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Basic and Clinical Science of Opioid Addiction

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Volume Editors

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Editor's Foreword

In 1998 a symposium called Basic and Clinical Science of Substance Related Disorders took place at the Psychiatric University Clinic of Basel. In the long tradition of PUK symposia and the publications of S. Karger AG, Basel, dealing with the medical prescription of narcotics, another symposium focusing on 'opioid-assisted treatment' was held in Basel in November 2001. Scientists and practitioners from Canada, Germany and Switzerland provided insights on important aspects of both methadone maintenance treatment and heroin-assisted treatment. Clinical practice, methodology, neuroscience and psychotherapy were among the wide range of topics discussed.

The conference and the subsequent publication of the proceedings were made possible because of support provided by Janssen-Cilag AG, Organon AG, AstraZeneca AG, Lundbeck (Schweiz) AG, Pfizer AG, the Swiss Academy of Medical Sciences and a generous grant from Novartis Pharma Schweiz AG as well as the Center of Applied Technologies in Neurosciences (COAT-Basel) – a competence center of the Psychiatric University Clinic of Basel. The organizers particularly thank Mr. F. Jenny (lic. iur.), Director of the Psychiatric University Clinic of Basel and the food and nonfood departments of the clinic for their personal support. Thanks are also due to Dr. Hannes Strasser and our secretary, Mr. Daniel Scheidegger, for their very efficient management support, and to the team of S. Karger AG, Basel, for their professional help with the publication of this volume.

M.F. Kuntze, A.H. Bullinger

Preface

Opioid use and abuse date back to antiquity. The pain-relieving and euphoric effects of opioids were known to Sumerians and Egyptians. International awareness of opioid abuse was stimulated early in the 20th century. The widespread use of methadone for opiate maintenance in the early 1960s and heroin-assisted treatment in the Netherlands and Switzerland in the early 1990s were major developments that led to moderation in the narcotic control policy.

Opioid dependence is a physiological, behavioral and cognitive-emotional symptom complex that involves the continuing use of opioids despite the significant problems associated with their use. The death rate of people who use opioids is disproportionately high compared to people who intravenously abuse other drugs. Opioid dependence is considered a biopsychosocial disorder. Pharmacological, social, genetic and psychological factors interact to influence abuse behaviors associated with drugs. However, pharmacological factors can be especially prominent, more so than is the case with other types of drug use disorders. Detoxification alone, without ongoing treatment, is not adequate to manage patients. Patients often benefit from cognitive, behavioral, supportive or other kinds of psychotherapy if they are added to standard drug counselling.

The outstanding experience in 'opioid-assisted treatment' of the Psychiatric University Clinic of Basel has made it possible to organize a symposium gathering well-known speakers and a huge audience to discuss difficult aspects of opioid addiction.

F. Müller-Spahn, D. Ladewig

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Critical Clinical Practice of Opiate-Assisted Treatment

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The various contributions in this booklet have something in common: they attempt to shed light on opiate-assisted treatment. Basic methodological considerations and research in neurosciences, primarily on dopamine and serotonin as well, focus on historical experiences and functional neurological systems. The historical and social conditions of a – partly controversial – treatment are important. Indeed it is precisely because of the controversy which surrounds it that serious scientific evaluation and basic as well as applied research are necessary. This is the only way in which efficient therapeutic care of the population can be achieved, and it is the only way in which the political changes that appropriate care might necessitate can be brought about [1–3]. On the one hand, this care utilizes the research results of neuroimaging technology, for example, and on the other hand it is itself subjected to critical review. The book ends with some thoughtful remarks by a practicing psychotherapist.

Neurological damage resulting from opiates and opioids cannot be simply ignored [4] and the question as to whether withdrawal treatment is always useful also cannot be answered with a simple ‘yes’ or ‘no’. What are the questions that arise in classical psychotherapy and what have longitudinal studies shown after patients have left professional treatment settings? These are some questions that this contribution addresses. It describes the framework in which the opiate treatment is typically made available.

Clinical Settings

The substances diacetylmorphine (heroin), methadone and buprenorphine, all of which are permitted for substitution treatment of opiate addicts in Switzerland and are paid for by health insurance, constitute the core or ‘props’

of the therapy. By a wide margin, methadone treatments are quantitatively the most important. Around 18,000 persons are currently receiving methadone-based treatment; roughly 2,000 are receiving abstinence-oriented long-term therapy and somewhat more than 1,000 persons are receiving heroin-based therapy [5]. A further 2,000 are receiving several different therapies such as withdrawal treatment. Thus out of an estimated 30,000 opiate addicts in Switzerland more than 23,000 are receiving therapeutic support.

The cost of substitution therapy is reimbursed in a lump sum and this varies from canton to canton. All the components of opiate-assisted treatment are covered: this includes the cost of somatic and psychiatric examinations, the procurement of all necessary information, the production of reports and the procurement of governmental permits, the treatment itself, and – last but not least – a quality control of the daily work. Quality control pervades all aspects of medical care. What does it mean in relation to a critical practice of opiate-assisted treatment?

The World Health Organization (WHO) offers a framework with reference to the evaluation of the treatment of disorders resulting from the use of psychotropic substances (ICD-10 F1). This eight-volume comprehensive workbook [6] was created in cooperation with the United Nations International Drug Control Program (UNDCP) and the European Monitoring Center on Drug and Drug Addiction (EMCDDA). The comprehensive contributions of the Swiss Federal Office for Health (FOH) in Bern to these books should be mentioned. Regarding their content, questions related to planning, organization, need checking, treatment procedures, costs, customer satisfaction and finally also clinical and economic results and their associated evaluations are discussed. According to the WHO definition, the focus of a critical clinical practice can be understood as follows: to meet the needs of the overall population as a result of the efficient use of scarce resources.

The Organization of the Treatment

A brief overview of the organization of the treatment should make a better understanding possible. The treatment of opiate addicts with methadone began in the 1960s in the USA and Great Britain [7]. Since 1984 the Psychiatric University Clinic (PUK) of Basel has offered a methadone-assisted therapy. Besides roughly 500 patients who are currently delegated to general practitioners, around 170 are being looked after at the outpatient clinic. Also in the 1960s, buprenorphine was developed as a semisynthetic opioid and it is often utilized in France for substitution treatment [8]. In Switzerland, a multicenter study of its application is planned for 2002.

Besides a documented opiate addiction of several years' duration, the acceptance criteria for an opiate-assisted treatment also include the addict being an adult and proven deficits in medical, psychological or social areas shown to be the result of the consumption of the drugs. An (at least verbally) expressed readiness to cooperate and the purchase of the prescribed substances for the patient's exclusive consumption are further preconditions for the acceptance to the treatment.

The aim of opiate-assisted treatment includes the improvement of physical and mental conditions, a strengthening of performance and the ability to work, abandoning delinquent behavior and prostitution, and abstinence from psychotropic substances which have not been medically prescribed. Lasting abstinence has always been the long-term goal. In addition areas such as general life competence, the living situation, how leisure time is spent and financial circumstances also stand in the center of goal planning. In order to achieve these aims, regular medical checkups and treatments take place. Support from a technically trained case manager should help the patient to discover his own resources and to use them as well as make the resources of the social system available. The relationship between patient and case manager is a central part of the opiate-assisted treatment system. There are a number of differing aspects attached to the concept of an assertive community treatment (ACT): counseling, making examinations possible, giving medications, involving the relatives, offering factual help, holding regular conferences with helpers, doing administrative jobs, arranging psychotherapy and much more. With regular proactive (initiating and follow-up) contacts – which go far beyond the taking of the substance – the case manager introduces the patient to a model for a self-reliant, self-determined and personally rewarding lifestyle [9].

The taking of the substances varies: methadone is consumed orally on a daily to weekly basis at the beginning under supervision, diacethylmorphine (newly accepted for use in Switzerland as Diaphin®) must be injected 2–3 times daily 7 days a week under medical supervision, and buprenorphine can be taken sublingually after a 2-week supervised regulation phase.

In the institutions which offer opiate-assisted treatment, these treatments are performed by multidisciplinary teams. With roughly 60% being nurses, followed by 19% medical doctors/psychiatrists and social workers each, psychologists with barely 2% represent a distinct minority. But even the large number of methadone maintenance treatments cannot be managed without the active and valuable cooperation of general practitioners and druggists.

The general treatment successes are meanwhile well-documented [10, 11]. A relevant number of patients attain stabilization from a medical and psychosocial viewpoint. Hygiene and nutrition improve and reliable medical care

is successfully realized. The overall conditions of health improve. In this way mental disorders can be efficiently treated, too. New infections with viral hepatitis and HIV occur seldom and problems related to abscesses, for example, decrease.

Starting Treatment

Two aspects which determine therapy should be singled out here for attention. On the one hand, the number and extent of comorbid disorders especially of opiate addicts have a quantitative meaning. On the other hand, the multiple drug use of nonopioid psychotropic substances represents a major threat.

Comorbid disorders are those which are listed in chapter F in the ICD-10 besides those in F1 (disorders caused by the use of psychotropic substances). In the 'ADS' (Outpatient Clinic I, Department of Substance Use Disorders) of the Psychiatric University Clinic (PUK) of Basel, methadone-assisted treatments were carried out. In 1998 in a group of 112 patients, we found a lifetime prevalence of 50% with a personality disorder, around 15% with schizophrenic disorders, over 25% with a depressive disorder and around 10% with anxiety disorders. In the 'Janus' (Outpatient Clinic II of the PUK Department of Substance Use Disorders) heroin-assisted treatments were done. In a group of 186 patients we found over 45% with personality disorders, 5% with schizophrenic disorders, around 20% with depressive disorders and around 5% with anxiety disorders. A study of the new admissions – for all of Switzerland – in the heroin-assisted treatment centers evaluated 85 patients between October 2000 and March 2001 and found (lifetime prevalence) that around 60% had a personality disorder, around 5% had a schizophrenic disorder, over 50% a depressive disorder and over 20% anxiety disorders. Figure 1 illustrates the comparison of this data together with a meta-analysis covering 16 trials and a total of 3,754 persons, which at least relativizes the data of the new admissions in the whole of Switzerland. In addition, it will be seen that only the PUK treats organic mental disorders at the same time during opiate-assisted treatment and the number of schizophrenics is overrepresented in the 'ADS' (Ambulanter Dienst Sucht; methadone outpatient clinic).

In December 2000, in 'Janus' (heroin-assisted treatment) with 144 patients, roughly 10% were HIV-positive with around 20% having an unknown status. Two thirds of the patients were positive for hepatitis B and around 80% for hepatitis C whereby the status was unknown in about 6% of each group. In Basel, regular annual surveys of all methadone-assisted treatments are made

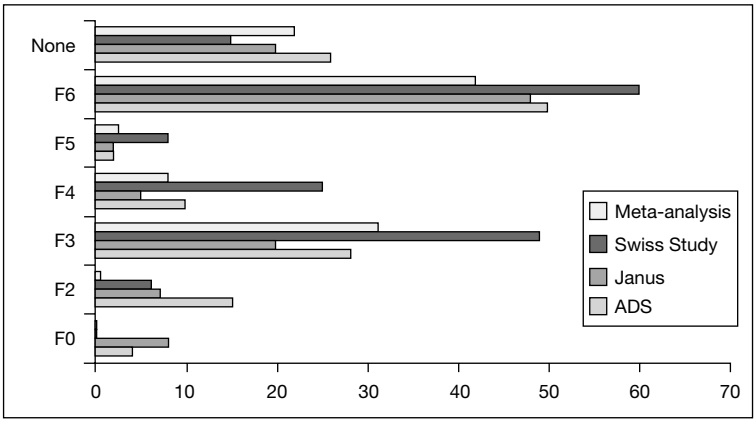

Fig. 1. Comorbidity in opioid-assisted treatment settings.

by the 'Kantonsarzt' (surgeon general of the canton) and the PUK. In 2000, data was obtained for 896 patients [12]. Of these, around 8% were HIV-positive with around 15% with an unknown status. Roughly 40% of the patients were found to be positive for hepatitis B and C each, with the status being unknown in roughly 40% (which is alarming).

Regarding the multiple use of nonprescribed psychotropic substances, it was established in the 'Janus' that over 20% of the patients take substances other than only diacethylmorphine, around 22% cocaine and around 13% methaqualone. These numbers tend to vary as we know from over 2,000 urinalyses done over a period of 5 years [13]. As a rule, urine samples are taken from all patients under visual supervision 4 times a year in order to do an overall evaluation at a certain point in time. In figure 2 the course with respect to cocaine-positive urinalyses is shown. The samples from October 2000 included only 49 patients who were purposely selected, which may explain the high percentage of cocaine-positive urine samples (43%).

The substance methaqualone has only been systematically looked for in 'Janus' since April 2000. Since then the number of positive urine samples has increased. Especially high is the percentage (29%) in the subgroup of 49 patients mentioned above with the cocaine-positive results which are just as overrepresented. Possibly there exists among some of the patients the desire for a stimulating effect from cocaine and – maybe as a result – for a hypnotic sedation to the same degree. With its number of cocaine-positive analyses 'Janus' lies in the middle of the distribution according to a poll of the FOH of 15 heroin-assisted treatment centers in December 1999.

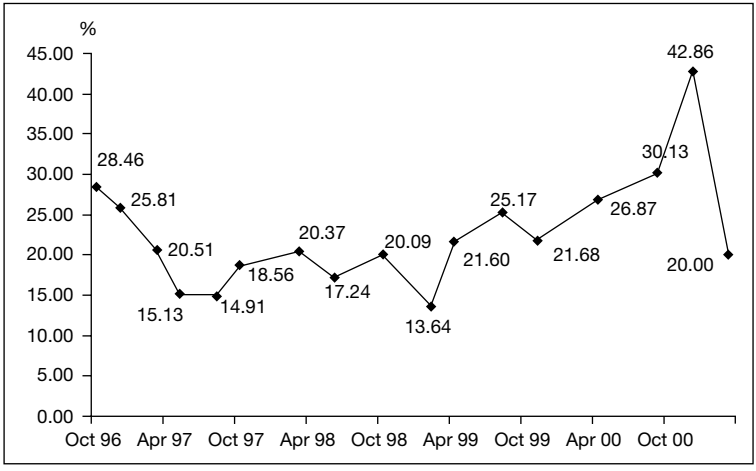

Fig. 2. Time course of cocaine-positive urinalyses.

