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In your opinion, when will advances in genomics and proteomics begin to impact on the discovery pipeline?
I think they are right now. The drugs that target activated pathways in cancer were not discovered so long ago and they are now already taken for granted. Those have been very powerful, basically genomic-based approaches. If you ask when the essential grammar of the discovery process will change, this still needs greater linkage between the genome and the disease. That is, I think, a process that will be continuous, but my guess is that drug discovery will look very different in seven to ten years than it does now.

During the development of Gleevec the collaboration with patients was much deeper. Will that continue and how will you ensure this?
As a physician, I can tell you I believe it is extremely important, for many reasons, to keep the patients involved. Let me give you an example of some of the ways we go about it. All of the disease-area groups at NIBR have to meet with patients during the year to find out what the disease really means to them. So, all of the scientists here should have some familiarity with the reality of the disease that they are studying. I work regularly and meet regularly with various advocacy groups to understand what they need and there are some areas where we are trying to work together. Therefore, patient care really permeates our whole discovery process.

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What new advances and technologies are you excited about at the moment?
Personally, I still am convinced that the application and the understanding of developmental genetics holds great promise for the discovery of new medicines and the potential of this is still untapped to a large degree. If you asked me about a technical advance, I would say a key one would be molecular imaging for understanding how these processes play out *in vivo*.

Who or what has been your greatest inspiration?
I can't say that there is any one person, rather an amalgam. I was fortunate in having a father who is committed to both medicine and science. As I matured in the field, I was also fortunate to have many close friends who are great scientists, such as Janni Nuesslein-Volhard and Bob Horvitz, now both Nobel laureates, who taught me that no challenge was too great as long as you understood where you were trying to go. The other key inspiration for me is people who have enough breadth to incorporate artistic or scientific motivations with very practical ones. There are those who are journalists and also fiction writers, such as Gabriel García Márquez, or those who are scientists, such as Leonardo, who are very engaged with their society.

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When counting sheep does not help: the growing incidence of sleep disorders

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> ***'O weary night, O long and tedious night, Abate thy hour! ... And sleep, that sometimes shuts up sorrow's eye, Steal me awhile from mine own company.'***
> Helena, *'A Midsummer Night's Dream'*, by William Shakespeare

We humans spend a third of our lives sleeping; an activity (or passivity) essential to our health and general well-being. Although sleep requirements between individuals vary, on average we indulge in a good seven to nine hours every night. Sleep is regulated by the hypothalamus, which releases specific neurotransmitters, such as serotonin, γ-aminobutyric acid (GABA), adenosine and endogenous opiates, all of which induce sleep. Electroencephalogram readings from sleeping subjects show that sleep oscillates between two states – passive, resting sleep and rapid-eye movement (REM) sleep, during which dreams occur.

Impact of sleep disorders

The term 'sleeping disorder' can mean any of a number of complaints, including insomnia, parasomnia (the symptoms of which include sleepwalking and night-terrors), narcolepsy, obstructive sleep apnoea, 'jet-lag syndrome', disturbed biological and circadian rhythms and restless leg syndrome. Current therapeutic treatments tend to target the symptoms of these disorders, rather than the underlying pathophysiology – often the precise cause of a sleeping disorder is, in fact, a different disorder entirely.

In the USA alone, the number of sleep disorder clinics and specialist physicians has

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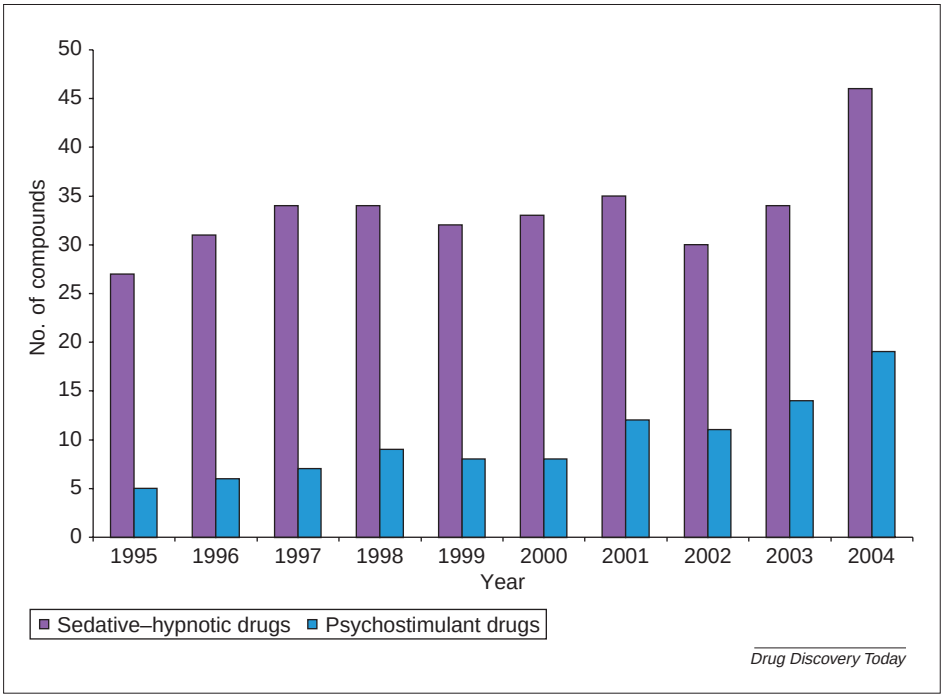

