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Review article

The early history of psychotherapeutic drugs

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Abstract. The four most frequently used groups of drugs in psychiatric therapy are: neuroleptics, antidepressants, anxiolytics, and lithium salts. Their introduction came largely during the past 3 decades. This review summarizes the history of the research that led to their discovery and to the present concept of their modes of action.

Key words: History – Neuroleptics – Antidepressives – Anxiolytics – Lithium

The centenary of the Societé medicopsychologique de France was celebrated in May 1952. The official congratulations were followed by scientific meetings, devoted to current problems. Among these was *Stress*. The main lecture was given by Professor Jean Delay, head of the psychiatric department in the Hospital Saint-Anne, Paris. His clear and elegant presentation of the subject was worthy of his later membership of the illustrous French Academy. After this followed a series of minor communications in which Delay and his colleagues, Professor Pierre Deneker and Dr. J.-M. Harl, presented the results of treatment of manic states with the phenothiazine compound RP 4560, later known as chlorpromazine. In a way, this communication inaugurated the modern era of clinical psychopharmacology (Delay et al. 1952).

Although the word psychopharmacology had scarcely been used before the end of the 1950s, psychopharmacological research had been carried out for many years, both on animals and on humans, e.g. mescaline, amphetamine and ethanol. The results were mainly descriptive. The use of drugs in the psychiatric clinic was extremely limited, with the exception of sedatives, especially barbiturates.

The general impression of the effects of psychotropic drugs in the years 1940–1950 may be summarised as follows. A few drugs had a specific effect on the central nervous system, e.g., morphine was analgesic, aspirin and similar drugs were antipyretic, caffeine and amphetamine were stimulants, and mescaline was hallucinogenic. The effect of sedatives such as chloral hydrate and the barbiturates was much less specific. Small doses produced sedation and facilitated sleep; increasing doses caused drowsiness, ataxia, anaesthesia, and finally respiratory paralysis and death. No real specific effect of the sedatives could be expected – the effect was only a matter of dose. Sedative drugs inhibited all functions of the brain and had no influence on any specific centre. A few other drug effects were regarded as exceptions, albeit interesting. For example, diphenylhydantoin was shown to diminish the frequency of epileptic fits, although it did not have the same sedative effect as its parent compound, phenobarbital. Psychiatrists actually had no drugs at hand either for major or minor therapy other than sedatives of the old type, and their effect was limited and unsatisfactory.

After 1952 an explosive development started, which in less than 10 years changed fundamentally the concept of the pharmacology of the central nervous system, in the clinic as well as in theory.

The neuroleptics

Shortly after the end of World War II, several clinically useful antihistamines (H_1-blockers) with different chemical constitution appeared, all having the same relieving effect on symptoms of allergy, especially hay fever. Some of them, such as diphenhydramine, had unexpected side-effects, of which a disturbing drowsiness was the most conspicuous. Furthermore, it was accidentally discovered that they also relieved motion sickness (Gay and Carliner 1949). In a way, the antihistamines could be regarded as sedatives, but with a different pharmacological action, which was emphasized by the fact that in large doses they caused convulsions, not anaesthesia. However, a certain connection between the two groups was shown by Winter (1948), who found that some antihistamines potentiated the anaesthetic effect of the barbiturates.

The many peculiar actions of the antihistamines challenged the pharmaceutical industry. Derivatives were made, with the intention of avoiding the disturbing side-effects, while retaining some of their special properties. Among others, the French firm Rhône-Poulenc had developed promethazine, a phenothiazine antihistamine, as well as other compounds of this type.

This work yielded some useful drugs, among which the antiparkinson treatment ethopropazine may be included. The most important was chlorpromazine, which showed unique pharmacological properties. The pharmacology of this drug was described by Courvoisier and her collabora-

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tors (1953). Their results are now well known, and include an antiadrenergic effect with hypotension and the inhibition of the cardiovascular reflexes, abolition of temperature regulation, and the characteristic catalepsy without anaesthesia. Moreover, the antihistaminic effect was minimal. In this investigation the main emphasis was laid on the peripheral neuro-hormonal effects. Behaviourally, chlorpromazine abolished conditioned reactions, but a profound psychopharmacological analysis was not done.