Strategies for Reaching the Goal

Repeated 5- or 10-min medical counseling sessions are more effective than no counseling at all. They can be just as effective as more demanding methods in the prevention of relapse of opiate addicts [14]! What makes up these 'more demanding' methods? Here via a meta-analysis the elements of effectiveness training and relapse-handling strategies could be identified. The systematic utilization of these elements is better than no treatment or counseling. They are just as useful as other forms of psychotherapeutic intervention. One of their special advantage, however, is that they reduce the intensity of the relapse, their effects last longer and they are well suited above all to the more dysfunctional, comorbid patients. Unfortunately these findings are based on only 14 relevant and statistically usable studies, the majority of which were undertaken in the context of nicotine dependency. Nevertheless, it does not seem presumptuous when in general one derives from this that the following elements are helpful for modifying drug use behavior.

- One must clearly distinguish between *lapse* and *relapse* in order to react appropriately.
- Early warning signs of drug use and individual risk situations should be recognized, described and functionally employed or avoided.
- Checking the consumption is the first interim aim.
- It must always be kept in mind that the patients are indeed experts on their lives and the life on the street but nevertheless their ideas about anatomy,

substance effects and the potential for damage are partly mistaken. Psychoeducation can help here.

- Usually the entire lifestyle of the patient must be critically looked at and reformed.
- The training of coping skills takes on a central role. Training in self-confidence is mentioned as an example.

Precisely such elements are also described in order to put together in a useful way the contents of the short contacts mentioned above. Usually a long-term treatment is based on a supportive relationship. Coordination and maintaining contact are important structural elements of therapy. In addition information about self-help structures should be imparted. The treatment of comorbid disorders with the corresponding psychopharmacological medications should be self-evident. Finally, the relatives should also be integrated into the treatment. They should be viewed as valuable resources and not primarily as guilty, codependent or 'only' lay persons.

The Safety of the Treatment

Two aspects should be emphasized here: generally unforeseen episodes or undesired incidents and the question of mortality.

In Switzerland a spontaneous notification system exists regarding undesired incidents during heroin-assisted treatment. Within the framework of this system a variety of 26 items have been specified so far. In the interval from September 1997 to December 2000, all treatment centers reported a total of 1,026 such incidents. The 'Janus' contributed 108 (10.5%). The 'notifying discipline' varied from 0 to 30% during that time. The most common problems had to do with respiratory depression, epileptic attacks, anaphylactic reactions and suicide attempts [15, 16]. Among these the first three concern incidents that occurred within the treatment rooms and were observed by the treatment staff, while deaths – irrespective of which kind – have not occurred in any treatment facility directly during the application. Of the 108 incidents reported by 'Janus', there were 14 with respiratory depression, the same number with anaphylaxis and 11 epileptic fits. The rest were individual incidents.

Figure 3 illustrates the frequency of the various reasons that were given for leaving heroin-assisted treatment. The data made available by the FOH is derived from 443 persons who left treatment between 1994 (begin of the PROVE study) and March 1999.

Among the 36% who switched over to methadone-assisted treatment there are also a few cases of disciplinary dismissals and further mediation, which was attempted in all cases. The frequency of 6% related to disciplinary exclusion

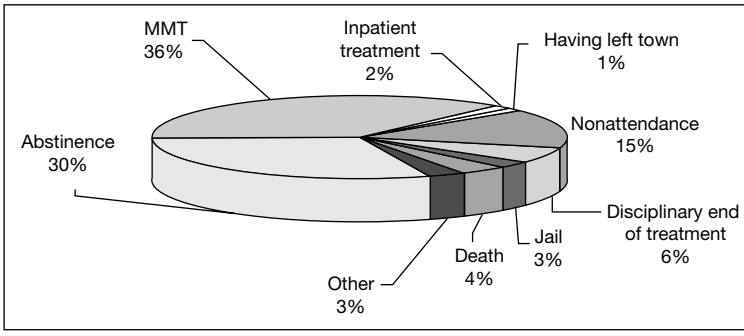

Fig. 3. Reasons for leaving heroin-assisted treatment. MMT = methadone maintenance treatment.

seems to be too low. Thirty percent 'abstinence' includes those patients who changed to an abstinence-oriented therapy. How many of these actually achieved abstinence and for how long is unclear. Four percent deaths includes 18 persons in 5 years, but here the cause of death also remains open. Especially in relation to an opiate-assisted treatment, the question of mortality is complex.

According to an evaluation made recently, the annual mortality rate for all Swiss heroin-assisted treatments is 1.78%. In 'Janus', there were 7 deaths between September 1997 and December 2000. Of these, 5 happened within a single 12-month period (1998/1999). They were 2 men and 3 women who were born between 1967 and 1973. They began their treatment at 'Janus' between December 1994 and June 1995. The treatment durations ranged from 6 months to 3 years and 8 months. Among these there was only 1 person who was at the time being treated (0.7%, n = 1 out of a total of 150 patients). Four persons died more than 4 months after the end of the treatment.

From 1992 to 1994 a survey was made of the annual mortality among opiate addicts in Basel (before 'Janus'), who were on some kind of methadone-assisted treatment. One hundred and two deaths were identified. The mortality rate decreased from 5.0% in 1992 to 3.6% in 1993 and to 2.9% in 1994. Fifty-six of them died of AIDS, 27 died of intoxication and 19 deaths were due to suicide, murder or infectious diseases other than AIDS [17].

International data concerning the annual mortality of the persons with heroin addiction clearly wavers between 1 and 4% [16]. The rate for persons in a methadone-assisted therapy lies between 1.14 and 6.8%. It is noteworthy, however, that in New York between 1976 and 1996 the mortality rate for those in methadone-assisted treatment programs was found to be 1.52%. For those who left such treatment programs it was 3.52%. A comparison with the annual

mortality rate of the entire population of New York during this decade has unfortunately not been made.

The Future

According to the WHO definition, 'critical clinical practice' implies meeting the needs of the overall population as a result of the efficient use of scarce resources. Aspects such as 'organization', 'therapy-disturbing behavior', 'goal achievement' and 'safety' were briefly explained in this report. They are all mainly related to 'needs' in accordance with this definition. If a critical clinical practice involving opiate-assisted treatment is going to be 'critical' in the truest sense of the word, the concept of 'efficient use of scarce resources' has to be discussed.

Available resources can be enlarged by networking: the provision of therapeutic drugs for the population, the knowledge about addiction medicine and research into disorders caused by the use of psychotropic substances are to be networked and more focused. This has to happen not only in terms of content but also in terms of personnel and organization. Opiate-assisted treatment provides an ideal framework for discussing fundamental aspects of drug therapy. With a view towards setting up and procedural organizational configurations, process teams with higher configuring competence have proven themselves superior to other forms. The principles of self-responsibility and self-direction could – and should – be effective here. Effective cost management coupled with a constant comparison with other approaches to the problem of 'addiction' (benchmarking) can prevent massive mistakes. Specialization in addition to the provision of widespread basic services, flexible offers and goal-oriented investments assume adaptability and a readiness for cooperation among all who are involved – even when this would mean that certain areas of competence are be lost. A multidisciplinary cooperation among medicine/psychiatry, nursing, psychology and social work can only lead to success through the definition of points for main emphasis which are focussed on interactively and encouraged. The involvement of all in planning the allocation of resources, knowledge and research is important.

In this sense the Basel PUK has introduced comprehensive education controlling in the area of addiction medicine, which has been structured and built up multidisciplinarily over 2 years and which involves external cooperation. In research the use of drugs such as cocaine, benzodiazepines and methaqualone should form a center of concern. The treatment of personality, depressive and anxiety disorders is a further field to be studied.

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Follow-Up of Substance Abusers Who Had Left the Heroin Prescription Programme in Geneva

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Many papers, articles and reports have been published about Swiss heroin prescription programmes and their results. However, little is known about what happens to patients who leave such a programme.

In this article we will briefly describe the background to the Swiss heroin prescription programmes and provide a summary of different reports, before presenting the results of a small prospective study of patients who left the heroin prescription programme in Geneva.

Background to and Objectives of the Swiss Heroin Prescription Programmes

In Switzerland, the law on illicit drugs of October 1951 prohibits fabrication and use of diacetylmorphine and other 'illegal' drugs for non-medical purposes. The experimental use of these drugs can only be authorised for a restricted range of medical purposes and only after obtaining special permission from the Swiss Federal Office of Public Health (SFOPH).

In the late 1980s to early 1990s Switzerland was confronted with an alarming heroin problem; many heroin users were also HIV-infected or had other medical, psychological and social problems. At that time only a few harm reduction strategies existed, and the only drug treatment available was limited to abstinence-oriented therapy and methadone maintenance. In 1989 the question of medical prescribability of heroin was addressed by the Günther motion, and Dr. Mino (Geneva) was given the task of writing a report on the subject.

Table 1. Objectives of heroin prescription [from 3]

Reaching a hard core group of injecting drug users who have repeatedly failed on conventional treatment
Improving treatment retention
Improving health, social conditions and working capacities
Decreasing parallel drug use and criminality
In the long term achieving abstinence

In 1991 the SFOPH proposed a Swiss drug policy called the four-pillar drug policy: prevention, treatment, harm reduction and repression. The medical prescription of heroin for severely addicted heroin addicts, who have failed repeatedly in conventional treatment, was allowed in 1992 as part of a diversified treatment offer. An 'ordonnance' was published containing the authorisation and regulations for the experimental heroin prescription programmes. The first programmes (PROVE) commenced in 1994.

The SFOPH is responsible for the coordination of centres and pharmacies as well as the production and distribution of diacetylmorphine. All treatment requests have to be addressed to the SFOPH who verifies compliance with treatment entry criteria. The evaluation of treatment results was delegated to an independent group of researchers (Addiction Research Institute Zürich).

The objectives of heroin prescription are listed in table 1.

Evaluation: PROVE 94–96

The first phase (PROVE 94–96) involved 1,146 patients in 17 centres. At the start of treatment the mean age of the patients in the cohort was 31 years and the mean duration of illegal drug use was 10 years; 91% had already been in a substitution programme and 89% had previously on at least one occasion tried to detoxify. The data suggest that the target group (patients presenting with severe opiate dependency and showing social and health consequences) was reached. Results after 18 months showed the following [1]: heroin use is feasible and safe, social conditions improve (fig. 1), illegal parallel drug use decreases, criminality decreases and psychological and somatic health improve (fig. 2).

A small randomised clinical trial in Geneva [2] suggested that heroin prescribing was superior to conventional drug treatment in several areas.

Based on these results the practice of prescribing heroin was allowed to continue ('arrêté fédéral urgent' 1998). The Swiss drug policy was confirmed

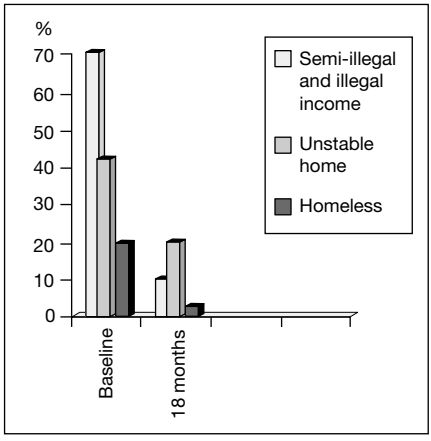

Fig. 1. Social conditions.

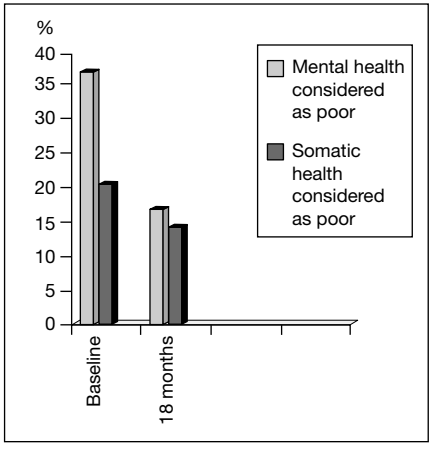

Fig. 2. Health indicators.

by a popular vote in 1999, when the experimental phase of the heroin prescription phase ended, and a phase of 'consolidation and quality improvement' began. The authorisation allowing heroin to be prescribed is valid until 2004, when heroin will become part of the Swiss pharmacopoeia.

Evaluation: Reports 1999 and 2000

The number of different centres prescribing heroin and the total number of treatment slots increased slowly. In 2000 the total number of heroin treatment slots was 1,194 in 20 centres. This means that 4% of the estimated 30,000 Swiss opiate addicts can benefit from these programmes.

After 6 years of experience, some facts have emerged. (1) The occupation rate is about 88%, and in most centres there are no waiting lists, (2) programmes address a chronic population: 34.8% of the patients are in the programmes for more than 4 years, and (3) this last group consists of patients whose social position and health situation had greatly declined before joining the programme and where heroin on prescription also serves to keep them within the health and social network [3, 4].

During the year 2000, 175 patients left the heroin prescription programmes, and of these 73% were considered as 'positive departures' (opting for methadone maintenance or abstinence-oriented therapy). In 1999 24% had opted for an abstinence-oriented program and 36% for a methadone maintenance programme [3, report 1999]. The so-called 'negative' reasons for quitting are also well established: 12% dropped out, 8% were excluded (the majority of these for violence), 4% died and 5% went to jail. There seems to be a slight increase in 'positive' departures over time, which could be related to staff's experience or simply the criteria used to select patients.

Nevertheless, there are several methodological problems that become apparent when interpreting these results: (1) those who leave for methadone maintenance treatment are probably a mixture of positive departures (those wanting to quit injecting before complete detoxification) and negative departures (e.g. those who are fed up with the constraints of the programme) and (2) 'negative' and 'positive' are two extremes; some patients have intermediate results.

Little is known about what happens to patients in the medium or long term after having left the programme. The objective of our study on patients who left the Geneva heroin prescription programme between September 1995 and December 2000 is to describe in greater detail why and how patients quit such a programme and what happens to them afterwards.

