The discovery and development of one new drug costs around $800 million (taking failures into account) and takes an average of 10 to 12 years. This degree of investment, with such a late return on this investment, is unparalleled in human activity.

Despite this investment, some areas of great therapeutic need do not have optimal treatments—acute stroke and Alzheimer’s disease, as well as other central nervous system (CNS) disorders. There are no drugs registered for the treatment of acute stroke, which is an area of great therapeutic need, being the third-highest cause of mortality and the second-highest cause of morbidity. Nevertheless, there are distinct methodological reasons in the clinical trials which can preclude demonstrating efficacy in stroke under many circumstances. Another area in which the pharmaceutical industry has failed to revolutionize therapy has been in the treatment of Alzheimer’s disease. However, preventive therapy by addressing hypertension using angiotensin-converting enzyme inhibitors (perindopril, in the PROGRESS study) has shown marked reduction in the incidence of stroke, and also of dementia and cognitive decline. Antidepressant drugs with higher efficacy and fewer side effects are much needed.

Effective drug discovery requires drug targets for therapeutic intervention which are pivotal points for the disease process, and up until now these have not been clearly identified for stroke (with the possible exception of tissue plasminogen activator for very early intervention) or Alzheimer’s disease.

Background

Only 35 new compounds were registered with the Food and Drug Administration (FDA) in 2003 despite a research expenditure by the major pharmaceutical firms...
of 33 billion dollars (Figure 1). Part of these costs are due to the costs of failure. Figure 2 shows the fate of a sample of 121 drugs put into phase 1 clinical trials by British pharmaceutical companies. The results are edifying. Although some drugs failed because of toxicological problems or metabolic issues, or were even stopped for commercial reasons, the major reason for failure was lack of efficacy. The drugs were stopped because they did not work. This may occur for several reasons. First, the original hypothesis may be wrong, and the end result is a useful experiment, albeit a very expensive one. Second, and this is perhaps just as likely, the animal models may not represent the tests used in phase I and phase II clinical trials—it is also possible that the tests used in phase I and II do not represent the true patient response. Indeed, of the 340 compounds entering phase I per year, four out of five fail, and even when registration is achieved, less than half of the compounds recoup their development costs. The failure of drugs to work in the clinical setting (lack of efficacy due either to the concept not working, or to the animal models or the clinical models not responding to the patients’ needs) is a key area for improvement.

Third, increasing safety requirements discourages risk. This is particularly the case for CNS-active drugs which may have cardiovascular side effects (effects on electrocardiographic [ECG] QTc intervals for example). It remains a truism that no drug can be effective without having some measure of risk. However, it is now possible to have high-throughput screens for safety, and to do a better job of selecting compounds at an early stage.

The difficulties faced by a drug discoverer are shown by the sequence below. First, he or she must find the optimal structure/activity, then exclude structure/activity at other sites:

1. Definition of structure/activity at site of action
2. Exclusion of structure/activity at cytochromes
3. Exclusion of structure/activity—mutagenicity
4. Exclusion of structure/activity—cardiac QTc
5. Start of toxicity studies.

Fourth, there is the realization of the increasing complexity of biological systems. Although there may be only 25 000 to 30 000 genes, many of which are drug targets (Figure 3), the gene products are much more complex because of alternative splicing, mRNA editing, receptor dimerization, functional trafficking (where drugs acting at the same receptor may have different effects) and the multiple post-translational controls and accessory proteins.

New technological opportunities

In vitro screening

Screening on recombinant proteins has proven to be immensely powerful, and can provide new leads from high-throughput screening on a scale which would be impossible with other technologies. Now the target proteins may even be crystallized, with the drug, or even with fragments of the drug, and the crystals analyzed to define the conformational changes induced in the target by different drugs. The throughput of this technology is such that entire chemical series can be analyzed for their direct effects on the protein of interest. Thus, hundreds
of thousands of compounds can be tested at the cellular target in a few months, and the “hits” can then be chemically optimized to make new metabolically stable drugs. (Figure 3). Different conformational states during cellular activation, particularly in the presence of accessory proteins, may easily change a single hydrogen bond or electrostatic attraction, changing affinity. Indeed, it must be pointed out that one additional hydrogen bond between the compound and the target can change the affinity thirty-fold. This complexity may induce inadequate responses to predict therapeutic efficacy. As compound selection is the crucial issue, we have argued that, after preliminary screens in recombinant systems, and following exclusion of inappropriate compounds (for metabolic or safety reasons), the selection of the final compound to proceed onto development should take place in pathophysiological models, and preferably, if breakthrough compounds are looked for, in novel pathophysiological models. However, this means a major investment in screening in animal models.