Later Decourt (review 1956) described experiments on lower organisms without a nervous system and found that chlorpromazine was able to inhibit the reactions of cells to noxious influences. No wonder that Rhone-Poulenc marketed their product RP 4560, under the registered name of Largactil (R), as "The drug with the many actions." At the time of its appearance, however, it was difficult to find clinical indications for this drug with the peculiar mixture of properties.

The initiative was taken by the French military surgeon Henri Laborit in collaboration with the anaesthesiologist P. Huguenard. Their theoretical starting point was based on well-known ideas about stress developed by the Canadian, Hans Selye. After severe damage to the organism the vegetative-hormonal system increases its activity, but when this regulatory system breaks down the organism is exposed to severe stress, sometimes with lethal outcome. Laborit distinguished between a "lesion syndrome" and a "reaction syndrome," the latter having more severe consequences. The two French investigators regarded the vegetative-hormonal system as essential for the development of shock and argued against Decourt, who believed that cellular reactions were more important. In their attempt to combat the state of shock pharmacologically, Laborit and Huguenard used a "lytic cocktail," to begin with, consisting of pethidine (meperidine) and promazine, of which the latter was substituted later by the much more effective chlorpromazine.

The potentiating effect of chlorpromazine on anaesthetics produced a deeper and more prolonged anaesthesia with smaller doses of the anaesthetic, but more important was the influence of chlorpromazine on the body temperature. By cooling the chlorpromazine-treated patient, it became possible to reduce body temperature to 28–30° C. This "artificial hibernation" perhaps had the greatest influence on preventing the shock state. It was claimed that treatment with lytic cocktail had saved the lives of thousands of French soldiers during the colonial war in French Indochina (now Vietnam). The use of lytic cocktail and its theoretical background has been described several times, e.g., by Laborit and colleagues (1952), who named chlorpromazine as a new "stabilizer of the neuro-vegetative system."

It seems natural that Delay and Deneker were inspired to use chlorpromazine – at that time under the name of RP 4560 – in cases of mania, a state that often leads to hyperthermia and even to lethal shock. In fact, the idea had also occurred to others. Hamon et al. (1952) found the lytic cocktail beneficial in cases of manic excitation. Delay, Deneker and their collaborators used chlorpromazine alone, however, without the addition of other ingredients. Their systematic and careful investigations produced a break-through in the treatment of psychoses. The most surprising was that chlorpromazine not only calmed manic patients, but also had an unexpected beneficial influence on other psychotic manifestations – acute and chronic – such as confusions and paranoiac states. *"A priori, on pouvait douter de l'action bienefaisant d'une drogue qui provoque du sommeil ou de la somnolence"* (A beneficial effect of a drug that provokes sleep or somnolence should be doubted beforehand).

During the following few years the results of Delay and Deneker were confirmed by psychiatrists all over the world. They literally revolutionized therapy in major psychiatry, and the indications, dosage, and side-effects of chlorpromazine were described in numerous publications. A detailed account of the discovery of chlorpromazine and its exploration in psychiatry has been provided by Judith Swazey (1974).

As mentioned, chlorpromazine represented a new group of pharmacologically-active substances, which had to be named. Delay and his collaborators used the term "neuroleptics" and talked about a "neuroleptic effect." They also used the term "ganglioleptic effect" or even, perhaps under the influence of Decourt, "histioleptic effect." The suffix "leptic" from Greek "lepto" means fine, delicate, in this sense "make fine." Later, the names "major tranquillizers" and "ataractics" were introduced, presumably under the influence of the pharmaceutical industry, which wanted to inform the medical profession that this effect was fundamentally different from that of the hitherto used sedatives and hypnotics. This confusion in nomenclature demonstrates how little the fundamental action of these drugs was understood at that time. Eventually the term neuroleptic was generally accepted.

The clinical success was rapidly followed up by neuropharmacological investigations in animals that defined the neuroleptic effect. The pharmacological profile of the neuroleptics is now so well known that detailed description is unnecessary. The effects include catatonia without anaesthesia, inhibition of conditioned reactions, and an antiemetic effect, e.g., against apomorphine. In a very short time, pharmaceutical industries all over the world produced a host of phenothiazine derivatives with neuroleptic properties, all acting qualitatively like chlorpromazine, but with different pharmacokinetics, lower effective dosage, fewer or different side-effects, and, as was subsequently shown, with some differences in their biochemical action.