Geneva: Study Setting

Geneva's population of addicts is estimated to be about 2,500–3,000 persons. In the early 1990s there was an alarming AIDS epidemic (up to 35% of drug addicts were HIV-infected), and very few addicts were in drug treatment. In September 1991 the council decided that every drug user who was prepared to give up drug use should have access to an institution that was able to help him to overcome his dependence and every drug user who was not prepared to give up drug use should receive help to survive. From that moment a real 4-pillar drug policy (consistent with the Swiss drug policy) developed: harm reduction programmes were introduced and public methadone maintenance programmes were opened. It is estimated that since 1998 over 60% of drug users remain in touch

with the health care system and that over 1,400 have been in a methadone maintenance programme.

The Experimental Prescription Program of Heroin (Programme Expérimental de Prescription de Stupéfiants, PEPS) began in 1995 with 40 treatment slots. It was designed initially as a randomised clinical trial. Eligible addicts were randomised either for immediate admission (n = 27) or for a 6-month waiting list (n = 24, on which 22 cooperated during the whole period). Patients on the waiting list received the best available treatment of their choice as well as help to receive this treatment; most of them opted for methadone maintenance treatment. After 6 months, both groups had improved in all of the aspects that were evaluated, but the heroin group had fared better than the conventional treatment group in terms of street drug use, illegal activities, mental health and social functioning [2].

The PEPS is part of the Substance Abuse Division of the Department of Psychiatry at the University Hospital in Geneva. There is a multidisciplinary team involving nurses, a social worker, a psychiatrist and a general practitioner. The programme has had 50 slots since 1999 and is open 3 times daily, 7 days a week. Treatment entry criteria are those defined by the SFOPH. At the start of treatment individual treatment objectives are defined and progress towards those objectives is evaluated regularly.

Methods

This is a partly historical, partly prospective cohort study of all patients who left the Geneva heroin prescription programme between September 1995 and December 2000. Data were collected by a systematic review of all standardised study and clinical charts of the patients while in treatment. For the period after the PEPS different sources of information were used: clinical charts in private and public substance abuse programmes or GP's offices, administrative databases of the general and psychiatric hospital, inspection of hospital charts and direct contact with different healthcare workers.

Treatment success or failure were defined as follows: success: patients having reached the treatment objectives defined at the start of heroin prescription, failure: patients leaving without having reached these objectives and intermediate: patients having partially reached the objectives.

Results

Between September 1995 and December 2000, 67 patients entered the programme. The average age was 37 years with the average duration of substance abuse treatment exceeding 10 years; the prevalence of psychiatric

Table 2. Retention within health care system and use of illegal drugs

	Months			
	6 (n = 22)	12 (n = 21)	18 (n = 17)	24 (n = 13)
Retention, %	82	86	84	86
Illegal drug use, %	80	70	55	46

Figures in parentheses represent patient number.

and medical comorbidity was very high. The mean duration of treatment was 22 months and the retention rate 88% per year. Globally, while in treatment, the patients' mental health and social functioning improved and illegal activities and the use of non-prescribed drugs decreased.

During the same period of time, 23 patients left the programme after a mean duration of 22 months of treatment (median 16 months). Of them 30% (n = 7) opted for an abstinence-oriented therapy, 61% (n = 11) for a methadone maintenance programme, 17% (n = 4) have been excluded, 3 of whom went to a methadone maintenance therapy, and 1 had to go to prison for an offence committed before entering the programme. The methadone group is a mixture of 'negative' and 'positive' departures: patients leaving on a voluntary base to quit injection, people being tired of the constraints of the programme and patients who were excluded and had to go back to maintenance therapy.

At the time patients were leaving, 35% (n = 8) could be considered as initial successes, 39% (n = 9) as failures and 26% (n = 6) as intermediate results.

Follow-up data were available for 22 of the 23 patients who left the programme (96%). Six months after exiting the programme a large majority of the patients had relapsed in illegal drug use but this decreases over time (table 2).

Retention within the treatment system is high and stable at over 80% in all of the periods reviewed. After 6 months, 82% are still being monitored in public or private institutions; 2 patients are in prison; 2 patients who went to a residential abstinence centre left their project and relapsed; 4 of the 5 patients who joined an ambulatory abstinence project also relapsed. One of these patients returned to the heroin prescription programme but has a cocaine habit at the same time. The patients on methadone maintenance therapy are, with 1 exception, in an intermediate situation.

We carried out the last assessment in February 2001 after a median follow-up time of 36 months. Data were available on 22 of 23 patients. Of them, 20 of

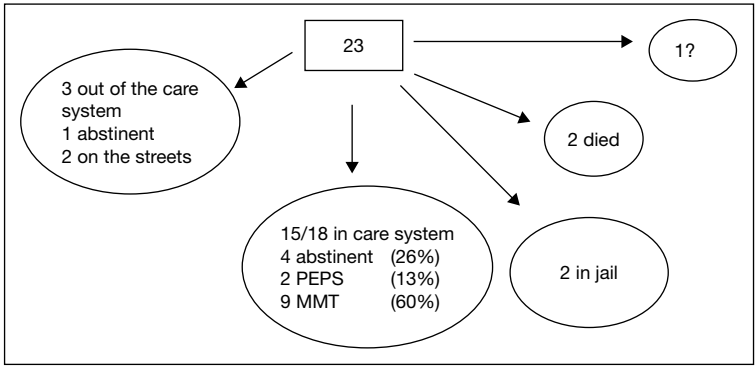

Fig. 3. Follow-up in February 2001 (median 36 months after having left the programme). MMT = Methadone maintenance treatment.

the 22 were alive, 2 patients had died (1 of chronic liver disease, 1 of overdose and endocarditis). Two persons were in jail for crimes committed after having left the PEPS. Fifteen persons were still within the net of the health care system: 4 were abstinent, 9 in a methadone maintenance programme and 2 back in the heroin prescription programme. Three persons were no longer in the care system, 1 being abstinent and 2 on the streets (fig. 3).

After a median follow-up of 36 months 6/22 (27%) can be considered as successes, 7/22 (32%) as intermediate results and 9/22 (41%) as failures. Four of the failures are dramatic: 1 patient died of endocarditis, he had also been infected with HIV and HCV after having left the PEPS. Two are in jail, 1 for assaulting nurses in a psychiatric hospital, and the other for a hold-up. One was on a liberty deprivation pronounced by a civil judge and had a very serious accident when trying to escape from the psychiatric hospital. These 4 patients were all initial failures and 3 of them are compulsive cocaine users.

Despite the small cohort, we tried to identify factors predictive of a bad outcome in the long term: 1) initial treatment failures: of 10 initial failures 8 had a bad outcome (80%) compared to 1 out of 13 non-initial failures (8%), 2) primary cocaine use: of 10 cocaine users, 7 (70%) had a bad outcome compared to 3 out of 12 non-cocaine users (25%) and 3) severity of psychiatric comorbidity: 6 of the 9 global failures have multiple or dissocial personality disorders.

Discussion and Conclusion

Our small study on patients leaving the Geneva heroin prescription programme over a 5-year period shows that at treatment exit 61% of the patients

had totally or partially reached their initial treatment objectives. After a median follow-up of 36 months posttreatment 59% continue to do relatively well. These statistics do not, however, necessarily reflect the progress of one and the same group of individuals over time.

Considering the fact that patients participating in heroin prescription programmes are among the most 'difficult' in terms of social situation and health status and in parallel drug use (they are those who fail repeatedly in conventional forms of drug treatments) these results can be considered as satisfactory.

It should be kept in mind that these data concern patients who quit the programme, and that the majority of the patients remain in a heroin prescription programme for a long time. The success or failure of the programme as a whole cannot be evaluated by considering those who quit. The results of this study do not have to be enlarged to global evaluation of heroin prescription.

Predictors of a bad outcome have been pointed out, even if these results, because of the small number of patients, have to be treated with caution: initial failures at the time of leaving (negative departures), primary cocaine use and the presence of severe psychiatric comorbidity. Among global failures, almost half have an extremely bad evolution. The very intense setting of and 'involvement with' the programme probably makes it difficult to leave. It has to be pointed out that patients have their own evolution, due to their psychopathology, family history, illegal drug use and that their good or bad evolution cannot be only related to the fact that they have left the programme.

We encountered a major methodological difficulty in defining clearly measurable indicators of success or failure in this specific group of patients. Abstinence seems to be the most politically acceptable outcome but it is clearly not a realistic nor desirable goal except for a small number of patients. Retention in treatment seems an adequate goal for most addicts.

Heroin prescription programmes are currently considered as a 'last resort' in the drug treatment offer after failure in abstinence-oriented therapy and methadone maintenance treatment. However, there are a few patients who do not benefit from a heroin prescription programme as much as it was hoped and who are then at risk for a difficult evolution when they leave. Is this due to the relatively high level of constraints of the programme, should we think of another alternative for this 'extremely extremely' difficult group?

It is worth noting that heroin prescription programmes seek to address a group of opiate addicts and not cocaine addicts. The currently increasing cocaine epidemic in Geneva, and the fact that patients who have a primary cocaine use are at risk for a more difficult evolution drove to the design of a specific intervention (individual and in groups, based on cognitive behavioral approach) within the evaluated heroin prescription programme [5]. The heroin

prescription programmes are excellent to introduce such therapeutic frameworks because of their high level of follow-up (up to three times a day).

Our results confirm the concept of addiction as a chronic disease with a high risk of relapse after a period of abstinence. One of the principle aims of drug addiction treatment is to reduce the frequency and the severity of relapses involving illegal use and its negative consequences. The Swiss experience suggests that most drug users who fail repeatedly in conventional treatment and who then enter comprehensive heroin prescription programmes will remain in long-term treatment and will globally improve. Our study suggests that, for those who want to quit such a programme, the departure should be carefully prepared and that relapse prevention or another form of aftercare should be proposed.

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Perspectives of Opiate Detoxification Treatment

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Goals of Opiate Detoxification Treatment

A central feature of opiate addiction is physical dependence. One reason why the addict carries on with the use of opioids is the occurrence of withdrawal symptoms some hours after the last heroin intake. Due to the development of tolerance the amount of drug needed to prevent withdrawal increases over time. In order to become drug-free the addict has to pass the period of withdrawal. It is known that the majority of addicts repeatedly try to detoxify without medical help, not least due to the fact that the supply of heroin is not always sufficient.

The goals of opiate detoxification treatment [1] are: alleviation of withdrawal symptoms, prevention of complications, e.g. withdrawal seizures in case of concomitant benzodiazepine detoxification, the diagnosis and treatment of comorbid somatic and psychiatric disorders and referral to further abstinence-oriented treatment.

As can be seen from this list, detoxification treatment has no end in itself. It is only a step in the process of establishing an abstinent lifestyle. Without further treatment the majority of detoxified opiate addicts will resume opiate use within the first months after detoxification. Therefore, opiate detoxification treatment has to include an evaluation of comorbid disorders, an elaboration of an individually adapted treatment plan, and motivational interventions to commence further treatment.

My report focuses on our own research work on improvements of opiate detoxification treatment.

Alternative Medical Strategies in Opiate Detoxification Treatment

The medical strategies to alleviate withdrawal symptoms are well established. One starting point for medical strategies is the hypothesis that the majority of signs and symptoms of opiate withdrawal are consequences of a rebound hyperactivity of the sympathetic nervous system due to a release from opiate-induced inhibition of the activity of the locus coeruleus in detoxification [2]. α_2-Agonists such as clonidine and guanfacine, which suppress sympathetic activity, are well-evaluated drugs alleviating withdrawal symptoms in patients after having given up heroin use [3, 4].

A second strategy is based on the assumption that the peak intensity of withdrawal is related to the elimination half-life of the respective opioid, e.g. the intensity of withdrawal from heroin with a half-life of about 6 h is more pronounced than withdrawal from methadone with a half-life of about 24 h. Therefore, the second strategy consists in a switch from heroin to methadone, which is gradually reduced over the following few days. Also, this strategy is well evaluated in its capability to alleviate withdrawal symptoms [4–6]. Sometimes the two strategies are combined. In addition, further symptom-oriented medication is administered, e.g. trimipramine or doxepin (against sleeplessness) and nonsteroidal antirheumatics such as diclofenac (against muscle and bone pain).

However, in spite of these well-established strategies about half of the opiate addicts commencing a detoxification treatment drop out prematurely [1]. Under the assumption that this high rate of treatment failures is due to the unbearable intensity or length of withdrawal symptoms, new medical strategies were tested. Some attention, even in the mass media, was given to the so-called ultra-rapid detoxification of opiate addicts. This detoxification method involves acute displacement of opiate drug molecules from the receptor of the endorphin system by administration of large doses of opiate antagonists such as naloxone. The patient, however, does not experience withdrawal symptoms as he is heavily sedated or anesthetized during this period. According to the proponents of this method there were only minor withdrawal complaints after the end of anesthesia [7].

In contrast to the extended claims of the proponents there is only a small number of scientific studies on opiate detoxification under anesthesia. Due to methodological shortcomings of these studies, e.g. small numbers of patients, short observation periods or no control groups, these claims have not been proven until now [8]. In one of our own studies 22 patients, exclusively addicted to opiates and pretreated with methadone, were included [9]. These patients were carefully selected during a preceding outpatient period of several weeks,

during which postdetoxification treatment was already planned. On the day of admission to the psychiatric hospital, a physical examination (including ECG, chest X-ray and urine drug screening) was carried out. The following day patients were transferred to the Intensive Care Unit. There the rapid detoxification procedure was carried out with maximum safety standards including invasive arterial pressure and hemodynamic monitoring, a Foley catheter and a gastric tube. During general anesthesia lasting about 6 h with methohexital or propofol, naloxone was administered with a starting bolus dose of 0.4 mg. The dose was doubled every 15 min. The total bolus dose was 12.4 mg delivered within 60 min, and was followed by a naloxone infusion of 0.8 mg/h until the next morning. On the day of anesthesia naltrexone (50 mg/day) treatment was initiated. In case of withdrawal symptoms, specific medication was added. The day after anesthesia, patients were transferred back to the psychiatric ward. There they stayed until the remission of withdrawal symptoms, which were monitored over 4 weeks using the Short Opiate Withdrawal Scale [SOWS; 10].

In contrast to the above-mentioned claims, patients were suffering from marked withdrawal symptoms for at least 1 week after detoxification. On average, patients were discharged after a total inpatient stay of 8 days. None of the patients encountered a life-threatening complication and only 1 patient failed to complete the detoxification procedure. Seventy-five percent of the patients could be referred for further treatment, in most cases naltrexone treatment. After this study the rapid detoxification procedure was stopped in Essen above all because of a lack of suitable patients, e.g. most patients interested in this method were polydrug users and/or not motivated for further treatment after detoxification.

