lidine. Our first results demonstrating such selectivity of zimelidine were published by Berntsson et al. [2], i.e. two years before the first publication on fluoxetine (1974) and actually at a time when the Lilly researchers started their work on fluoxetine. Claims by the Lilly researchers that fluoxetine was the first SSRI (Wong et al. 1995) are thus not warranted. Zimelidine was also the first SSRI demonstrated to be an efficacious antidepressant agent (see Carlsson et al. [3]). It was marketed in several countries and was well received but was withdrawn following the disclosure of some rare but serious side effects.

[1] Carlsson A, Fuxe K, Ungerstedt U. J Pharm Pharmac 1968; 20: 150–151.
[2] Berntsson PB, Carlsson PAE, Corrodi HR. Belgian Patent 1972; 781105 (72—4–14).
[3] Carlsson A, Gottfries C-G, Holmberg G, Modigh K, Svensson T, Ögren S-O. Acta Psychiat Stand, 1981; 63: Suppl 290.

THE INVENTION OF ANTIDEPRESSANTS

D. Healy. *Department of Psychological Medicine, University of Wales College of Medicine, Hergest Unit, Ysbyty Gwynedd, Bangor, Gwynedd LL57 2PW, United Kingdom*

It took several years from the discovery of the mood relieving properties of certain psychotropic drugs to the "invention" of the antidepressants. In 1955 Kuhn and colleagues first discovered the thymoleptic effects of Imipramine but Geigy hesitated over two years before marketing the compound because of disbelief about the proposed action and uncertainty regarding the market size. The decision to run with an antidepressant was only taken after Nathan Kline had created the antidepressant bandwagon by publicising the psychic energising effects of Iproniazid against the wishes of Roche and in the face of company "non-compliance". As early as 1953 both Max Lurie and Harry Sulser in the USA and Jean Delay and colleagues in Paris had discovered the effects of Isoniazid on mood but neither discovery led to action by the pharmaceutical industry or the psychiatric profession nor was there any action following the demonstration by the double-blind placebo control randomised trial by Shepherd of the beneficial effects of Reserpine in out-patient anxious depressions in 1955. The watershed was the discovery of the antidepressant properties of Amitriptyline, in which Merck, Roche and Lundbeck had a stake and which Merck marketed by selling both a discovery — Amitriptyline and an invention — Depression.

THIOXANTHENE ANTIPSYCHOTICS

V. Pedersen. *Research and Development, H. Lundbeck A/S, 9 Ottiliavej, DK-2500 Copenhagen-Valby, Denmark*

The thioxanthene antipsychotics represent a series of compounds that are chemically related to the phenothiazine antipsychotics. The difference is that the aromatic N atom of the central phenothiazine ring has been replaced by a carbon atom. It was hoped that the "carbon analogs" would be devoid of some of the unwanted effects observed with chlorpromazine. In 1958 Petersen et al. (Arzneimittelforschung 1958;8:395–397) published the first paper describing the pharmacology of a number of thioxanthene derivatives. One of them was chlorprothixene, which was introduced in 1959. It became a popular broad-spectrum antipsychotic. In 1962 the Lundbeck research team published a study on the pharmacology of a large number of thioxanthene derivatives, and they demonstrated a fairly close parallelism between the structure-activity relationship of the thioxanthenes and that of the phenothiazines. A double bond from the central carbon atom 9 to the side chain greatly increased the neuroleptic activity. Owing to the double bond and the asymmetry of the molecule, there were two isomers of each substance, and only one of them was neuroleptically active. Later very active substances without the double bond were synthesized. The second thioxanthene antipsychotic was clopenthixol, which was later replaced by zuclopenthixol — the pure active isomer. In the mid-1960s, Lundbeck introduced flupenthixol in Europe, and Pfizer launched thiothixene in North America. Depot formulations of zuclopenthixol and flupenthixol are now widely used in the maintenance treatment of schizophrenia. In 1987 zuclopenthixol acetate was introduced as a parenteral formulation for the treatment of acute psychotic episodes. It has a rapid onset of effect and a duration of effect for 2–3 days. It is interesting that in contrast to the phenothiazines, there are no phenolic metabolites of the thioxanthenes. This may be the reason why certain unwanted effects are very rare after thioxanthene antipsychotics. The newest development in the Lundbeck laboratories, the atypical antipsychotic sertindole, has not been found among the thioxanthenes.