At first, the chlorpromazine molecule was altered. The phenothiazine family grew: mepazine (1954), perphenazine (1957), and trifluoperazine (1958). In 1958 was launched a new group derived from another tricyclic nucleus, thioxanthene. The first drug of this type, chlorprothixine, appeared almost simultaneously in Denmark (Petersen et al. 1958) and in Switzerland.

A real surprise was the discovery of haloperidol by Paul Janssen and his collaborators in 1957–1958. The discovery seemed to be accidental. Janssen's group studied the possibility of developing new opioids based on the 4-phenylpiperidine nucleus. Among the synthesized substances, pharmacological analysis revealed some with a strong neuroleptic effect, the first of which was the butyrophenone, haloperidol (Janssen 1965).

Shortly after the introduction of phenothiazine neuroleptics in Western medicine, it was found that the root of *Rauwolfia serpentina*, a plant that for centuries had been used in Indian folk medicine to treat many diseases, including hypertension and "insanity", had similar pharmacological properties. A short note in the New York Times reported that the Indian doctor Hakin had been awarded

a gold medal for the presentation of a paper on the use of rauwolfia root and other indigenous Indian drugs in the treatment of schizophrenia (Kline 1955). Even earlier, the root of *Rauwolfia serpentina* had been used by Indian psychiatrists. Their results had been published in English (Sen and Bose 1931; Gupta et al. 1943), but had been neglected in Western psychiatry, in spite of the fact that their publications equalled in quality many contemporary Western articles. By 1952, a number of pharmaceutical companies had become interested in using Rauwolfia alkaloids to treat hypertension.

Muller et al. (1952), of Ciba Pharmaceutical Products, isolated the major active component of Rauwolfia, reserpine, and studied its pharmacology. In animal experiments, the effects of reserpine appeared by very similar to those of chlorpromazine: sedation and catatonia without anaesthesia, antiadrenergic effect, hypothermia. Rauwolfia could undoubtedly be regarded as belonging to the group of neuroleptics.

Nonetheless, the first clinical trials of Rauwolfia and reserpine were for treating hypertension. It quickly became recognized as the first really effective drug treatment for this disorder. During these clinical trials, the peculiar sedative properties of the drug became evident. Finally, pharmaceutical companies, inspired by the reports of success in treating psychiatric conditions with chlorpromazine, began trials in psychiatric patients. European psychiatrists started trials with reserpine almost simultaneously with Kline's group in the US, obtaining more or less the same favourable results.

The results of treatment of psychiatric disorders with reserpine were almost as dramatic as those obtained with chlorpromazine. However, the drug produced a number of unpleasant side effects, such as nasal congestion, diarrhea, and depression, which made it somewhat less acceptable. It was also unpatentable, being a natural product, which markedly diminished the enthusiasm of drug companies for its commercial potential. Thus, within a short span of time, reserpine was superseded by the phenothiazines for psychiatric use. It remained the prime antihypertensive drug for many years, however.

The biochemistry of the neuroleptic action

Early on, it was recognized that the central nervous system contained various amines that in some way might play a role in the function of the brain. At first it was believed that they regulated the blood supply to various parts of the brain tissue. "Sympathin" was first demonstrated in autonomic ganglia by von Euler (1946). It was known to be separate from adrenaline and was ultimately identified as noradrenaline.

Much of this progress in mapping neurotransmitters in brain was due to technical advances in analytical methodology, especially spectrophotofluorometry. Thus, in fairly rapid succession, both noradrenaline and serotonin were identified and mapped in the brain as possible neurotransmitters. In addition, it became possible to determine their metabolic pathways, due to availability of specific enzyme inhibitors.

Fundamental investigation of the biochemistry of psychotropic drugs was conducted in the laboratories of the National Institutes of Health, Washington, DC, where Brodie et al. (1955) found that the effect of a dose of reserpine outlasted the presence of reserpine in the brain for several days. They also found that the administration of reserpine caused a depletion of serotonin in the brain. Serotonin was slowly restored and, more important, sedation and the other signs of reserpine intoxication lasted until the serotonin concentration had approached normal values. Soon it was shown that reserpine also caused a depletion of noradrenaline in the brain (Holzbauer and Vogt 1956).