At the present time, rapid detoxification under anesthesia cannot be finally assessed [8, 11]. In one of our own multicenter evaluations [12] there were no life-threatening complications. This might be due to the high safety standards, including rigorous indications, a thorough pretreatment evaluation and extensive monitoring during anesthesia. However, there are still doubts regarding the efficacy of this procedure. Also, in the multicenter study relevant withdrawal symptoms lasted for several days on average.

Alternative Setting for Opiate Detoxification Treatment

As stated above, there are well-evaluated medical strategies to alleviate withdrawal symptoms in opiate detoxification. This leads to the question of whether opiate detoxification treatment can be carried out in settings other than an inpatient ward of a psychiatric hospital, e.g. in an outpatient clinic and or a day treatment clinic. As with the treatment of other psychiatric disorders these

alternative settings could have several advantages, e.g. attracting patients for treatment who would not undergo an inpatient treatment, e.g. mothers with young children, and inclusion of the social situation of the patient in the treatment, which is of special importance regarding relapse prevention.

There might be the disadvantage that detoxification outside an inpatient ward is expecting too much of opiate addicts. However, there already exist some encouraging experiences regarding opiate detoxification in a day treatment clinic [13]. In April 2000, a day treatment clinic for opiate detoxification opened at the Psychiatric Department of the University Hospital in Essen. The clinic has seven places. Treatment is offered for seven days a week from morning to afternoon. Day treatment on weekends was established, in order to minimize the risk of relapse. The day treatment is offered by a multiprofessional team including psychiatrists, a psychologist, nurses, a social counsellor and a work therapist. The multiprofessional team corresponds to a multidimensional structured treatment plan including psychotherapeutic group sessions and responsibility on part of the patients in the involvement in planning and carrying out daily activities.

The day treatment unit is in close collaboration with an inpatient ward for detoxification treatment. Thus, inpatient treatment can be shortened by a transfer to day treatment, and in case of failure of day treatment a transfer to the inpatient ward is possible. In these cases, continuity of care by almost the same team is guaranteed. Opiate detoxification is carried out using the above-described strategy of a temporal methadone administration. Contraindications are current psychiatric or somatic disorders, which make inpatient treatment necessary, e.g. current schizophrenic episode, suicidality or endocarditis, severe complications during former detoxification treatments, e.g. seizure during benzodiazepine withdrawal, and homelessness.

Until now, day treatment detoxification has not been finally assessed. At Essen University, an analysis comparing inpatient and day treatment detoxification is under way. According to the clinical impression, day treatment detoxification can be successfully carried out. There were no life-threatening complications.

Conclusion

So far, opiate detoxification treatment has had only a limited success. Only about 50% of patients complete detoxification up to drug-free urine or to remission of withdrawal symptoms, and even fewer patients are referred for further treatment. This might be partly due to the fact that the addicts admitted to detoxification wards do not always want to detoxify from opioids, but just seek

a time-out from the strenuous life in the drug scene. In these cases, detoxification treatment is not indicated. According to the literature and our own experience there are doubts of whether an increased rate of completed withdrawal depends upon an improvement of medical strategies to alleviate withdrawal intensity. Until now, there has been no evidence that experimental strategies, especially opiate withdrawal under anesthesia, is superior to conventional withdrawal treatment. The real problem of opiate detoxification treatment is not the alleviation of withdrawal symptoms, but the motivation of patients to complete detoxification and commence further treatment. With respect to these problems, the investigation of psychological interventions is of major importance.

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Opioid Maintenance Treatment: The Development of Therapeutic Strategies

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General Goals

Each treatment has to be adapted to the latest findings. New methods are superior to previously practiced ones – an opinion held by the mainstream of those who believe in progress. This can produce a dilemma: should proven methods be ignored in order to pit oneself against the idea of novel and presumably better techniques? Is abstinence or maintenance the better goal of therapy? A patient recently complained that treatment used to be conducted according to stricter rules. After he himself had received abstinence-oriented treatment, and subsequently received heroin-assisted treatment for several years, he thought treatment had to be more flexible, since the health of the people on the streets today had deteriorated. Flexibility is an important method of achieving therapeutic goals.

It is often forgotten that we are always influenced by the spirit of our times. In the 1950s addiction was regarded as the expression of a profound disturbance, specifically in the sense of a personality disorder that predisposed a person to addiction; this view based on the neurosis model could also be valid for other disorders. In addition the addict was seen within a moralizing context featuring attributes such as flaws of character, prevarication and antagonism. The illegality of drug use and the numerous concomitant forms of delinquency resulted in the logical conclusion that it was necessary to punish the drug delinquent. The large penal institutions for narcotic addicts in the USA, where convicted opiate users were incarcerated and treated from the 1930s to the 1960s corresponded to a strategy that sanctioned abnormal behavior and attempted to correct it by training and reformation.

At the end of the 1960s, this strategy was fundamentally altered by two diametrically opposed schools of thought: namely, the idea and putting into practice of a therapeutic community (Synenon), and the hypothesis that opiate use could be grounded in a biological deficit that might be relieved by an opioid. This resulted in two different strategies, one social-psychologically oriented and the other biologically oriented. Common to both was the view that deficits were the cause of the disorder, on the one hand socialization deficits, on the other biologically grounded deficiency syndromes. Both views also held that incarceration, however long, could not facilitate full improvement. The latter was particularly emphasized when Abraham Wikler in Lexington, Ky. determined that conditioned withdrawal syndromes were elicited when former opiate addicts left the sheltered settings of the institutions and returned to their home town environments resulting in renewed consumption. It was, therefore, concluded that learning to live with disruptions in the community whether supported by a therapeutic group or by using methadone could facilitate an improved lifestyle.

For me, the question of abstinence or maintenance is less important than the necessity of adopting a basic position and of diagnosing and treating substance-related disorders. This should allow the person concerned to have a certain degree of emotional well-being in the sense of ameliorating his or her complaints in order to learn to cope effectively with the problems of life and, further, to control threatening emotions such as shame, guilt, pain or despair. As a result the patient can eventually be shown realistic ways of living a life of abstinence. This knowledge will permit him to experience respect and trust in himself and others.

The 4-Pillar Model

When this basic position becomes a feature of public debate, a basis for drug policy will be established, which is neither exclusively repressive nor exclusively permissive. In many Swiss cities drug commissions were set up in the early 1970s. A special feature of the Basel commission was that it was headed by two magistrates of the Basel government (city councilors). This made necessary a dialog between the justice and police authorities on the one hand and the medical and social institutions on the other. Over the years this dialog produced the Basel drug policy with its 4 pillars consisting of prevention, harm reduction, therapy/rehabilitation and law enforcement. The aim of law enforcement measures is to reduce the availability of drugs. Prevention aims to reduce the demand for drugs. Proponents of harm reduction and therapy/rehabilitation often find themselves sandwiched in between proponents

of sanction and proponents of prevention. The necessity of pushing through methods of harm reduction in a number of Swiss cities led to the setting up of injection rooms and needle exchange programs, to a significant increase in methadone therapies and finally, to the inauguration of heroin projects. At the same time the prevention of an open drug scene resulted in ongoing repressive measures. To this day, this dual strategy has made necessary a continuous formation of consensus between representatives of social and psychiatric services, justice and police departments as well as representatives of politics and the general public. An important basis for the balancing out of these various interests and the safeguarding of the constantly jeopardized 4-pillar model includes structural requisites such as a drug task force (as in Basel) meeting regularly to discuss current problems with the aim of ensuring a coherent drug policy.

Public safety and promotion of individual health are two objectives of this coherent drug policy. The volatile nature of the ever-changing and ever-topical drug problem requires the maintenance of a low-threshold availability of therapy together with the creation of incentives for drug users not yet included as well as keeping public places safe while preventing the formation of a drug scene. It must always be borne in mind that therapeutic measures should not take on law enforcement functions. In addition, it should be prevented that with the disappearance of the problem from the public eye, it is passed into other government agencies.

Medicine is oriented towards the causes, emergence and development of disease and morbid processes (etiopathogenesis). Another approach results from the concern with the biopsychosocial origins of health (salutogenesis). The promotion of factors to protect against the risks of addiction, i.e. the consideration of individual and environmental resources, has become an important matter. From the salutogenetic point of view the promotion of self-empowerment appears to me to be significant. In a recent study, we were able to demonstrate that alcohol-dependent patients who already had greater confidence in achieving abstinence at the start of treatment showed significantly fewer relapses during treatment and during the follow-up period [1] (fig. 1).

General Therapeutic Strategies

The first and primary aim remains making contact with target groups. Access to treatment should continually be improved by reducing barriers and creating therapy incentives. The secondary goal is the entering into a therapy commitment with an adequate period of treatment or, alternatively, preventing the discontinuation of therapy. The tertiary goal may be formulated as the abstention from substances which have not been prescribed (concomitant

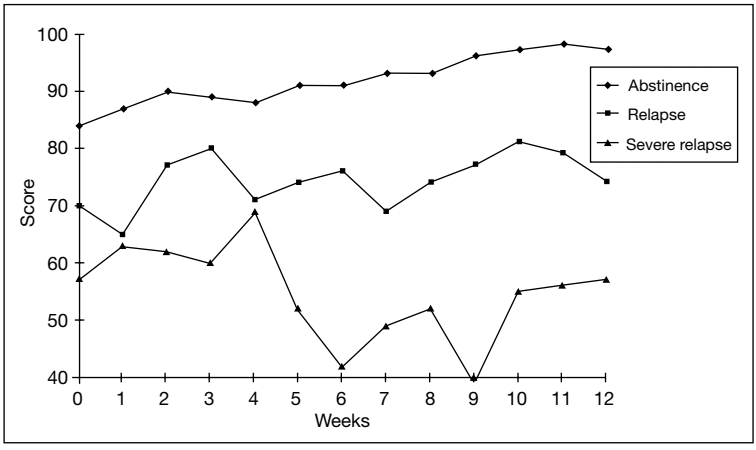

Fig. 1. Abstinence confidence and treatment outcome.

substance use). The ultimate goal as ever is the attainment of lasting freedom from addiction.

What type of intervention and what form of relapse prophylaxis should be used here continues to be the object of medical care research [2]. During the 1990s, the necessity of diversification and differentiation of treatment could be seen to emerge. The realization that there were various user groups and various age groups, different patterns of concomitant substance use and comorbid psychiatric disorders necessitated a diversification in the range of treatments offered.

At the same time, the cost factor of treatment became more and more important and in the years ahead will bring cuts in the relatively broad range of treatments offered today. If improved treatment is to be striven for, treatment costs need not increase regularly; on the contrary, a reduction in direct and indirect costs should be made possible by efficient treatment. In a pre-/postcomparison study of heroin-dependent patients in Basel it was shown that the number of hospitalizations per month and year as well as the number of days spent in hospital and the costs they produced dropped following the initiation of heroin-assisted treatment. On the other hand, there is no doubt that the additional costs arising from the treatment of AIDS and other long-term consequences of drug use are enormous.

Wherever possible economic pressure should not diminish the quality of treatment. Methadone maintenance treatment can be very inexpensive if it is confined to the prescribing of methadone. Without taking into consideration necessary psychosocial interventions and urgently required treatment of

Table 1. HIV seroprevalence between 1992 and 2000

Year	1992/93 n = 501	1994/95 n = 830	1996 n = 919	1997 n = 913	1999/00 n = 896
HIV positive (%)	**29.0**	12.5	10.8	11.5	**9.4**
HIV negative (%)	34.0	61.0	75.8	84.6	90.0
Unknown (%)	37.0	26.5	13.4	3.9	0.6
Total	100.0	100.0	100.0	100.0	100.0

comorbid psychiatric disorders, however, methadone substitution runs the risk of becoming the cause of chronicity of the disorder. Today the phenomenon of hospitalism can be observed not only in stationary psychiatric settings but in outpatient settings as well. Therapy research is confronted with the necessity of investigating the problem of chronicity and, where applicable, of determining whether and when maintenance treatment should be discontinued.

A particular aspect of opioid substitution concerns the prevention of HIV infection. During the yearly evaluation of methadone maintenance treatment in Basel [3] it was observed that between 1992 and 1999 the rate of HIV-positive methadone patients fell from 29.0 to 9.4%, while at the same time the percentage of the rate of unknowns fell from 37.0 to 0.6% (table 1).

Particular attention should be given to concomitant substance use as well as to comorbid symptomatology. In addition to benzodiazepines, which as anxiolytics are quite justified in the treatment of comorbid psychiatric disorders and also in methadone substitution, the use of cocaine and alcohol by some of the patients maintained on methadone is problematical. The endangering of cognitive functions and the resulting negative effects as well as the risk of developing a polysubstance dependence have occasioned a multitude of studies. Psychological interventions and pharmacological strategies are not capable in every case of putting a stop to concomitant substance use. Combinations of various methods appear to be the most promising strategy. To overcome relapse situations, interventions which include a broad spectrum of addiction-specific risk behavior and general lifestyle are necessary (table 2). The basis of these is motivational interviewing [4].

Modalities of reducing substance use and relapse situations include community reinforcement, contingency management, social skills training and various token-economy methods. In a study of our's [5], a combination of token economy methods or the prescribing of methylphenidate was compared with standard treatment for the reduction of supplementary cocaine use during

Table 2. Interventions promoting relapse management

Self-monitoring and functional analysis of risk situations
Self-discipline
Disapproval training
Gradual exposure to risk situations
Coping with craving
Self-management following initial substance use
Lifestyle counseling
Relaxation training
Self-confidence/assertiveness training
Taking comorbid disorders into account

Table 3. Quota of Cocain negative urine tests during the study

Group	%neg total (%)		%neg conservative (%)	
	M	SD	M	SD
Token (n = 10)	**68.4**	35.6	**64.3**	34.8
Ritalin® (n = 8)	**62.8**	37.4	**50.8**	31.9
Control (n = 10)	**23.4**	30.2	**27.5**	33.5
Collective (n = 28)	**50.7**	39.1	**47.3**	34.8

Table 4. Mann-Whitney-Significane Test of Cocain Abstinence

Group	%neg total (%)		%neg conservative (%)	
	U	p	U	p
Token vs Control	13.0	**0.0025***	20.0	**0.011***
Ritalin® vs Control	16.0	**0.016***	25.0	0.090
Token vs Ritalin®	33.5	2.81	27.0	0.122

*significant at $p \leqslant 0.05$
U: test quantity in Mann-Whitney-Test
p: Probability of errors for partial significance test

methadone maintenance treatment. Both interventions resulted in a significant temporary reduction of cocaine use (table 3 and 4).

