist knows.

Pain is an example of an area of disease where the number of people affected is tremendous. The suffering is chronic. The economic opportunity therefore exists, yet the companies openly withdraw from competing in this area. This is calling for serious governmental entry into the field at the level of both basic and clinical research, which would help to define more valid, more reliable, and more translatable models, so that the existing argument of “whatever works in animals may or may not work in humans, and we will only know it $500 million dollars and 3 years later” will no longer be valid. Directive research by governments could change the situation and would, therefore, change the daily lives of tens of millions of people with chronic pain.

The huge medical need and market opportunity in neuropathic pain is thus dominated by gabapentin, a drug developed as the anti-epileptic Neurontin by Parke-Davis (now Pfizer), which is now more than 18 years
old. It was approved in 1994 and has spawned many generic forms such as Fanatrex, Gabarone, Gralise, Nupentin, and so forth. Those who work in pain clinics are using a mixture of dedicated painkillers, anti-inflammatory drugs, tricyclic antidepressants, and anti-epileptic drugs to treat neuropathic pain, but their success is very limited.

**Cancer**

In the 1970s and 1980s, the 20 large pharma companies, of which today exist less than 10 because of mergers and acquisitions, were not very interested in the area of oncology. The argument was that cancer, leukemias and solid tumors, are often discovered too late to do anything and that many cancers will not be treated easily because breast cancer, prostate cancer, lung cancer, renal carcinoma, pancreatic cancer, and so on, are clearly different diseases of different organs that will require completely different medications; therefore, the market is very fragmented. So, not only are the patients diagnosed late but there are also too few patients for each cancer form, maybe with the exception of some leukemias and lymphomas (see Table 5.3). However, it turns out we knew too little about some of the underlying cellular pathways and that certain controls of the cell division that runs amok in cancer are general in many cell types; thus, there will be carry over from developing a drug for one cancer indication (see the section “Effective governmental & societal intervention”). We were too organ focused, and not focused on cellular pathways.

In any clinical trial, the industry would not want to use, as the comparison, the most commonly used chemotherapy: the cytotoxic agents. These nucleotide analogs are still among the most efficacious cancer drugs, but with terrible side effects like hair loss, nausea, and weight loss. They are still used frequently, and these are drugs that are very cheap to make and very cheap to buy.

Big companies are not leaving the therapeutic area of oncology, although 2010–2011 was full of great disappointments when it came to clinical trials. This has shaken some of the best-selling cancer drugs such as bevacizumab (Roche-Genentech’s Avastin), which has been approved for treatment of
The Future of Drug Discovery

| All invasive cancer sites                  | All    | Males  | Females |
|-------------------------------------------|--------|--------|---------|
| Brain and nervous system                  | 126,000| 67,000 | 60,000  |
| Breast                                   | 2,605,000| 13,000 | 2,592,000|
| Cervix                                   | 247,000| 0      | 247,000 |
| Colon and rectum                         | 1,112,000| 541,000| 572,000 |
| Endometrial cancer and uterine sarcoma    | 575,000| 0      | 575,000 |
| Esophagus                                 | 29,000 | 22,000 | 7,000   |
| Hodgkin's disease                        | 165,000| 85,000 | 80,000  |
| Kidney and renal pelvis                   | 281,000| 165,000| 117,000 |
| Larynx                                   | 90,000 | 72,000 | 18,000  |
| Leukemias                                 | 244,000| 137,000| 107,000 |
| Liver and bile duct                       | 28,000 | 19,000 | 9,000   |
| Lung and bronchus                         | 371,000| 173,000| 198,000 |
| Melanoma of skin                          | 793,000| 385,000| 408,000 |
| Multiple myeloma                          | 62,000 | 34,000 | 28,000  |
| Non-Hodgkin's lymphoma                    | 438,000| 227,000| 211,000 |
| Oral cavity and pharynx                   | 249,000| 161,000| 88,000  |
| Ovary                                     | 177,000| 0      | 177,000 |
| Pancreas                                  | 33,000 | 16,000 | 17,000  |
| Prostate                                  | 2,276,000| 2,276,000| 0     |
| Stomach                                   | 66,000 | 37,000 | 28,000  |
| Testis                                    | 196,000| 196,000| 0      |
| Thyroid                                   | 434,000| 96,000 | 338,000 |
| Urinary bladder                           | 535,000| 395,000| 140,000 |
| Totals                                    | 11,715,000| 5,353,000| 6,361,000|