THE BEGINNING OF PSYCHOPHARMACOLOGY: DEEP-SLEEP THERAPIES

Edward Shorter. *Hannah Chair in the History of Medicine, University of Toronto, 88 College Street, Toronto, Ontario, Canada M5G 1LA*

Psychopharmacology began with the use of bromides and barbiturates to produce prolonged sleep in patients with major psychiatric disorders. In 1897 Neil Macleod, a Scottish physician in Shanghai, initiated sleep therapy with sodium bromide in patients with mania and other disorders. First to use barbiturates was Giuseppe Epifanio at the university psychiatric clinic of Turin in 1915. Five years later Jakob Klaesi at the Zurich university psychiatric clinic popularized sleep therapy, giving it a worldwide vogue. The quite successful sleep-therapy programs came into disfavor in the 1950s following the experiments of D. Ewen Cameron at the Allan Memorial Institute in Montreal. Thereafter sleep-therapy was discarded in psychiatry without ever having received a thorough scientific appraisal.

S81. Sleep and psychiatry

Chairmen: R Kerwin, ND Minton

DIAGNOSIS OF THE NARCOLEPTIC SYNDROME

M.J. Dahlitz, J.D. Parkes. *The Institute of Psychiatry, De Crespigny Park, London SE5 7DH UK*

The narcoleptic syndrome consists of excessive daytime sleepiness (narcolepsy) and episodic paresis associated with sudden changes in emotional arousal (cataplexy). Common additional features include episodic paresis associated with sleep onset and offset (sleep paralysis), pre-sleep dream timing and disturbed nocturnal sleep. There is neurophysiological evidence for abnormal timing of rapid eye movement (REM) sleep. The prevalence of the narcoleptic syndrome is about 2–6/10,000 and it is a lifelong condition. It usually presents between 15–25 years of age and may be familial.

The prevalence of the HLA DQ1 (6) B1*0602 haplotype in the narcoleptic syndrome is 98%. This very strong HLA association only applies to excessive daytime sleepiness with cataplexy. Excessive daytime sleepiness with sleep paralysis, although previously considered to be clinically equivalent to the narcoleptic syndrome, is not HLA associated.

Two percent of subjects with the narcoleptic syndrome do not have the HLA DQ1 (6) B1*0602 haplotype. These subjects are clinically indistinguishable from HLA associated subjects and there

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is often a strong family history of the DQ1 (6) B1*0602 negative syndrome. As yet, no other disease susceptibility loci have been identified.

Many subjects with the narcoleptic syndrome do not attend a sleep disorders clinic or have laboratory investigations. A study of subjects who have undergone diagnostic investigations showed that the accurate clinical diagnosis of cataplexy is the most specific discriminatory feature of the syndrome and should take precedence over any laboratory findings.

SLEEP, OFFENDING AND THE LAW

Peter Fenwick. *Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, SE5 8AF*

With a change in social attitudes which has led to young adults sleeping over in friends' houses, and often in the same room, after parties, there has been an increase in sleep related sexual offending. Sexual offending in sleep can arise because the perpetrator sleepwalks in a sexually offensive way, eg, walking nude through the streets. It can also occur as a direct assault on a sleeping colleague in which contact is made with the sleeper's genitals.

Finally sleepers may be approached by an awake person who requests sexual intercourse. Misinterpretation of sleeping behaviour can lead the perpetrator to believe that the sleeper is awake. A detailed knowledge of sleeping behaviour is required by the examining neuropsychiatrist to decide whether or not the perpetrator had reasons to believe that the sleeping victim had given their consent for the sexual approach. Aggressive attacks are common during either sleepwalking or REM sleep disorders.

Fortunately, assaults leading to serious injury are rare, the law in England interprets sleepwalking as insanity. This has the advantage that the normal sleepwalker is stigmatized as being insane.

HYPNOTICS AND DAYTIME PERFORMANCE

I. Hindmarch. *Human Psychopharmacology Research Unit, University of Surrey, Milford Hospital, Godalming, Surrey, GU7 1UF*

It is now widely accepted that daytime tiredness, resulting from, among other things, sleep debt, sleep apnoea and insomnia is a major determinant of road traffic accidents and fatalities.

Most of the pharmacological substances used to manage patients with sleep disturbance (hypnotics, antihistamines, antidepressants) are, by their very nature, powerful sedatives. The psychopharmacological actions of many putative sleep inducers cause residual sedative sequelae which can interfere with daytime functioning on a variety of psychometric analogues of the activities of daily living.