Strategic considerations also involve the search for new opioids which would be useful in maintenance treatment. I am of the opinion that for the purpose of setting priorities methadone will continue to remain the medication

of choice for maintenance treatment. Buprenorphine (Subutex®), now available in Switzerland, will be the object of further studies. According to my personal estimate, it can be employed in the treatment of 10–20% of opiate-dependent persons. Injectable diacetylmorphine (pharmaceutical heroin) in a controlled clinical setting will continue to be the third choice of medication, particularly for those patients, who as a result of their need for a strong psychotropic effect, meet with little success in the usual opioid maintenance treatment.

With the inclusion of other substances in maintenance treatment, research must bear in mind their effects, side effects and potentially damaging effects. In particular the impact of opioids on the central nervous system has not yet been sufficiently evaluated. The short-term deoxygenation of cortical hemoglobin resulting from intravenous application of heroin has been the object of important investigations [6, 7].

The abstinence-oriented therapies outside the range of opioid maintenance treatment mentioned at the outset are considered as follows. In Switzerland, a substantial number of stationary, social-pedagogically oriented facilities remain. The heterogeneity of these institutions is remarkable. The number of persons treated there probably amounts to about 1,000 per year compared to about 18,000 opioid-maintained patients per year in Switzerland. At the same time this ratio highlights an additional problem. Many substance-dependent persons (including those maintained on opioids) have no or only an insufficient structure in their day-to-day lives. While housing conditions in general are relatively stable, the availability of meaningful occupation and employment is often insufficient. The goals of the therapeutic community are updating and tailoring the therapy to today's needs of the patients so that they can better cope with the tasks of daily life.

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Scientific Evaluations of Opioid-Assisted Substitution Treatment

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Randomized Clinical Trials as Gold Standard

Scientific evaluations of medical treatment have a gold standard: the randomized controlled double-blind clinical trial against the available standard medication [e.g. 1, 2]. If new opioid-assisted treatments are to be introduced, they should ideally be evaluated against this standard. As an example, let us take the introduction of heroin-assisted substitution treatment. In the case of introducing heroin-assisted treatment, the so-defined gold standard would look as follows:

- Comparison against methadone as the available standard medication in most European established market economies [e.g. 3, 4].
- Randomization of patients into heroin and methadone arms [5].
- Blindness of patients with respect to medication condition, i.e. methadone- versus heroin-assisted treatment.
- Blindness of caregivers with respect to medication condition.
- Blindness of others, especially the people responsible for the assessment of the outcome [6].

As can easily be seen, there are a number of problems with implementing this gold standard scenario in the given example of evaluating heroin versus methadone. First, heroin-assisted treatment usually is combined with methadone to avoid withdrawal symptoms during the evenings [e.g. 7]. Thus, we are comparing methadone alone as a substance against methadone plus

heroin as a substance, and any biological effect of methadone is likely to be present in both groups. Second, randomization is often not practical. Depending on the culture and the treatment system, it may well turn out that persons randomized into the methadone branch will not start the trial. Certainly in Switzerland this was the case to a certain degree. Of course one could still undertake an 'intent to treat' analysis, but part of the research questions cannot be answered in this way [for a discussion of the consequences of this in the area of substance dependence, see 8]. Third, methadone is a long-acting opioid, whereas heroin is short-acting [e.g. 4]. It cannot be imagined that patients will actually be kept blind with regard to their condition. Fourth, it is in principle conceivable that the caregiver is blind. However, standard treatment of methadone would be oral intake of a liquid, whereas application of heroin is usually intravenously. Moreover, circumstances such as the frequency of intake (once a day versus several times per day) would clearly indicate to the environment including the caregiver, which treatment is taken. Finally, with regard to the last point, it is conceivable that the assessment of the outcome is done blindly.

However, in sum, the gold standard methodology for evaluating a new opioid-assisted substitution treatment does not seem to be feasible. Different forms of evaluation designs have to be found. These forms will be discussed in the following, taking the gold standard and its components as a yardstick [e.g. following the line of arguments in 9, 10].

Comparison of Different Opioids

It is not possible to compare only the effectiveness of different opioids; for ethical reasons all treatment is given in conjunction with other treatment (e.g. somatic medical care, treatment for comorbidity or psychosocial interventions). Thus, assuming the 'other treatment' is kept constant, the comparison is still between a treatment package including one opioid (e.g. heroin in the chosen example) and a package without this specific opioid. That the control package contains another opioid, in this example methadone, does not seem particularly problematic. The conclusions from such a trial have to be different, however. They should state that in a given setting, the addition of heroin or another opioid as a pharmacological agent to be tested caused the effect.

If different components of treatment and their interactions have to be disentangled, the other components have to be systematically varied in a two-factor design, as in the starting German trial [for theory 11; for the German trial see http://www.heroinstudie.de].

Randomization

Randomization is in principle possible in opioid substitution trials (see for example the designs of the ongoing Dutch trial [12] or the German trial [http://www.heroinstudie.de]). Often waiting list designs are used in such trials where randomization basically determines the time when patients receive which opioid. The design may then be made more complex by planning crossover trials.

The fundamental problem with a waiting list design in the case of opioid substitution trials are the expectancies of the patients and caregivers as both groups cannot be blinded (see below). For example, let us examine the case where patients believe and expect that heroin substitution is a better treatment than methadone treatment. If such a patient is randomized into a methadone-first treatment group and his or her results are then compared to the results of the heroin-assisted group, they may be influenced strongly by the expectation that by staying in methadone treatment, he or she will receive heroin-assisted treatment later, e.g. in some months. Such a result is not transferable to a normal treatment situation with methadone maintenance treatment where this expectation is lacking. Thus, even a waiting list design, which is accepted as one of the standards in biostatistics for conducting controlled trials, may not give practically relevant results.

At this point it should be stressed that by no means all drug-dependent patients have the same preferences for opioid maintenance treatment. In England, when patients could choose to a certain degree, the majority selected heroin-assisted treatment but there was a sizeable minority [13]. It is important to realize, however, that in the case of opioid-assisted treatment preferences and expectations of patients may play a role and should be incorporated into the design.

Blinding of Patients

There are clear limitations for blinding in opioid trials. It may be that certain opioids are not distinguishable, but even very similar and functionally equivalent substances such as heroin and hydromorphone (Dilaudid) appeared subjectively distinguishable when given intravenously. Thus, the overall blinding of patients does not seem to be feasible and expectations of patients do have to be considered in all opioid trials (see also above). This fact interacts with considerations about randomization and should be included in all conceptual planning of opioid substitution trials.

Blinding of Caregivers

Substitution is usually long-term and blinding of caregivers may be practically infeasible. This means that we also have to take into consideration expectations of the caregivers. If such expectations cannot be avoided it may be of value to know them explicitly and to actually measure the level of care given in the unrandomized and unblinded trial. This would allow statistical control of these factors. Randomization [11] and blinding [6] as well as other precautions such as concealment of treatment allocation [14] are all measures to avoid threats to internal and external validity [10]. By incorporating at least some factors into the design, their potential influence can be measured and statistically controlled.

Blinding of Assessment of Outcomes

There is no reason why assessment in clinical trials on opioid should not be blinded to avoid detection bias [see 6, 10].

Conclusions with Respect to Randomized Controlled Clinical Trials in Opioid-Assisted Substitution Therapy

Randomized controlled clinical trials did not seem to be feasible in research on opioid-assisted substitution therapy. Specifically blinding of patients and caregivers seems to be impossible. It is thus suggested that such trials be conducted unblinded but incorporate expectations of patients and caregivers and explicitly measure content and level of the care given.

With respect to other standards of control, randomization may be possible but effects of expectations should be carefully considered in design and interpretation. In certain circumstances, unrandomized control groups may be more appropriate. If such an unrandomized group is chosen for control, subjects should be matched by severity of addiction and other indicators known to influence treatment success. In all cases, outcome should be assessed blindly.

Controlled studies are not the only possibility to gain knowledge on the effectiveness of medication. The Swiss prescription trials have shown that even a natural cohort design allowed some conclusions on feasibility and overall success [7, 15, 16]. However, causality and comparability with other treatment options cannot be determined by such a design [16]. Thus they can only be seen as a first step to more controlled trials and in this respect, the better the controls the more knowledge can be obtained to improve our treatment system [17].

Other Methodological Issues in Conducting Research on Opioid-Assisted Substitution Therapy: The Selection of Outcome Criteria

A major issue in conducting evaluations on opioid-assisted substitution therapy concerns the selection of indicators for effectiveness. In principle, indicators of effectiveness historically have come from several areas: somatic health of the patient (e.g. infectious status), mental health of the patient (e.g. level of depression), somatic health of others (e.g. risk of infection by patients), social integration (e.g. number of friends or number of friend outside the drug scene), criminal behavior (e.g. burglary), consumption of illicit substances, and social costs, i.e. are the benefits derived from therapy larger than the costs of untreated users [18, 19].

Often the official main outcome criterion of effectiveness, as relevant in the process of licensing of pharmaceuticals, is a combined measure of the above [see 12]. The problem with these measures is that they confound different perspectives. Who would try to measure the success of an operation on a broken leg by the degree with which this operation allows social reintegration, e.g. partying? Or who would measure the success of depression therapy by using the relief of pain and suffering for the family of the patient as a main criterion? The above list with the major emphasis on social variables shows clearly that opiate substitution therapy has many goals which go far beyond health and are purely in the social interest. In fact, in many cases a therapy is called successful, if criminal behavior and consumption of illicit substances can be reduced, independent of the health status of the patient.

The selection of social outcomes as key variables is unique to the area and suggests that important goals of substitution therapy go beyond health, and thus are not consistent with a medical model or 'disease concept', which has been stressed in addiction sciences as a result of the pioneering works of Jellinek [20, see also e.g. 21]. Even more astonishing is the fact that this shift in emphasis and this discrepancy are not discussed very much in the field, nor has the medical profession problematized it. However, it should be made explicit that in the framework of disease, the main outcome criterion should be related to alleviating the symptoms of this disease or to improving the health-related quality of life for the patient [see e.g. 22]. Thus, a reduction of social costs or criminality in this model can only be treated as secondary outcomes which become relevant in ceteris paribus situations, when the main outcomes are equal for the different conditions.

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Dopaminergic Dysfunction – A Common Final Pathway of Addiction to Alcohol, Opiates and Nicotine?

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Numerous studies have shown that natural rewards, including food, drinks and sex and many drugs of abuse interact with the central brain system by enhancing dopamine turnover in certain sites following acute administration, especially the mesolimbic-mesocortical circuitry [1]. Psychostimulants, like cocaine, are known to increase extracellular dopamine by blocking the presynaptic transporter in the dorsal striatum (rather than in the nucleus accumbens). In contrast, opioids increase dopamine release in the nucleus accumbens by disinhibiting GABA interneurons in the ventral tegmental area. Several lines of evidence indicate that ethanol also activates the mesolimbic dopamine system in an indirect manner; however, the precise mechanism is still unclear. Nicotine as the primary ingredient of tobacco activates a group of proteins called nicotinic receptors that ultimately bring about the release of dopamine in the nucleus accumbens at doses known to maintain self-administration [2]. However, recent studies have also shown that dopamine acts beyond the pleasure principle; memory and motivation systems are also targeted as evidenced by the responsiveness of dopamine neurons to appetitive rewards and reward-predicting stimuli [especially in the frontal cortex; 3].

Repeated administration of psychoactive drugs can have neuroadaptive consequences that lead either to a decrease (tolerance or desensitization) or an increase (sensitization) in their behavioral effects. In the case of psychostimulants and opioids, in vivo measurements of extracellular dopamine levels have provided direct evidence that these drugs, when administered under an

intermittent injection schedule, can lead to a more pronounced increase in dopamine levels than the increase seen after acute administration of these drugs [1]. However, rats that received repeated intermittent injections of alcohol did not show sensitization of alcohol-induced dopamine release in the nucleus accumbens. Current conceptualizations of the significance of sensitization in compulsive drug-seeking behavior hold that rather than enhancing the reward, repeated drug use leads to a progressive and persistent hypersensitivity of neural systems that mediate incentive salience, possibly resulting in drug or alcohol craving and relapse [4–6].

In humans, several research groups used a neuroendocrinological approach to determine dopaminergic sensitivity by assessing the responsivity of post-synaptic dopamine receptors after stimulation with apomorphine and measuring growth hormone concentration in the blood; techniques and results had been described elsewhere [7, 8]. However, there are few studies that investigated subgroups of addicted patients with the same research design. Therefore, we report findings that had been obtained in patient subgroups with alcohol, opiate and nicotine addiction. These subjects were clinically and neuroendocrinologically evaluated before and after detoxification or during abstinence and compared to normal subjects. It was the aim to provide evidence to the effect that dopaminergic dysfunctions might be a common final pathway in different forms of addictions.

Methods and Patients

Male and female subjects were prospectively recruited among patients seeking treatment at the Department of Psychiatry of the Free University of Berlin, which offers ambulatory consultations, subsequent hospital detoxification and an outpatient rehabilitation program. Patients meeting sufficient criteria for the ICD-10 [9] alcohol or opiate dependence syndrome were assessed in our outpatient unit for demographic and psychiatric history data, including information obtained by the substance abuse section of the Composite International Diagnostic Interview [10].

Clinical characteristics of alcoholic patients were given in more detail elsewhere [11, 12]. Patients were admitted to hospital while being intoxicated. Withdrawal symptomatology occurring during the 1st week of hospital stay was treated using clomethiazole when symptoms of the CIWA scale [13] exceeded 12 points.