**In vivo screening**

Animal models are often the limiting factor in research (particularly for cognitive issues), and finding staff skilled in their handling is not easy. Previous drugs have been tested for in the established models, and the way to test benzodiazepine anxiolytics is to use the classic anxiety screening models, defined by diazepam. However, novel drugs working in new ways may need new models. Thus, compounds should be selected using a model of pathophysiological conditions. However, this needs skilled pharmacologists with an integrative vision of pathophysiology.

How are new drugs discovered?

New drugs may be discovered in very many ways, but discovery nearly always involves tight collaborations between chemists and pharmacologists, who must identify the cellular and genetic factors important in pathophysiology, produce appropriate hypotheses, and design new test systems. Screening new molecules can be done in a number of ways.

**Target identification**

Ideally, the target should be the cause of a specific disease which can be targeted on a molecular level. There has been immense progress made in defining the receptor systems in the human genome, by analogy to existing 7-transmembrane receptors. This marks a unique moment in science, because many targets are becoming known. Lists of these receptors have been produced (eg, ref 5). Furthermore, new targets remain to be discovered, and the existing targets are known to have many different forms (alternative splicing, messenger ribonucleic acid (mRNA) editing, single-nucleotide polymorphisms, etc) which may allow selective targeting of disease states. The bioinformatics industry provides an immensely powerful tool to scientists, and many of these data are in the public domain.

**Target validation**

A crucial issue is to validate the target, in animal and preferably in human models. This is critical, because of the high cost of discovering a new drug for a target and performing the clinical experiment to find out whether the new drug works in a disease state in man. As there are tens of thousands of potential targets, target validation is a crucial issue. Fortunately, transgenic models may help in this regard, but their predictivity is only relative.

**Figure 3.** Signaling genes in the human genome.
Lead identification

A lead compound is usually selected by high-throughput screening of compound collections, or libraries (Figure 4). These compound libraries may consist of thousands, or hundreds of thousands, of compounds, built up by the pharmaceutical company over the years. Virtual screens can now be performed by modeling the interactions of the target with virtual libraries consisting of all the compounds which are commercially available—the best compounds can then be selected for screening. The “hits” or compounds which are active in the first round of screening are then optimized so that they possess the properties needed in a new drug. Testing is then done on each of these molecules to confirm its effect on the drug target.

Lead optimization

Lead optimization compares the properties of various lead compounds, allowing selection of the compound or compounds with the greatest potential to be developed into safe and effective medicines. The metabolism is optimized in high-throughput screens to produce compounds which retain their activity at the target of interest, while being metabolically stable and well absorbed.

Drug testing in humans

Testing an investigational new drug requires submission of all the information about the drug for permission to administer to healthy volunteers or patients. Not only...
regulatory authorities, but also institutional or independent review boards (IRB) or ethical advisory boards approve the experimental protocol, well as the informed consent documents signed by the volunteers. The clinical testing of the drug passes through Phase I, Phase II, and Phase III clinical studies. In each successive phase, increasing numbers of patients are tested, but the success or failure of the drug depends not only on its mode of action, but also on the good methodological quality of the testing schedule used in the clinic.

**Phase I clinical studies**

Phase I studies must verify the safety and tolerability of the new drug in volunteers, showing the maximal tolerated dose, and how it is absorbed, distributed, metabolized, and excreted. This phase takes 6 months to a year. Healthy volunteers are administered the drug acutely and then chronically. The hypothesis of action may be tested pharmacologically with indexes of brain penetration, brain imaging, and electroencephalogram (EEG). However, it must be borne in mind that healthy individuals may not react in the same way as patients. Some drugs cannot be tested in healthy volunteers (eg, in oncology).

**Phase II clinical studies**

Phase II studies are a critical research area designed to show effectiveness, define dose-response for the critical phase III approval studies, and demonstrate a measure of safety in the patient population. This phase of development generally takes from 1 to 3 years with several hundred patients. It is here that an appropriate choice of drug effectiveness criteria for drug effectiveness, linked to animal models, yet providing a realistic test of the drug in the patient population, can make a real difference.

**Phase III clinical studies**

Phase III studies show effectiveness and safety in randomized and blinded clinical trials involving thousands of patients. This phase can take 2 to 5 years, and is the most expensive clinical testing phase.