Table 5.3: Estimated cancer prevalence in the United States in 2007
Data include the 23 most prevalent cancers; totals include other less prevalent cancers, of which there are many.

non-small cell lung carcinoma and for colorectal cancer, but which has failed to show efficacy in breast cancer. This also may be initiating a possible re-evaluation of the original approval in non-small cell carcinoma, thereby endangering one of the best-selling cancer drugs from Roche.
Several of the spectacular clinical trial failures of 2010 were in oncology (Table 5.4), but so were three of the most spectacular successes (Table 5.5). Oncology remains a highly successful area, both medically and economically, for pharmaceutical companies. We also saw the first new therapeutic modalities such as the antibody-drug conjugate (ADC) brentuximab vedotin (Seattle Genetics’ Adcetris), approved in August 2011 for anaplastic large cell lymphoma (ALCL) and Hodgkin’s lymphoma; many others are in trials.

Effective governmental & societal intervention
There are 40 times as many drugs being tested for cancers than for schizophrenia. Why? In short, the explanation is government-sponsored basic research. Today oncology\textsuperscript{94} is the most drug target-rich area, 

\begin{table}
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Drug name} & \textbf{Company} & \textbf{Indication} \\
\hline
Dimebon & Pfizer & Alzheimer’s disease \\
Ocrelizumab & Roche-Genentech Biogen Idec & multiple sclerosis \\
Taspoglutide & Roche & type 2 diabetes \\
Semagacestat & Lilly & Alzheimer’s disease \\
ASA404 & Novartis & lung cancer \\
NOV-002 & Novelos & lung cancer \\
Zibotentan & AstraZeneca & prostate cancer \\
Vicriviroc & Merck & HIV \\
Recentin & AstraZeneca & colon cancer \\
NV1FGF & Sanofi-Aventis & critical limb ischemia \\
\hline
\end{tabular}
\caption{The top 10 phase 3 failures of 2010}
\end{table}

\textsuperscript{1} http://www.fiercebiotech.com/special-reports/top-10-phase-iii-failures-2010

\textsuperscript{94} Perhaps together with inflammation.
whereas large chronic diseases, which affect up to 1-2% of the population over their entire lifetime, like schizophrenia, are extremely poor in drug targets.

| Drug name                  | Company              | Modality                        | Indication                        |
|----------------------------|----------------------|---------------------------------|-----------------------------------|
| carfilzomib (PX-171-007)   | Onyx                 | proteasome inhibitor            | multiple myeloma                  |
| crizotinib (Xalkori)       | Pfizer               | anaplastic lymphoma kinase (ALK) and ROS-1 inhibitor | lung cancer with companion diagnostics |
| vismodegib (Erivedge)      | Roche                | small molecule antagonist        | basal cell carcinoma               |
| vemurafenib (Zelboraf)     | Plexicon-Daiichi (Roche Group) | protein kinase inhibitor       | melanoma with companion diagnostics |
| brentuximab vedotin (Adcetris) | Seattle Genetics | antibody-drug conjugate         | Hodgkin’s lymphoma, anaplastic large cell lymphomas |
| trastuzumab emtansine/(T-DM1) | Roche               | antibody-drug conjugate         | breast cancer                      |

**Table 5.5: Advances in cancer therapies: new approvals 2009-2011**

New drugs, new antibody-drug conjugates, and new orphan drug strategies by both small and large companies; phase 3; and approvals in 2009-2011. It is important to note three trends in this table: (1) companion diagnostics appearing and improving responder rate from 5–10% to 60%; (2) we have become—after 10 years and dozens of failures—good at designing protein kinase inhibitors that are less toxic than the first ones were (by not binding to the ATP-binding site of the enzyme), and we can often design a selective compound for the mutated protein kinase that leaves the non-mutated, non-cancer-related form free from inhibition; and (3) the therapeutic antibodies are coming in different formats and armed with different cell-killing mechanisms on top of selectively recognizing some marker of the cancer cell. Most of the entries in this table are first in class drugs, proving that we can, when we put the resources into it, innovate with cancer drugs. Why can we not in AD or pain?