Opiate addicts received a hospital detoxification treatment based on abrupt withdrawal of opiates with the option of tricyclic antidepressants (doxepin or trimipramine) to alleviate withdrawal symptoms if the intensity was subjectively experienced as painful [14]. In case of unendurable symptoms benzodiazepines were additionally given. The group of opiate addicts consisted of 23 males and 8 females with a mean age of 30.3 $\pm$ 5.4 years consuming on average 0.8 $\pm$ 0.5 g heroine daily. Six patients were on methadone maintenance, 9 subjects regularly consumed cocaine and 4 reported that they drank more than 50 g of alcohol per day; all subjects were smokers. A subgroup of 10 opiate addicts were treated with

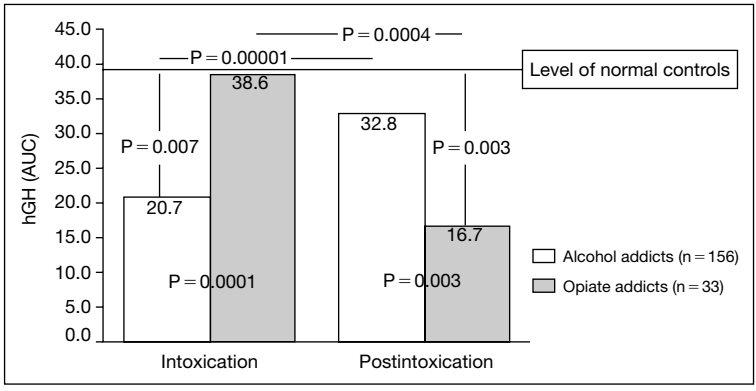

Fig. 1. Dopaminergic responsivity in alcohol and opiate addicts. hGH = Human growth hormone; AUC = area under the curve.

ultra-rapid opiate detoxification using the opiate antagonist naltrexone under general anesthesia conditions [15].

All patients were asked to participate in a neuroendocrine test procedure using the growth hormone response to a D2 receptor agonist apomorphine injection (0.01 mg/kg s.c.). Dopaminergic responsivity was assessed on the day of admission to hospital (chronic intoxication) and after the 1st week of hospital stay (postintoxication). Blood samples were collected each time at 2 p.m. for baseline and thereafter at 30-min intervals, i.e. 30, 60, 90 and 120 min after apomorphine stimulation [8, 16, 17].

A sample of 37 smokers was recruited by advertisements. Tobacco dependence was assessed by ICD-10 and by the Fagerstrom test for nicotine dependence (FTND); urinanalysis was done to exclude any other consumption of drugs. Smokers were assessed with the same neuroendocrinological test system like alcoholics and opiate addicts but under two specific conditions: during ad libitum smoking and after an overnight smoking abstinence (1 week later).

Eighteen healthy controls were also studied. Neuroendocrine data of 156 alcoholic patients and of 33 heroine addicts were available. Growth hormone data are presented as area under the curve with concentrations in ng/ml/120 min for alcohol and opiate addicts and in μg/l/min in nicotine-dependent patients. The study was approved by the Ethical Committee of the Rudolf Virchow Klinikum of the Free University of Berlin.

Results

Dopaminergic responsivity was reduced in alcoholics during intoxication in terms of a lower growth hormone secretion after apomorphine challenge and restored in a postdetoxication state 7 days later (fig. 1). However, in opiate addicts the responsivity was not different from normals, but significantly

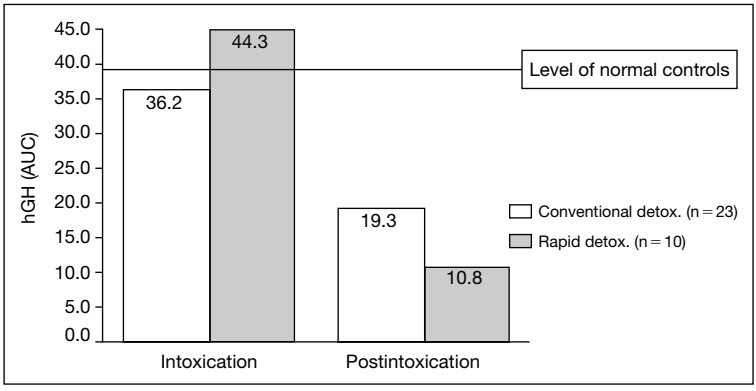

Fig. 2. Dopaminergic responsivity in subgroups of opiate addicts. hGH = Human growth hormone; AUC = area under the curve.

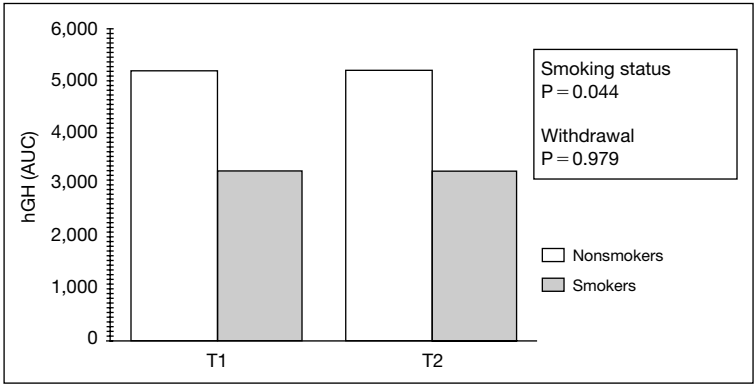

Fig. 3. Dopaminergic responsivity in smokers. hGH = Human growth hormone; AUC = area under the curve; T1 = ad libitum smoking; T2 = overnight abstinence from smoking.

decreased after 7 days. When neuroendocrine data were analyzed separately for patients with conventional and rapid detox treatment, there was no difference in the responsivity between subgroups (possibly with a more pronounced decrease in patients after rapid detox with an opioid antagonist; fig. 2).

In nicotine addicts growth hormone responsivity was reduced compared to normals (3,285 vs. 5,173 μg/l/min; $p < 0.05$) during smoking conditions and was in the same range after overnight abstinence conditions (3,375 μg/l/min; $p < 0.05$; fig. 3).

Discussion

Due to the 'dopamine hypothesis of addiction' activation of the mesocorticolimbic system is known to be a fundamental principle of reinforcement by drugs of abuse that elicits psychomotor and motivational responses [18–21]. Increased mesolimbic dopamine-mediated transmission was shown to occur after acute administration of drugs of abuse, while longer-lasting neuroadaptive changes have been observed during chronic drug use. In the case of psychostimulants and opioids they may result in an augmented increase of dopamine release in the nucleus accumbens (sensitization), while for ethanol the results are inconsistent [1]. In contrast, drug withdrawal is often followed by a decrease in dopamine function that was shown for psychostimulants, opioids, ethanol and nicotine [1, 22].

As most of these findings were obtained in animal studies, we were interested in neurobiological changes of the dopamine function in various subgroups of human addicts. Therefore, the growth hormone secretion pattern following a dopamine challenge was chosen to assess the central dopamine function. However, it is unclear to what extent a hypothalamically mediated, dopaminergic response is indeed informative about the functions of the mesolimbic-mesocortical system.

Dopamine responsivity in alcoholics was demonstrated to be reduced during chronic intoxication and tended to normalize with abstinence. We know from other studies that the dopamine function is more compromised with a higher intake [8] and there is a better treatment outcome in patients with a less compromised dopamine system [16, 17]. Our finding that secretion of human growth hormone after stimulation with the dopamine agonist apomorphine was significantly lower or blunted in nonsmoking alcoholics (during chronic ethanol intoxication) compared with findings in smoking alcoholics could mean that smoking leads to a restoration or normalization of ethanol-induced dopamine dysfunctions. The mechanism by which this effect is produced is not clear, but one explanation might imply the release of dopamine by the interaction of nicotine with nicotinergic receptors [2, 20].

Interestingly, neuroendocrine data in nonalcoholic smokers pointed to a reduced dopaminergic responsivity possibly due to changes in postsynaptic receptor functions as a consequence of increased dopamine release during ad libitum smoking conditions. This interpretation would fit the finding of Salonkangas et al. [23] evidencing high levels of dopamine activity in the basal ganglia of cigarette smokers. After overnight abstinence dopaminergic responsivity in smokers was again shown to range within decreased levels. It might be speculated whether decreases in brain function during nicotine withdrawal might reflect a low dopamine release [22, 24] that was not compensated on a postsynaptic level as measured within our neuroendocrine test design.

Growth hormone levels after dopaminergic stimulation tended to be normal in opioid addicts. A normalization of neuroendocrine or other brain function could be due to a longer lasting adaptation of postsynaptic dopamine receptors or altered gene expression during chronic opiate intoxication [25]. After opiate withdrawal a dramatic decrease in dopamine function could be observed even 7 days after the discontinuation of drug opiate that had been even more pronounced when an opioid antagonist had been used for rapid detoxication.

Taking these results together, there is ample evidence that dopamine dysfunction is a common final pathway in various forms of the addictions. The alterations, however, differ with regard to the type of drug abused and the state of disease.

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Brain Imaging in Opiate Addiction

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Brain imaging in opioid addiction can be used for different purposes, such as the assessment of structural or functional abnormalities or the measurement of receptor occupation by the medication used as a substitute for heroin intake. In the last decade, new brain imaging methods have been developed such as magnetic resonance spectroscopy or positron emission tomography (PET) with radioligands that bind specifically to opioid receptors. These methods increase our knowledge of the effects of acute and chronic opiate intake on the central nervous system. In this review, we focus on three types of studies:

Firstly, brain imaging studies with cranial computed tomography (CCT) or magnetic resonance imaging (MRI) that assess structural defects associated with chronic opiate intake. Perfusion deficits associated with structural pathology have been assessed with single photon emission computed tomography (SPECT) and with PET and the radiotracer fluorodeoxyglucose which measures glucose utilization [1]. A more recently developed tool is magnetic resonance spectroscopy that can assess changes in neuron markers such as N-acetyl-aspartate or changes in phosphate metabolism associated with chronic drug intake [2].

Secondly, we describe studies that assessed the degree of receptor occupancy by methadone or other opioids that are used as substitutes in heroin abuse. Such studies used PET and radioligands such as carfentanil, which binds specifically to a subtype of opiate receptors (μ-opioid receptors), which are supposed to mediate the rewarding effects of opiate intake [3].

Thirdly, SPECT, PET and functional MRI (fMRI) can be used to assess the effects of acute and chronic opiate intake as well as withdrawal effects on activation patterns in the central nervous system. Specifically, these methods can be used to assess brain activation during opiate intake and during the presentation of opiate-associated cues [4–6]. While functional activation measured

with fMRI depends on changes in blood flow, brain activation can also be measured by observing changes in brain perfusion or glucose utilization [7, 8]. Such studies show that opiate-associated cues activate brain areas that are associated with the emotional evaluation of stimuli and with drug memory and they help to identify neuronal networks that are associated with motivational states predisposing to further drug intake [6].

Structural Changes in the Central Nervous System of Opiate-Dependent Patients

In several studies carried out with CCT and MRI as well as in perfusion studies performed with SPECT, it has been observed that some opiate-addicted patients show ischemic lesions in the basal ganglia and pallidum [1]. The ischemic lesions seem to be due to several factors associated with chronic opiate intake, such as hypoxia resulting from an opiate-induced depression of respiratory function [9–11], thromboembolic strokes in patients suffering from endocarditis [12–14] and central vasculitis [1]. Specific diseases include a spongiform leukoencephalopathy that follows inhalation of preheated heroin. Clinically, patients suffering from this disorder show cerebella ataxia, spasticity, myocloni and central hyperpyrexia. In CCT scans, hypodensic areas are found in the white substance; these lesions are hypointense in MRI T1-weighted images and hyperintense in T2-weighted images [15, 16]. Pathoanatomically, spongioses and astrogliosis are found in white matter. Pathoanatomical changes such as nerve cell losses in the hippocampus and thalamus have also been observed after chronic opiate intake in the absence of spongiform leukoencephalopathy. However, it is not clear whether opiate intake per se may induce brain atrophy [1], as it has been described after chronic alcohol intake [17].

Magnetic resonance spectroscopy is a more recently developed tool that can assess concentrations of certain metabolites found in the brain that give a magnetic resonance-strong signal. Specifically, magnetic resonance spectroscopy can be used to assess phosphate metabolism in chronic opiate intake. In one such study, Christensen et al. [2] observed increased phosphomonoesters, which may indicate that phospholipid metabolism is increased and an anabolic state is present among chronic opiate-dependent patients. Furthermore, these authors observed a dysfunction of the metabolism of highly energetic phosphates that can also be found in ischemia. A limitation of the study is that the authors examined patients with polydrug abuse and included patients who consumed both cocaine and opiates, so that ischemic lesions may not be associated with opiate intake but result from the vasoconstrictory effects of cocaine and

psychostimulants. In a second study, Kaufman et al. [18] used the same MRS technique and scanned 15 polydrug abusers on methadone maintenance therapy. In 7 patients with a short duration of methadone treatment (9 months on average), phosphocreatine levels were found to be reduced and phosphomonoester as well as phosphodiester levels were significantly increased compared with control subjects, while no significant differences were found in 8 patients who had been substituted with methadone for 32 months on average. Only the phosphocreatine levels were reduced in these patients with a long treatment duration. The authors conclude that long-term methadone maintenance might be associated with improved neuronal integrity in polydrug abusers.

Spectroscopy can also be used to assess the neuron marker N-acetylaspartate, which is present in neurons but not in glial cells. A reduction in this neuronal marker is commonly associated with neurodegeneration or other disorders of the central nervous system [19]. However, such studies have so far not been published in patients with opiate addiction.

Assessment of Opiate Receptors with PET

Although externally applied opiates such as heroin stimulate central opiate receptors, no consistent changes have been observed in receptor density after acute or chronic opiate intake. Often, drug effects on receptors within the central nervous system are balanced by counteradaptive changes such as a downregulation of the affected receptors; in the opioidergic system, this does not seem to be the case, and rather, second messenger systems that are associated with such opioid receptors are changed in a compensatory way. For example, it has been observed that acute stimulation of μ-opiate receptors inhibits a G-protein-associated adenylyl cyclase, and that there is a compensatory upregulation of this adenylyl cyclase in subjects after chronic opiate intake [20, 21].

PET with radioligands that specifically bind to opiate receptors or subtypes of opiate receptors such as the μ-opiate receptor can be used to assess the degree of receptor occupation induced by the intake of opioids, e.g. in drug substitution programs [3, 22]. In such a study, it has been observed that a buprenorphine dose of 2 mg occupies 36–50% of all μ-opiate receptors, while a higher dose of 16 mg induces a receptor occupation in the range of 79–95%. Such studies may be used to assess the degree of receptor occupation in patients who do not adequately respond to a given substitution regime. They may also help to decide whether a simple increase in dosage is recommendable or whether a patient may respond better to a different opioidergic drug.