The residual actions of ligands of the GABA-Cl ion receptor, sedative antidepressants and antihistamines on daytime performance will be reviewed and evidence presented to show that sedative tricyclic antidepressants old antihistamines and certain benzodiazepines destroy the integrity of daytime function in populations of sleep disturbed patients. At the same time it will be demonstrated that specific benzodiazepines, cyclopyrrolones and imidazopyridines have few, if any effects on daytime performance.

THE PHARMACOLOGY AND THERAPEUTICS OF SLEEP

M.H. Lader. *Institute of Psychiatry, De Crespigny Park, London SE5 8AF*

The complaint of insomnia is common occurring in about 5% of young people but rising to 35% in those over 65. It may be short term or chronic. Most common causes of insomnia fall under one of "5 P" headings: Physical, Physiological, Psychological, Psychiatric, and Pharmacological. If non-drug methods of treatment are inappropriate or ineffective, hypnotic medication is indicated.

Currently, hypnotic medication comprises a few older drugs such as chloral, antihistamines, often available without prescription, a range of benzodiazepines, and two newer benzodiazepine-like drugs, zopiclone and zolpidem. Some benzodiazepines used as hypnotics such as nitrazepam are long-acting, producing residual effects the next day and accumulating, to toxic levels in the elderly. The shorter-acting compounds such as triazolam may result in rebound insomnia on discontinuation. Adverse neuropsychiatric reactions such as depression and amnesia may occasionally be reported. Abuse of benzodiazepines is an increasing worldwide problem. Zopiclone is short-acting, zolpidem even shorter-acting, and neither is associated with appreciable residual effects. They also do not disrupt sleep patterns as the benzodiazepines do. Zaleplon, a drug in development, is ultra-short-acting, also with beneficial effects on sleep patterns. All these newer drugs need careful monitoring to assess any dependence or abuse potential.

The use of hypnotic medication in short-term insomnia is uncontroversial. If the cause of the insomnia is identifiable and self-limiting, then the use of a short-acting hypnotic is indicated for a few nights. If, however, the insomnia is, or is likely to become, long-term, the use of hypnotic medication may also become long-term. It is debatable whether the risks of long-term use outweigh any therapeutic advantages. Non-drug strategies should be vigorously pursued before resort to medication, unless the patient is greatly distressed by the insomnia, in which case intermittent or p.r.n. use may be most appropriate.

NORMAL SLEEP PHYSIOLOGY

T. Roth. *Henry Ford Hospital, Sleep Disorders and Research Center, 2921 West Grand Boulevard, Detroit, Michigan 48202*

Sleep is a behavior characterized by very low level of motor activity, a stereotypic posture, reduced responsibility to external stimulation, and reversibility. These measures are traditionally used to define physiological sleep in the EEG, the EOG, and the EMG. In wake, the EEG alternates between low voltage fact activity (10–30 cps) and a sinusoidal 8–12 cps pattern called alpha. NREM sleep is characterized a progression for mixed frequency fact activity with occasional sleep spindles to predominance of slow high amplitude lower (delta activity). Eye movements are rare and EMG is low to moderate. During REM sleep, the EEG reverts to a low voltage, mixed frequency pattern similar to that of Stage 1. Bursts of prominent rapid eye movements appear. The background EEM is virtually absent, but many small muscle twitches may occur.

NREM and REM sleep alternate cyclically through the night. Except in certain pathological conditions, a night of sleep begins with about 80 minutes of NREM sleep, followed by a REM period of about ten minutes. This 90 minute NREM-REM cycle is then repeated about 3–6 times during the night. In the successive cycles of the night, the amounts of Stages 3 and 4 decrease, and the proportion of the cycle occupied by REM sleep tends to increase.

It should be clear from this pattern of NREM and REM sleep that sleep is not the simple, uniform suspension of activity which many had assumed it to be for centuries. Rather, sleep shows a complex, highly organized pattern of diverse physiological variables.

Although the EEG, EOG, and EMG measures do a pretty good job of state discrimination, there are occasions when states are not clearly differentiable. State changes do not switch off and on like light switches. Rather, they change more or less gradually, which can make it difficult to draw very sharp dividing lines between states. Even more vexing is the fact that the different processes may change at different rates. For example, during the transition from