FIGURE 1

Changing trends of sedative–hypnotic and psychostimulant drugs, 1995–2004.

more than doubled since 1996. Nearly half of all Americans have a sleeping disorder and, according to the Sleep in America poll conducted in 2001 by the National Sleep Foundation (www.sleepfoundation.org/publications/2001poll.cfm), nearly seven out of ten Americans said they frequently have sleep problems. Furthermore, an estimated five million people in the UK suffer from a sleep disorder. Incidence is notably high in the over-65s and, because the number of people now living well into old age is rising, the prevalence of sleep disorders is bound to increase still further. Predictably, the development of drugs to treat sleep disorders has burgeoned, with a particular rise in the number of sedative–hypnotic compounds and psychostimulants on the market since 2002 (Figure 1).

Sleepless nights

It is not difficult to appreciate the importance of sleep when one considers insomnia, which is the most common sleep disorder. Insomnia is thought to affect 10–15% of humans, with the transient form striking up to 50% of the population at any one time. In the USA, the prevalence of insomnia in the elderly is estimated at 33%. Worryingly, it remains largely undiagnosed; in the USA, the majority of insomnia sufferers do not seek help for their condition.

The inability to obtain satisfactory quantity or quality of sleep takes many forms: difficulty falling asleep; restless sleep; re-awakenings during the night; early waking; and, in extreme cases, complete wakefulness. Insomnia is classified as transient (short-term), intermittent and chronic (constant). Chronic insomnia is defined as the occurrence of sleeplessness on most nights for more than a month. Insomnia often occurs as a symptom of another disorder, and usually the cause is emotional in nature – depression, stress and anxiety all have powerful influences, and particularly affect the chronic sufferers. Behavioural factors, such as excessive intake of caffeine or alcohol, can also contribute.

Naturally, insomnia leads to other adverse effects. Sufferers report that they experience – perhaps unsurprisingly – tiredness, fatigue, broken concentration, memory problems, irritability and difficulties with interpersonal relationships. Chronic insomnia is more destructive, leading to the development of psychiatric illnesses, depressive illnesses, anxiety and alcohol abuse.

From lavender to non-benzodiazepines

Folk remedies for insomnia have existed since antiquity – lavender, lettuce, onions and warm milk are all credited with soporific powers. The use of drugs to treat insomnia is normally recommended only as a last resort, because they can be addictive, have serious side-effects and often fail to treat the underlying cause of the disorder; nevertheless, the number of sedatives reaching the market has steadily increased over the past decade (Figure 2). Bromide was the first classified sedative–hypnotic drug (used in the mid-19th century), but lost its popularity because of the risk of poisoning. Soon after came the barbiturates; from 1912 until 1960, nearly 50 of this class of drug were available. Barbiturates are nervous system depressants, facilitating the activity of GABA, and so creating calming, sleep-promoting effects. For a while, at least, they seemed to be the ideal solution to sleeplessness. However, as they became widely available and popular, issues of dependence came to light, and they were also implicated in cases of suicide. Growing concern over this led to the search for agents with more selective sleep-associated actions on the CNS. And so, a new, safer alternative class of drugs was born – the benzodiazepines. These drugs displaced barbiturates as the dominant sedative–hypnotics; benzodiazepines were also favoured because they have a considerably lower potential to cause fatal respiratory and cardiovascular depression. The first benzodiazepine was chlorodiazepoxide, presented in 1961, which caused the sedative, muscle relaxant and anti-convulsant and anxiolytic properties common to benzodiazepines. Benzodiazepines are also GABA inducers, causing increased binding of GABA to multi-subunit chloride channels on GABA receptors. Of drugs in development for insomnia today, 26% are GABA agonists (Figure 3).

The existence of different receptor subunits led to the discovery of non-benzodiazepine medications that act selectively on one or more of these subtypes, and as a result possess better adverse-reaction profiles compared with benzodiazepines. One such compound is zolpidem, which is an omega-benzodiazepine receptor agonist, originally developed by Sanofi-Synthelabo (now Sanofi-Aventis).