Functional Brain Imaging Studies to Assess the Effects of Opiate Intake and Withdrawal

Several studies with functional brain imaging assessed the effects of acute and chronic opiate intake on brain activation. It is often difficult to distinguish between the effects of opiates on respiration (e.g. the induction of hypoxia and a general reduction in brain activation) and specifically activating effects on certain brain areas mediated by direct activation of opiate receptor subtypes. In an animal experiment, Xu et al. [23] distinguished between these factors by assessing both general brain activation in animals that breath spontaneously after opiate application and brain activation in animals with externally controlled respiration. Rodents with spontaneous respiration showed a general reduction in brain activity after opiate application due to respiratory depression induced by opiate intake. On the other hand, rodents with externally controlled respiration showed an increased activation of the frontal, olfactory, parietal and temporal cortices, the cingulum, hippocampus, amygdalae and the ventral and dorsal striatum.

In a study by London et al. [24] the effect of morphine on glucose utilization was assessed with fluorodeoxyglucose and PET in 12 polydrug abusers. To control for respiratory depression, the $PaCO_2$ was measured. When the contribution of $PaCO_2$ was partialled out, a significant reduction of glucose utilization was found in 6 cortical areas (superior and middle frontal gyri, postcentral gyrus, paracentral lobule, anterior cingulate cortex and gyrus rectus). In a later study from the same group [25], a reduced glucose utilization under buprenorphine treatment was found in 19 of 22 bilaterally assessed brain regions and in all 4 midline brain areas. The effects of morphine and buprenorphine treatment on glucose utilization were similar in both studies.

In a pilot study with 4 opiate addicts Sell et al. [26] used fMRI to investigate the effect heroin on functional activation. They found a marked reduction in BOLD activation in the visual cortex in response to visual simulation.

Schlaepfer et al. [27] measured differences between the effects of μ- and κ-agonists on the central nervous system. While μ-agonists are supposed to mediate the pleasant effects of opiate intake, a stimulation of κ-receptors seems to induce negative mood states. This hypothesis was confirmed in the SPECT study of Schlaepfer et al., who observed that μ-agonists induced a subjective 'high' and activated the anterior cingulum, both amygdalae and the thalamus, while the application of a mixed κ- and μ-agonist was subjectively unpleasant and activated the bilateral temporal cortices.

When the effects of chronic opiate intake and methadone substitution were assessed, Krystal et al. [8] and Galynker et al. [7] observed patterns of a brain activation that were similar to some activation patterns observed after acute opiate application. Krystal et al. [8] used SPECT and the radiotracer HMPAO to

assess regional cerebral blood flow (rCBF) during chronic opiate intake. They observed an increased blood flow in the thalamus and reduced blood flow in the frontal and parietal cortices among patients with chronic opiate dependence compared with healthy control subjects. Among opiate-dependent patients on methadone maintenance therapy, Galynker et al. [7] observed an increased glucose utilization in the anterior cingulum compared with healthy control subjects in flourodeoxyglucose PET scans. In patients that were abstinent in the long term the increase in glucose utilization was even more pronounced.

Concerning effects of opiate withdrawal and abstinence on rCBF several SPECT studies with HMPAO were performed [8, 28–32]. The van Dyck group studied the effects of naltrexone-precipitated withdrawal from buprenorphine on rCBF in 11 opiate-dependent patients. They found that the severity of naltrexone-precipitated withdrawal was inversely correlated with rCBF in the anterior cingulate cortex. During withdrawal, Krystal et al. [8] observed an increase in thalamic blood flow and reductions in blood flow in the frontal and parietal cortices. In another SPECT study, Rose et al. [30] found perfusion deficits, especially in the frontal, parietal and temporal cortices among patients who had abstained from heroin for 1 week. Two weeks later, a second scan was done and showed a general increase in cortical perfusion. This study indicates that initial perfusion deficits may be partially reversible during abstinence. Danos et al. [28] measured rCBF in 16 heroin-dependent patients during withdrawal. They studied different areas with hypoperfusion, mostly in the temporal lobes. There was no correlation between the severity of opiate withdrawal and rCBF. Gerra et al. [29] found a nonsignificant reduction of whole brain perfusion values of opiate addicts having been abstinent for at least 4 months. This latter finding may indicate a reversibility of opiate-induced alterations after long-term abstinence. Presently, the functional importance of the described changes in blood flow or glucose utilization during chronic opiate intake or withdrawal is unclear.

Wang et al. [32] assessed dopamine D_2 receptor availability in 11 opiate-dependent subjects using PET and the radioligand raclopride at baseline and during naloxone-precipitated withdrawal. They found decreases in D_2 receptors in opiate-dependent subjects (which may be due to opiate-induced dopamine release), but no significant changes in striatal dopamine concentration during acute withdrawal.

Cue Exposure, Craving and rCBF

fMRI and PET can also be used to assess short-term changes in brain activation, which are associated with changes in rCBF. In a PET study that used heroin and heroin-associated cues, both conditions activated the brain stem in

an area that includes the center of origin of dopaminergic and serotonergic projections to the striatum and other brain areas [5]. This observation is specifically interesting since dopamine and serotonin release in the ventral striatum may be strongly rewarding. It has been postulated that drug or cue-induced activation of these systems may promote a conditioned drug-seeking reaction and subjective experiences of drug craving [33]. In a second study, Sell et al. [6] measured brain areas that are activated in association with a subjective 'high' or craving for heroin after the presentation of heroin or heroin-associated cues. Schlaepfer et al. [27] had observed that a 'high' induced by a μ-agonist was associated with an activation of the interior cingulum, both amygdalae and the thalamus. In the study of Sell et al. [6], an activation of different brain areas was associated with the 'high' induced by heroin intake. Sell et al. observed an increased brain activation of the hippocampus, a central area for explicit memory and learning of stimulus-stimulus associations, the dorsolateral prefrontal cortex, which plays a major role in behavior planning, and the nucleus accumbens, a part of the ventral striatum and a core region of the brain reward system. Craving for heroin, on the other hand, was associated with activations in the orbitofrontal cortex, a central area associated with emotional behavior assessment, the posterior cingulum, which plays an important role in conscious memory recall, and the left insula, an area that is strongly involved in memorizing the emotional significance of cues. The insula is also activated in anxiety states, and Sell et al. [6] postulated that a craving for heroin may reflect a mixture of desire for the positive rewarding effect of heroin as well as anxieties associated with drug withdrawal or the drug effects per se.

In another PET study, Daglish et al. [4] investigated the effect of drug-related auditory stimuli on rCBF and craving. A comparison of the drug-related and neutral stimulus conditions revealed an activation of rCBF in the left medial prefrontal and left anterior cingulate cortices and a bilateral deactivation in the occipital cortex in response to the drug-related stimulus. Interestingly the duration of abstinence was positively associated with the size of the difference in rCBF in left anterior cingulate between both conditions. Whereas the subjective rating of craving was not associated with blood flow in the areas mentioned, it was positively correlated with blood flow in the left orbitofrontal cortex.

Taken together both studies provide evidence that cue-induced craving is associated with activations in the orbitofrontal cortex.

Summary and Clinical Implications

Altogether, functional brain imaging studies performed during opiate application or the presentation of opiate-associated cues show an activation of

cerebral brain regions that are closely associated with the executive control of behavior (such as the dorsolateral prefrontal cortex), the emotional evaluation of behavior (such as the orbitofrontal cortex) and with a recall of the emotional significance of certain cues or stimulus constellations (mediated by activities in the posterior cingulum, insula and hippocampus). Furthermore, activation of brain reward systems such as the ventral striatum (nucleus accumbens) and structures such as the amygdalae, which mediate associated learning and emotional evaluation of incoming stimuli, may strongly contribute to the affective responses associated with the presentation of heroin-associated cues. Finally, the anterior cingulum plays an important role in the attention network and may direct attentional resources to the drug-associated cues.

Although these findings are promising, the current database is small and not without contradictions. The rather limited number of studies on drug- and cue-induced brain activation already show a considerable variance in individual responses to heroin and heroin-associated cues [5, 6]. In these studies an activation of all the brain areas which were previously found to be stimulated by acute and chronic opiate intake could only in part be replicated [7, 8, 23, 24, 25, 27]. A high individual variability in brain activation induced by drug cues was also observed in alcoholics [34]. Studies in larger patient samples are necessary to achieve a more complete picture of drug- and cue-associated brain activation. In any case, such studies are clinically important since they can be used to identify the neurobiological correlates of drug- and cue-induced motivational states that are associated with a high relapse risk. If patients are followed up in prospective studies, it can be assessed whether brain activation in circuits associated with the reward system or the emotional recall of drug effects characterizes a population with an increased relapse risk. Pilot studies in alcoholics indicate that cue-induced activation of the ventral striatum, the core region of the brain reward system, is more pronounced in patients with a prospectively high relapse risk [2].

Altogether, brain imaging in opiate-dependent patients can be used for different clinical purposes. Of primary clinical interest may be the assessment of structural damage associated with chronic opiate intake and the diagnosis of potential infectious complications due to unclean injection techniques or secondary effects on the immune system. Assessment of receptor occupation by PET and of cue-induced brain activation with functional brain imaging is currently of scientific rather than clinical interest. However, if developed further and replicated in larger patient samples, these methods can be used to asses clinically effective doses of different opioids in substitution programs and to identify patients with a high relapse risk upon exposure to conditioned, opiate-associated cues. Brain imaging studies may thus help to support the notion that heroin-dependent patients suffer from a disease with defined

consequences and that they should be respected like all other patients suffering from a disease.

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Opioids and Neurological Sequelae

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Since the late 1960s, there has been growing evidence of neurological sequelae of street use of heroin. The growing number of such reports is most likely related to the growing number of heroin users that has occurred since then.

Apart from disorders associated with a lifestyle involving drug abuse (e.g. those caused by adulterants, infections, malnutrition, overdoses, severe states of withdrawal or intoxication, and trauma), there are reports about alterations occurring on a molecular level [1], like down- or upregulations of different receptor types, upregulation of CREB and pathological modulations of certain neuronal loops [2]. Furthermore, acute and delayed leukoencephalopathies, neuroendocrine changes, infarctions and epileptic seizures have also been reported.

Is Maintenance Treatment with Intravenous Heroin an Exception?

Heroin maintenance has been available in Switzerland as a treatment option for heroin dependence since 1994. This has given us an opportunity to investigate directly whether some unwanted neurological effects are also present in patients on medically prescribed, stable-dose heroin. The results of these studies were – generally speaking – in line with the notion that, at least in respect of some patients and certain regimens, maintenance heroin might not differ greatly from street heroin in aggravating or even causing some of the above neurological complications.

Six Different Forms of Brain Affections

A synopsis of the available findings suggests the existence of six discrete, but nevertheless overlapping, entities of neurological sequelae that are not solely due to life circumstances.

(1) There are those that evidently bear a close temporal relationship to pronounced overdoses [3]. These entities comprise the so-called postanoxic or posthypoxic or posthypoxemic encephalo- and neuropathies.

(2) The second group consists of the rare and delayed forms of hypoxia-induced cerebral leukopathies [4] that may not manifest until days or even weeks after the event.

Both of these leukopathies do not seem to be specific with regard to etiology, as similar alterations may also emerge from hypoxic events not linked to substance use. Heroin however can promote their occurrence via some of its well-known properties. It exerts a depressant action not only on the respiratory system but also on cardiac performance [5], thereby hindering compensatory mechanisms like enhanced cardiac output. Moreover, heroin interferes with a compensatory upregulation of cerebral blood flow, e.g. via altered vessel tonus [6].

As opposed to hypoxic states resulting from high mountain climbing (also associated with impaired neuropsychological functioning according to some studies [7]), those resulting from heroin overdoses concomitantly may be aggravated by hypercapnia (similar to the sleep apnea syndrome [8]). Hypercapnic states have been found to enhance the risk of neurological sequelae after hypoxia [9]. The high prevalence of preexisting neuronal impairments [10] among these patients might be a further risk factor.

(3) A further complication that is usually [11], but not always [12], associated with the application of heroin by chasing (inhaling of heroin vapors from a heated tin foil) has been termed spongiform leukoencephalopathy.

There are about one hundred case reports in the scientific literature [13]. These cases all show similar features including white matter spongiform degeneration with relative sparing of U fibers and intramyelinic vacuolation with splitting of intraperiod lines. Hypotheses concerning pathophysiological mechanisms on the other hand differ widely as some authors suggest a so far unknown substance, possibly used as an adulterant by heroin dealers, that could be activated during the process of heating [9]. Others prefer to implicate a predisposition like a blunted arylsulfatase activity in those affected by this condition [14]. There is, however, agreement among authors as all stress the necessity for a pronounced hypoxia to be present as a contributing factor.

(4) Different forms of strokes [15, 16] are more prevalent in the heroin-abusing part of the population [17].

Angiitides or emboli are among the most plausible causes [18].

(5) There is a high prevalence of epileptiform disturbances among heroin users [19].

A clinical investigation at the heroin-prescribing facility in Basel, Switzerland has found EEC alterations immediately (and up to half an hour postinjection) after the application of intravenous heroin [20].

(6) There are some studies showing impaired cognitive functioning in long-term intravenous heroin users [21].

Because of the wide range of confounding factors, like e.g. the use of additional substances and malnutrition, no clear picture of the extent and the specific kind of these impairments has so far emerged.

This short overview points to the importance of closely monitoring the neural functioning of patients in intravenous heroin treatment, since it may be difficult to differentiate impairments from states of intoxication.

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Experiences of a Practicing Psychotherapist

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There was a time when Professor Kielholz – former head of the Psychiatric University Clinic in Basel known as 'Friedmatt' – was able to categorically state that substitution therapies are a pharmacological absurdity. Developments, however, have taken another direction, which should perhaps teach us to always retain a certain amount of skepticism.

I would like to relate to you my experience with a 40-year-old patient whom I have seen as an outpatient since 1990. During these 11 years, 79 sessions have taken place, a number of sessions per year which should not even trouble the health insurance authorities.

