a methadone prescription dispensed from a community pharmacy, regular counselling appointments with a community nurse and a treatment objective of detoxification or a place in a methadone maintenance programme where they attended daily to take their methadone on the premises and had stable maintenance as the treatment goal. Subjects who refused to accept their allocated treatment were offered the other condition. They were assessed at intake and again 1, 2, 3, 6, and 12 months after entering treatment.

Results: 119 subjects entered the trial, 75 went to CDT treatment, 47 randomised 28 chosen, and 44 to MMC treatment 33 randomised and 11 chosen. The CDT group stayed in treatment for a mean of 5.76 months, the MMC group for 8.69 months. 91% of the whole sample were contacted for follow up at 12 months. Data on the conduct of the study will be presented, alongside preliminary outcome data and analysis.

Conclusions: Randomising subjects to different treatment modalities presents special problems in the addictions field. Monitoring the process of treatment may also prove difficult. However the follow up of subjects when they have left treatment in order to obtain good quality data is feasible.

COMMONALITIES IN METHADONE SUBSTITUTION THERAPY PROGRAMMES IN EUROPE: A CASE FOR A UNIFIED POLICY?

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A muticentre survey of treatment practices related to Methadone Substitution Therapy was conducted in a cluster of eleven MST programmes in nine European countries (eight EU countries plus Switzerland) during the summer of 1995. The following practice variables were investigated: type of MST; eligibility criteria for admission; treatment contract; pre-treatment orientation of patients; informed consent; dosing policy; length of treatment; and policies on discharge and readmission. The detailed analysis of data revealed the following common practices across programmes: established links with hospital services and family doctors; prescription of methadone only by licensed medical practitioners; programmes are directed primarily by psychiatrists; specialist training in addiction not a prerequisite for employment; multidisciplinary personnel, with nurses in the majority; self referral is the predominate pattern; established interagency collaboration; treatment is predominantly Methadone Maintenance Treatment (MMT); mandatory patient identity common; verification of physical dependence by urinalysis; oral preparation for methadone; and on-site dispensing.

The findings of this survey suggest the possibility of a Europe-wide policy on Methadone Substitution Therapy and the implementation of Article 129 of the Maastricht Treaty as it affects a European health policy on drug dependence, is discussed.

THE ROLE PHARMACOKINETICS AND PSYCHOPATHOLOGY IN THE PREDICTION OF CRAVING AMONG OPIATE ADDICTS IN METHADONE MAINTENANCE THERAPY

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Objective: The aim of the study is to determine the role of pharmacokinetics and psychopathology in the prediction of craving among opiate addicts in methadone maintenance therapy (MMT).

Methods: A consecutive series of 20 long-term opiate addicts currently enrolled in MMT was recruited from a closed ward. During the study period of four days, craving was assessed 10 times per day using the experience sample methodology. On the first day, psychopathology was measured with the 28 item General Health Questionnaire (GHQ-28) and the 90 item Symptom Check List (SCL-90). During the second day 8–9 plasma samples were drawn and plasma methadone concentrations were determined using a newly developed high pressure liquid chromatography (HPLC) procedure.

Results: A significant positive relationship was observed between oral methadone dose and craving ($r = 0.55$). No significant relations were found between craving and pharmacokinetic parameters (plasma methadone through level, methadone half-life) or existing psychopathology. Two specific craving patterns were identified: a very high peak around 9 a.m. (methadone dispensing time clinic) and a slightly smaller peak around noon (methadone dispensing time in outpatient MMT).

Conclusions: The results suggest that factors other than pharmacokinetics and (axis I) psychopathology are responsible for craving in MMT clients. It is hypothesized that anticipatory conditioned responses or circadian rithms are responsible for the observed fluctuations in craving. Consequences of these findings and their interpretation for the clinical management of MMT clients are discussed.

S80. The history of physical treatments in psychiatry

Chairmen: P Pichot, D Healy

A HISTORICAL NOTE ON THE DEVELOPMENT OF ZIMELIDINE, THE FIRST SELECTIVE SEROTONIN REUPTAKE INHIBITOR

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In the early 1960s the development by Hillarp and his colleagues of a histochemical method for the visualisation of monoamines at the cellular level led to the demonstration of monoamines in specific neuronal systems in the brain and opened up possibilities for a precise localisation of different synaptic events in the monoaminergic systems. Together with members of the Hillarp school we were thus able to demonstrate the occurrence of a transmitter reuptake mechanism located to the cell-membrane of serotonergic neurons and to show that imipramine is capable of blocking not only the reuptake of noradrenaline, until then assumed to constitute the major mode of action of the tricyclic antidepressants, but also the reuptake of serotonin [1]. Our subsequent work revealed that the relative power of blocking noradrenaline and serotonin reuptake differed among the tricyclics. For example, the tertiary amines were more potent blockers of serotonin relative to noradrenaline than the secondary amines, and clomipramine was found to be an especially strong blocker of serotonin reuptake. We thereafter discovered a number of antihistamines with relative strong action on serotonin reuptake. Dr. Hans Corrodi and I started a synthetic programme based on one of these antihistamines, i.e. brompheniramine, in order to develop a selective serotonin reuptake inhibitor (SSRI). It turned out that a couple of modifications of the brompheniramine molecule sufficed to arrive at a highly selective serotonin reuptake inhibitor, i.e. zime-

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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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