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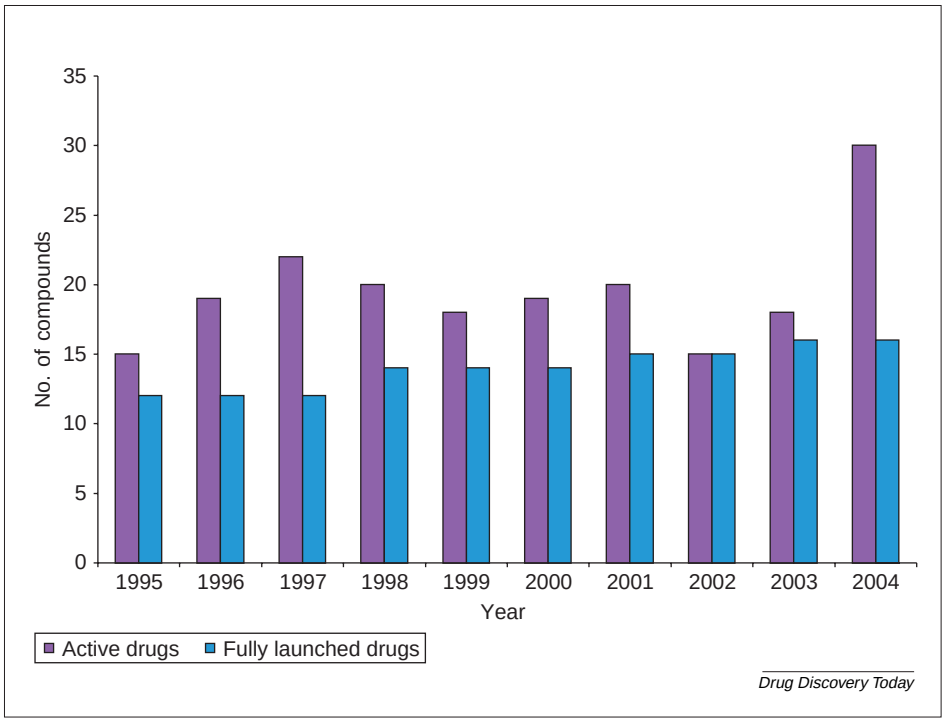

FIGURE 2

Development of sedative or hypnotic drugs, 1995–2004.

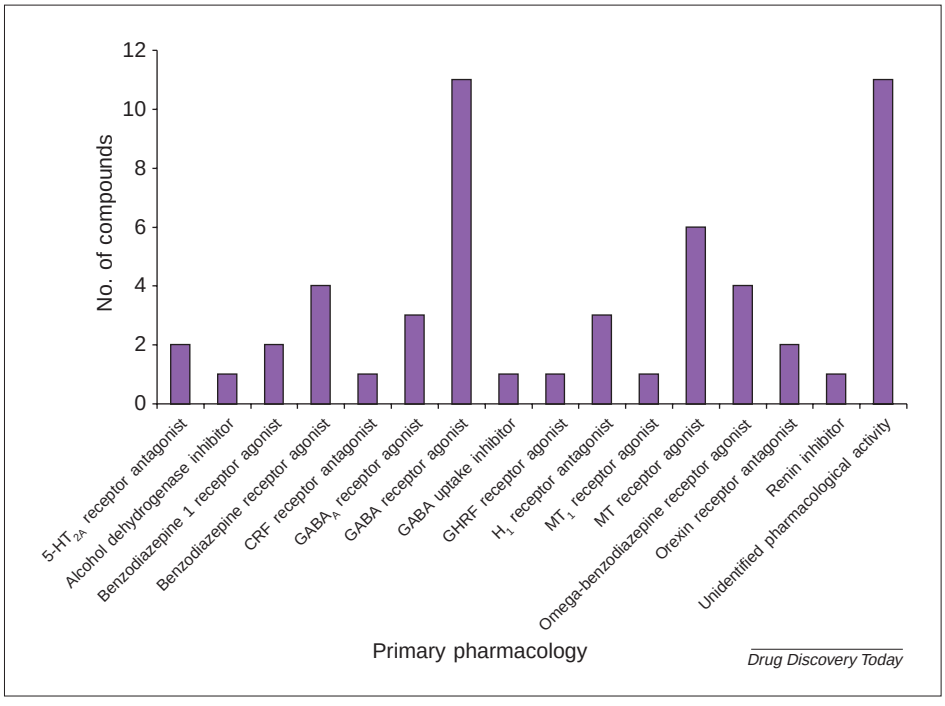

FIGURE 3

Pharmacological activity of insomnia drugs. Abbreviations: CRF, corticotropin-releasing factor; GHRF, growth hormone-releasing factor; H_1, histamine 1; 5-HT_{2A}, 5-hydroxytryptamine 2A; MT_1, melatonin 1.