1 Antibody drug conjugate of the antibody trastuzumab (Herceptin) linked to the cytotoxic mertansine.
The reason for the richness of drug targets in oncology is twofold. One is the decision by governments and NGOs, such as cancer societies, to engage large-scale sponsoring of basic research over several decades starting in the 1960s. Firstly, this research has shown that many molecular mechanisms are common in very different cancer forms. Therefore, even though on the surface prostate and ovarian cancer are clearly different and occurring in different genders, there are molecular pathway similarities. Effective drugs may affect basic underlying mechanisms of the repair of DNA, or the formation of vasculature, which is needed to supply the tumor with blood, and so on. These putative drugs might be used to treat more than one cancer form. Secondly, the discoveries of drug targets in leukemias and then in solid tumors have accelerated as a result of major public spending. When considering the importance of this, one has to remember that until the 1960s the pharma industry had been responsible for the basic research in most areas of life sciences (except embryology), which was the foundation for most of the drug developments. Since the 1960s, government-sponsored research in physical and life sciences in the United States and Western Europe has increased (the “Sputnik effect”) and has almost completely replaced the basic research efforts of big pharmaceutical companies. It is true that pharma spent $92 billion on research and development in 2009, but a very small portion, maybe $10 billion, of this was considered basic research. This is to be compared with the more than $60 billion spent annually on basic research by public and other sources. The NIH alone in the United States has a budget of over $30 billion.

The example of oncology shows that when politicians recognize the need either for popular or other reasons to support research, then they can initiate sustained and large-scale efforts that eventually produce scientific breakthroughs. HIV treatment is another area serving as a good example of the joint forces of patient interest groups, relatives of patients, celebrities, and governments to put pressure on a pharma industry that had not been in general very successful in developing antiviral agents. Yet, in the relatively short period of 20 years, HIV has switched from being a 100% deadly disease to a chronic disease that
can be managed at several levels. This is one model, in which society can influence pharma by spending on basic research (to provide basic functional understanding and drug targets). Society would then rely on different sized companies, small ones first and bigger ones later, to pick up the scientific breakthroughs and apply them in the development of novel drugs. This is a very long-term, indirect way to find new drugs, but it has worked and it does not rely on specifying the commercial entities that will use the scientific results; instead it hopes that several will, and that they will do it in competition with one another.

There is also post-drug development encouragement and incentive by allocating NGO budgets to guarantee the purchase of a very large number of doses for developing countries. They exert a push-pull mechanism: the push on development and pull on production.

The examples of oncology and HIV cannot be underestimated. They are extremely important if we are not to give up work on Alzheimer therapies and on finding drugs against neuropathic pain and, for example, against schizophrenia, where the present drugs have relatively low response rates and are associated with severe metabolic side effects in many cases leading to early type 2 diabetes in young schizophrenics.

There are many good reasons to protect the freedom of researchers and not to direct all research, mostly because we really are not that good at predicting the truly innovative breakthroughs, many achieved through studying systems such as *Escherichia coli*, yeast, nematode worms, sea slugs, and fruit flies, and leading to cancer drugs. Nevertheless, one must not shy away from directing a much larger portion of the research budget to AD and antibiotics resistance than is happening presently. NIH and European research agencies already have large directed programs, but they are not large enough. Biotechs would be most helped if phase 2 and phase 3 clinical trials in AD were made possible with the partnership of government as an alternative to partnering to Big Pharma, which is currently not interested in these trials.