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 It was marketed in several countries and was well received but was withdrawn following the disclosure of some rare but serious side effects.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

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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

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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

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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

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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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