Normally administered for transient insomnia, it has specific agonist activity at omega-1 receptors and has the advantage over benzodiazepines of a low dependency potential.

A second launched non-benzodiazepine transient insomnia treatment is Wyeth's zaleplon (marketed under the name Sonata). Zaleplon has a rapid action and a short half-life, thus causing lower levels of daytime sedation or memory loss. In a Phase III trial in 615 insomnia patients, zaleplon lowered sleep latency and increased sleep duration. However, side-effects are associated with the best of drugs, and zaleplon is no exception; adverse reactions of zaleplon included headache, light-headedness and decreased co-ordination. A modified-release version of zaleplon, currently in development by licensee King Pharmaceuticals, has reached Phase II trials, and progress continues.

Another relatively new insomnia drug is Sepracor's eszopiclone, the (*S*)-isomer form of the non-benzodiazepine zopiclone, which is currently approved in the USA, under the name Lunesta, for the treatment of transient and chronic insomnia.

Unwanted sleep

Although the disorder is far less common, the disruption that is brought to the lives of narcoleptics is no less significant. Narcolepsy affects a much smaller proportion of the population than insomnia – approximately one person in 2000 suffers from this complaint in the USA, and about one in 600 in Japan. It is characterized by excessive daytime sleepiness, cataplexy (short-lived intermittent muscle weakness) and disturbed nocturnal sleep. Narcolepsy can be described as an intrusion of REM sleep into the waking state. The causal mechanism is, again, not fully understood (although the involvement of some genetic component is probable). However, unlike insomnia, it never occurs as a symptom of a different complaint, but is a disease in itself. Recent discoveries indicate that sufferers lack hypothalamus neurotransmitters called hypocretin peptides, or orexins, which normally stimulate arousal and help in sleep regulation. It affects people of any age, but symptoms usually start to appear between the ages of 15 and 30, in response to emotional triggers or strenuous activity.

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As with insomnia, narcolepsy is underdiagnosed; in one recent study, the average time between the onset of symptoms and correct diagnosis was 14 years and, because the symptoms are recognized after adolescence, most narcoleptic patients are diagnosed too late to prevent the impact of the disorder on their personal and professional development. On the upside, it is usually easy to diagnose narcolepsy if the symptoms are clearly present. When the symptoms are mild, as is often the case, a nocturnal polysomnogram, followed by a multiple sleep latency test, is used to confirm the diagnosis by showing a latency of less than five minutes.

Treatment for narcolepsy can help with symptoms and markedly improve quality of life, but cannot cure the condition. Combined with behavioural changes, recommended medical treatment has traditionally included amphetamine-like stimulants to improve alertness and antidepressants for controlling cataplexy, hypnagogic hallucinations (the hypnagogic state is that between wakefulness and sleep) and sleep paralysis. Common stimulants include dextroamphetamine sulfate, pemoline and modafinil. There are few drugs currently listed in *Pharmaprojects* for the treatment of narcolepsy itself, which is surprising considering the devastating impact of the disease and the scope for improvement of current, launched therapies to include those that can regulate hypocretin levels in the brain.

Modafinil, known by the tradename Provigil, was launched in the USA in 1999 for the treatment of excessive daytime sleepiness, where it has orphan drug status for this indication. It is also launched in Canada, South Africa and several European Union countries. Although its exact mechanism of action is unknown, its usefulness in controlling daytime sleepiness has been confirmed in numerous clinical trials. In two Phase III narcolepsy trials, modafinil led to significantly improved average scores of wakefulness and daytime alertness. More promisingly, a longer-acting single isomer formulation of modafinil, (*R*)-modafinil, is being developed by Cephalon. To date, it has reached Phase III trials and a New Drug Application filing is due in 2005.

Neurocrine Biosciences was developing what was perhaps the most exciting, and certainly novel, product in development. This stimulant, a hypocretin receptor agonist, was in preclinical trials and was the first candidate to address hypocretin levels directly, suggesting an unrivalled specificity in the treatment of narcolepsy. The National Institutes of Health awarded a Phase I Small Business Technology Transfer grant for this project. However, there is no evidence that Neurocrine is continuing to develop this candidate and it can only be hoped that its brief pipeline existence triggers the initiation of similar projects.

An era of hope

It is clear that the development of treatments for sleeping disorders such as insomnia and narcolepsy are dependent on the delineation of the basic mechanisms that regulate sleep. As research continues and more is learned about the process of sleeping, so therapies to treat sleep disorders will improve. Already drugs are in development that have more favourable side-effect profiles than medications in the past, and their increasing specificity means that they not only reduce the possibility of adverse effects but also have greater potential in successfully treating the disease itself. We are venturing out of the dark and into an era of increasing hope for the millions of sufferers of sleep disorders. And for those who suffer from sleep disorders, this promise might be just what they need to get a good night's sleep.

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