It is the course of a psychotherapy which is relatively successful (as is fitting for an occasion such as a symposium); relatively I said because the path the patient has had to travel, even though he has not consumed heroin or cocaine since 1991, has nonetheless been rough. I also do not wish to suggest that his psychosocial stability is connected with my therapeutic efforts. It is much more a result of a series of accidents, which have had a positive influence or, when put in philosophical terms, 'We humans are always more our habits than our choices… thus the non-absolute of human philosophy [psychotherapy! – the author] must be this: The apology of the habits' [1]. I hope that this case report will make this perspective more palatable.

In what follows I shall begin by relating the previous history of the patient (whom we will call Francesco). I shall proceed to discuss the initial phase of the treatment and the social rehabilitation program, the further course and finally the role of the therapeutic relationship.

The Previous History

Francesco comes from a rural area, not far from Lecce in Italy. His parents emigrated to Switzerland shortly following his birth. As has often been true in the history of emigration, they came to this country with the intention of soon returning to Italy. And as so often happens, they remained in Basel for two decades. Francesco stayed with his grandparents. When he was 3, his grandmother became ill and he was put into an 'Istituto', a euphemism for an orphanage used by those who had to live there, and where he remained until he was 14. His sister, who is 4 years younger, was born in the meantime and she, in contrast to him, was allowed to stay with their parents.

Our patient seldom speaks about his experiences as a deprived child. However, he is intensively occupied with the familial situation. His parents quarreled incessantly. They separated several times but, under pressure from their parents, were reunited. Events took a catastrophic turn when his mother bore an illegitimate child who was given for adoption. This 'shame' affected him too, because Francesco was even more rejected by his father's family as a result. Only a spinster aunt was able to offer him affective continuity. This aunt has remained a trusting and motherly figure for him throughout until the present day.

At the age of 14 (1975) after finishing junior high school in Italy, he came to be with his parents in Basel, who despite daily fights now lived under the same roof. Thus Francesco found himself in what was for him a foreign world with a language he could not understand and with hopes and expectations of his parents that they could not fulfill. It was the drama of the 'ricongiunti', a term of the immigrants ('ricongiunti' literally means the 'reunited'), that is the children who only in their adolescence move in with their parents. Our patient found himself in a family who did not understand him, who criticized him and who favored his sister. Displaced and confused Francesco came into contact with other youths who introduced him to drugs (cannabis).

He decided to return to Italy where he lived with his aunt and earned his living as a waiter. He continued to shuttle back and forth between Italy and Switzerland without really finding a place to call his own. After completing his military service, he came to live permanently in Switzerland at the same time as his parents and his sister returned to Italy.

To summarize, Francesco experienced the fate of a deprived child (orphanage); he was rejected by his parents and grandparents. His hopes of finding an intact world in Switzerland were disappointed. It is not surprising that during his journey through life he would increasingly seek a way out in drugs.

The Initial Phase of Treatment

'Precisely as little as there is *that* drug problem, is there a *solution* of the same' Dieter Ladwig.

At the age of 23, Francesco was addicted to drugs with all the accompanying features. He lived together with his girlfriend who was also addicted to heroin. Intermittently, he worked in a storehouse and he had debts. When he was about 27 and his relationship with his partner became difficult, he sought medical help. At first he received methadone in decreasing dosages over 4 weeks (from his private physician), then he took part in a longer methadone program (from a druggist). Later he tried a cold withdrawal ('cykade'). In the end, he tried out Temgesic (buprenorphine) which was his own idea. During this period he had become the father of a son whom he was forced to acknowledge following a court decision.

This life of suffering with its zigzag course is well-known to us all. Francesco, however, possesses an ability which has allowed him to conquer his drug addiction: I am thinking of his talent to win people over for his cause and to accept their help.

Our meeting illustrated his resourcefulness to me in an impressive way. I saw the patient for the first time (in December 1990) in this clinic together with a colleague who was taking care of him. A second consultation was arranged but the patient did not appear. However, on Christmas eve I received telephone call from him from southern Italy. He emphasized thereby his readiness to come and see me and explained the reason why he had not made contact earlier.

This telephone call had a special meaning for me: somehow the patient was able to win me over for his cause and had motivated me to be concerned about him. This is why I mentioned his ability to win people over for his cause. During the entire course of his rehabilitation he was constantly able to convince others of his motivation.

Psychosocial Rehabilitation

You may remember that, according to our main thesis, favorable influences are either simply accidents of destiny or lifetime habits [2]. I would like to mention two main episodes in this psychotherapeutic encounter, which are supposed to support this thesis.

- Francesco independently decided to cease taking Temgesic. This occurred approximately 3 months after our initial meeting at the PUK. Why? Because he believed he could no longer breathe after taking Temgesic. Francesco developed panicky fear which he had transferred to heroin and cocaine, and this after 10 years of heavy dependence. It must be said that beforehand he had lost a friend who had died from an overdose, a loss that left its traces.

- After another extended stay in his home village, he came back to see me. He had decided to participate in a work-related rehabilitation program (OeGA construction site). He was taking benzodiazepine occasionally. After this experience, which had been very positive, he wanted to train to become an orderly (an old dream of his). Francesco had a lucky break when a psychologist from the invalidity insurance company supported his ambition and was ready to pay for 2 years of training in a Tessin hospital. This is not all: the psychologist went personally to the Tessin when a crisis situation developed and was able to persuade the department to give Francesco another chance. What had actually happened? A variety of things: Francesco had shown little motivation and had not been punctual. Things came to a head when it became known that he was infected with hepatitis C and that he was an 'ex-drogato'. Innumerable telephone calls with the head nurse and the hospital director had at least the effect that he was permitted to finish his year of practical work. I would also like to mention that Francesco drove every second week from Locarno to Basel for a consultation with me. He wanted to discuss his difficulties. He felt himself to be depressive and fearful. At this time (1993) he began taking Floxyfral (antidepressant), a medication which he continues to take in various dosages.

This rehabilitation phase, which lasted 3.5 years, enabled the patient above all else to gain self-confidence. Subsequently he lived a further year on unemployment benefit until he had acquired sufficient courage to take a course offered by the Red Cross. Since then (beginning of 1995) he has been working for Spitex (home visitation for housebound people) and completed 2 years' training and passed the examination necessary to become a Spitex caregiver.

All's Well That Ends Well? Or the Further Course

The further course has indeed been unspectacular. Francesco has continued to work 50% for the Spitex services and he continues to see his girlfriend. He often perceives himself as weak and without initiative. After work he needs a long time to recuperate. I do not know if there are sufficient indices for a psychiatric diagnosis, but it was possible to convince the invalidity insurance to award him a 50% pension and this has calmed the patient down considerably.

The Therapeutic Relationship or a Crucial Factor for Success

Francesco has survived 10 years and 11 months with me as his psychiatrist. In order to objectively ascertain the reasons for his perseverance I have to ask

whether this was simply fortuitous or whether he was able to gain something for himself from this therapeutic encounter? But what was it that could have helped him? The clear hints he was given about his destructiveness? The reconstruction of his family history? The correction of some cognitive distortions? Or was it confronting him with his feelings of guilt about his son whom he sees so seldom?

Francesco would answer these questions along the lines that for him I have been and continue to be a therapist with whom he can talk about his daily problems, who supports him, who encourages him and who prescribes Floxyfral, a substance he swears by.

A modest result? Possibly. On the other hand, I think that 'therapy' is derived from the Greek word 'θεραπεία' which according to its etymology means 'serving, friendly treatment, respect and honor' and a therapist is in this sense of the word the servant of the patient, as Francesco himself using different words characterized the relationship.

To conclude, my objective was to show that accidents do not play a subservient role in a complex rehabilitation/psychotherapy. Favorable (and unfavorable) acts of fate can set the switch points. The role that must be played in therapeutic exchanges is to accompany and support (the role of the servant), not in any negative sense of the word, but, as Gadamer [3] put it, ever cognizant of the fact that '… the human being (is) not only a product of nature but foreign and mysterious to himself and others, as a person, as a fellow human being, in a family and profession, with innumerable imponderable actions and influences, burdens and problems. Time and again the unforeseen plays a role. There are still fully other incomprehensibles than the sought for lawfulness of nature, which highly developed research brings more and more to light.'

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Learning, Interneurons and Addiction Medicine

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Many of us have noticed that after consuming alcohol a dull party becomes suddenly 'much more fun!'. This is an important learning process: we are teaching the brain to take drugs, and drugs are good tutors – the lessons hardly get forgotten. Our brain processes experiences and decides whether a strategy was good and, if yes, it maintains it for future reference.

Psychotropic substances alter the activity-dependent gene expression evoked by sensory inputs and consequently alter protein synthesis. Memory is proteomic. In other words, afferent neuronal signals release neurotransmitters which activate ionotropic and metabotropic receptors and metabolic processes. Gene expression and translational processes will finally lead to new proteins which alter the structure and function of neurons. If protein analyses had been conducted in all of us before reading this book, and if these were to be repeated now, there would be clear differences. If you want to undo this process, you probably have to wait until these proteins have been converted or have disappeared (extinction).

Memories imprinted in our reward system will remain there permanently with only some modifications taking place in a life span. So much of the information, e.g. adopted from parents and peer groups and the cultural environment, will be permanently stored in this neuronal circuitry. Drugs exert their influence by usurping this system, leaving a significant impression on the individual. The individual under the influence of drugs will acquire and maintain information as an important signal that formerly was not recognized as such (incentive salience). For example, the shape of a bottle (of alcohol) or a needle

will become associated with emotion and may become a strong trigger for drug-related behavior. Following such a classical conditioning the individual has no longer the option to consider whether or not such an act ought to be carried out and, at the final stage, a cognitively not controllable mechanism takes over.

The substrate of addiction is the brain as a whole. On the cellular level, dopamine-containing neurons in the ventrotegmental area (VTA) controlled by GABAergic, inhibitory neurons and excitatory glutamatergic afferents from frontal cortical areas projecting to these neurons play a key role in this reward circuitry. When these neurons are activated they release dopamine in the nucleus accumbens, frontal cortex, striatum and various other rostral structures. While these systems are fairly well understood in the rat and mouse and even in primates, the mechanisms in humans are considerably more complex than we would like to believe. Contrary to earlier beliefs, dopamine does not play such an exclusive role in the reward system, although this neurotransmitter undoubtedly constitutes an important factor also in humans.

Glutamate, a neurotransmitter involved in all learning processes, is of prime importance in addiction. The great majority of synapses for fast excitatory synaptic transmission in the central nervous system use glutamate as their neurotransmitter. Glutamatergic transmission enhanced by cocaine leads to long-term changes in neuronal excitability via long-term potentiation (LTP) in VTA neurons. LTP and long-term depression involve cellular processes probably closely related to learning and memory. It is noteworthy that LTP-like neuroplastic changes can be induced by a single cocaine bolus in these neurons. It appears that these processes have to be experienced just once for them to be retained. A large number of glutamatergic afferents project from the frontal cortex onto interneurons in the VTA. Glutamate activates highly divergent receptor subtypes linked to multiple intracellular postsynaptic protein structures and the cytoskeleton. These proteomic mechanisms are involved in postactivity internalization and trafficking of receptors from extra- to subsynaptic sites. There is convincing evidence that chronic alcohol consumption influences, not only the activation of membrane receptors and gene expression, but also the scaffolding proteins in the postsynaptic neuron. It takes only a few days of alcohol exposure for neurons in culture to upregulate distinct NMDA receptor subunits. It is feasible to assume that also in alcohol abusers the observed neuronal hyperexcitability which could lead to epilepsy while undergoing withdrawal is due to an upregulation in the glutamatergic synaptic transmission. Transgenic animals lacking the CRH1 receptor start to drink alcohol after a stressful event and upregulate selectively an NMDA receptor subunit (NR2B).

In principle there are two ways to increase dopamine levels in target sites of VTA neurons such as the nucleus accumbens: either by blocking the GABAergic, inhibitory system of tonically active interneurons, or by directly

stimulating the dopamine-containing neurons. Diacetylmorphine (heroin) and alcohol suppress inhibitory neurons and, thus, indirectly increase the discharge rate of dopamine-containing neurons through disinhibition. Single neuron recordings in vivo and in vitro show that opioids injected into the vicinity of such VTA neurons inhibit GABAergic, inhibitory interneurons. As a consequence, the release of dopamine in the target sites will be enhanced. The inhibitory effect of opioids is evoked by various mechanisms: the opening of K^+ channels which hypopolarizes the membrane potential, the blocking of voltage-sensitive Ca channels and an alteration of glutamatergic transmission, probably through an effect on the phosphorylation status of NMDA and AMPA receptors. Opioids typically lower cAMP levels. There is evidence that NMDA effects, which are of crucial importance for learning processes, are potentiated, whereas AMPA receptor-mediated glutamatergic transmission is reduced. We still do not fully understand the implications of these processes for drug-related behavior. Opioids also reduce the release of glutamate from presynaptic terminals in various systems. Other drugs of abuse, such as cocaine, amphetamines, or nicotine directly activate the dopamine-containing neurons in the VTA or alter the release or the reuptake properties of nerve endings.

Enkephalins, which are enzymatically processed from a precursor molecule, tonically control the excitability of neurons in the VTA and the nucleus accumbens. Opioid peptides, such as the enkephalins, are inactivated by enzymatic degradation. If this inactivation is reduced the endogenous opioidergic tone will be enhanced. In other words, a reduction of degradation could lead to an endogenous substitution therapy helping a physiological system to be restored.

Opioids and cannabinoids share some of their molecular targets, i.e. channel blocking or channel opening. However, the metabolic pathways leading to the production of endorphins and endocannabinoids is totally different: opioid peptides are enzymatically generated from precursor molecules and presynaptically released whereas endocannabinoids are produced directly from components of the postsynaptic membrane and then diffuse back as a retrograde signal to control transmitter release at presynaptic terminals. Animals devoid of cannabinoid receptors show a reduced response to the chronic use of morphine, and cannot extinguish aversive memories as effectively as their wild type.

In conclusion, researchers present us more often with stimulating questions rather than answers. Nevertheless, addiction is an example where the elucidation of molecular mechanisms has resulted already in the advent of novel compounds and new therapeutic strategies for the treatment and the prevention of relapse. There are excellent animal models, as well as good cellular

correlates, for the learning processes involved in addiction. However, it goes without saying that the significance of these findings can only be proven in a clinical setting, and by working with and through the patient. The individual disciplines have to join forces to continue this story of success.

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