**New Drug Application/Marketing Authorization**

A New Drug Application (NDA), in the US, or Marketing Authorization (MA), in Europe, documents the safety and efficacy of the proposed drug, and the applications contain all the reports from the drug development process. At the end of phase III, the evidence proving efficacy and safety are submitted. The approval process can take 1 to 2 years, followed by post-marketing surveillance and extension of the therapeutic indications and patient populations.

**Fast-tracking**

Several regulatory issues may be seen as opportunities. Fast tracking for very urgent therapeutic needs, such as treatment for acquired immune deficiency syndrome (AIDS), has been introduced by the FDA. Furthermore, the FDA have issued guidelines on pharmacogenetic subtyping of patient populations (responders, patients at risk for side effects, rapid metabolizers, etc).

**Partnership**

Modern drug discovery and development depends on a constant partnership between the actors in the project, in the many disciplines which are involved. The partnership between industry and academia is a critical issue, because basic research can lead to many unexpected breakthroughs, of which the researcher may not appreciate the industrial and medical importance. It is correct that financial return should be associated with inventiveness. However, the fewer industrial partners there are (as in France), the fewer local industrial partners there are for startup biotechnology companies. There is thus a delicate balance between support of pharmaceutical companies and small biotechnology companies. As the main industrial experience (to avoid the pitfalls shown in Figure 2 for example) is located in pharmaceutical companies, this pragmatic feedback and review is an essential part of the health of the local industrial environment. It is also essential that research remains very medically oriented, because the patients’ needs come first. Partnership with clinicians and top medical teams is therefore also a key element for success. However, all of the stages of drug discovery remain an experiment, and must be designed as such. After the initial selection process which finds the drug, the only thing which does not change in the development process is the molecule; all the others—the scientists, sometimes even the therapeutic area—may change. However, the molecule can do no more or less than on the day when it is chosen, which is why the tests which select the molecule are so important.
Table I shows the factors influencing success in the drug discovery process.

Key points for definition of new ways forward in psychiatric disorders

1. **Molecular**—the multiple intracellular signaling cascades have key nodal points which can be targeted. Cancer drugs are targeted at key points, and now the same situation is being extended into CNS research, where drugs for bipolar disorder, such as lithium, may interact with key signaling molecules such as glycogen synthase kinase 3 (GSK3).

2. **Epigenetic changes** where the genes expressed relate to the past history of the individual. Furthermore, many gene products are modified by alternative splicing or mRNA editing which can change the function of key proteins in pathophysiological conditions.

3. **Cell plasticity**. Neurotrophins and cytokines have major effects on cell plasticity and integrity. Many genes can interact within the neurotrophic signaling cascades, and these are major points for therapeutic interventions. For example, we have shown that brain-derived neurotrophic factor (BDNF), the key neurotrophin involved in activity-dependent resculpting of neuronal networks, can also change the respiratory coupling efficiency of mitochondria, indicating a new way forward in the links between cellular activity and coupled metabolism.

4. The **neurotransmitters** involved in modulating brain systems are well defined, and still represent sources of drug discovery (noradrenaline, 5-HT, dopamine, etc). However, the multiple states of receptors and their signaling pathways warn against oversimplification.

5. **Chronobiological issues** are important in resetting biological rhythms, and may be even more important than previously thought. The finding that agomelatine, a melatonin agonist and 5-HT2C antagonist, can be an effective antidepressant with a low side-effect potential reconfirms the interest in chronobiological systems, because their dysreg-
ulation is a common feature of ageing and psychiatric disorders.

6. **Cell firing on specific nodal points.** The systems in the brain are becoming well defined, and it is now possible to intervene on brain switch-points, which may be deregulated. These can be quantified electrophysiologically, or by microdialysis of the main neurotransmitters, or by brain imaging techniques.

7. **Neuronal networks** for brain functions (e.g., the main systems involved in cognition, decision, and emotion and fear (prefrontal cortex, amygdala, hippocampus, Figure 5). An example of research in this area is the finding that stress blocks long-term potentiation (LTP, a measure of plasticity) in the hippocampal to ventromedial prefrontal cortex, and these effects are reversed acutely by an atypical antidepressant, tianeptine. McEwen’s group have shown that these acute effects change into effects on dendritic arborization. Furthermore, there is now proof of concept that this pathway is of critical importance for depression because Mayberg’s group have implanted electrodes into the white matter behind Cg25 (the equivalent in man of the ventromedial prefrontal cortex in rodents) and found immediate antidepressant effects in patients who had been entirely treatment-resistant. Targeting these brain areas therefore opens up new perspectives in drug discovery for depression. Furthermore, reengineering animal models to study these brain areas will allow the selection of new classes of molecule.

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