The next step was by Chessin et al. (1957), who demonstrated that if a monoamine oxidase inhibitor was given to the animals before the administration of reserpine it not only prevented the depletion of serotonin, but the animals did not show sedation or any other signs of reserpine effect. Instead, the animals became hyperactive and showed signs of increased sympathetic tone. Clearly, the reserpine effect was mediated through the depletion of the amines. Treatment with the precursor of serotonin (5-hydroxytryptophan) prevented the depletion of serotonin in the tissues, but had no effect on the behavioural effect of reserpine administration. On the other hand, *l*-dihydroxyphenylalanine (levodopa), the precursor of the catecholamines, prevented the behavioural effect of reserpine, but surprisingly did not prevent the depletion of noradrenaline (Carlsson et al. 1957).

The puzzle was soon solved. The dopamine concentration was restored after levodopa administration to reserpine-treated animals concomitant with the abolition of the behavioural reserpine effects (Carlsson et al. 1957). This observation by Carlsson's group in Gothenburg for the first time disclosed the role of dopamine in the central nervous system. Up to then, noradrenaline had been regarded as the only effective catecholamine in the human central nervous system, and dopamine as its precursor, presumably because dopamine in the peripheral system had a much smaller effect than had adrenaline or noradrenaline. It thus became evident that the catecholamines played an important role in the function of the central nervous system. Dopamine seemed to be intimately connected with the extrapyramidal signs of the reserpine effect, as a high concentration of dopamine was found in the basal ganglia.

Very soon a new problem emerged. The "classical" neuroleptics such as chlorpromazine or haloperidol did not cause any depletion of amines, although they gave the same signs in animal experiments and, grossly speaking, had the same clinical effects as had reserpine. Obviously, the chlorpromazine type of neuroleptics influenced the same brain areas as reserpine, but the mode of action must be different. At the end of the 1950s and in the beginning of the 1960s it became generally accepted that the explanation was that the neuro-amines were acting as transmitters in parts of the brain and that the postsynaptic receptor sites of the aminergic system in the brain were blocked by the neuroleptics.

Many further experiments supported this explanation. Carlsson and Lindqvist (1963) showed an increased turnover of the catecholamines after the administration of neuroleptics, which they interpreted as a compensatory effect of a specific receptor blockade. Van Rossum (1966) demonstrated that neuroleptics were able to block the effect of dopamine. These are only a few of the experimental results that appeared during the period. The concept of receptors, transmitters, and their pharmacological blockade in the peripheral system, well established in earlier decades, was extended to the central nervous system. The idea was in the

air and actually proposed by many investigators at the same time as the most plausible explanation of the many observed facts.

The antidepressants (thymoleptics)

Neuroleptics had little effect on the other major type of mental disorder – the depressions. Many attempts were made to find drugs as effective for endogenous depressions as neuroleptics were for schizophrenia. Clinical trials had only an empirical background. Cocaine, amphetamine, and other drugs that induced signs of excitement in animals or humans were submitted to clinical trials, without much success.

In 1952 iproniazid was introduced in the chemotherapy of tuberculosis by Selikoff et al. (1952). The effect was dramatic, perhaps a little too much so. Newspapers showed pictures of patients dancing in the corridors of the hospital from joy at their recovery, but this seemed rather to be a side-effect, as the drug also induced euphoria. Other, more noxious side-effects of iproniazid led to its replacement by isoniazid, which has remained the primary antimycobacterial drug ever since.

Isoniazid was tested as an antidepressant, but without conclusive results (Delay et al. 1952). Meanwhile, Zeller et al. (1952) showed that iproniazid – but not isoniazid – inhibited monoamine oxidase. Chessin et al. (1957) used iproniazid to reverse the effect of reserpine. Inspired by these observations as well as the well-recognized depressogenic effect of reserpine, John C. Saunders and Nathan S. Kline used iproniazid as an antidepressant (Kline 1958). The encouraging clinical effect was confirmed by investigators in the US and Europe. Once again toxicity of iproniazid led to its abandonment, but other drugs with the same inhibiting effect on the monoamine oxidase, different from iproniazid in chemical constitution, were substituted.

Monoamine oxidase inhibitors remained as major antidepressants for several years. Enthusiasm about their use was diminished by the observation that they reacted with other drugs or with amines, such as tyramine in food stuffs, causing attacks of severe hypertension. This now well-known phenomenon started a wave of interest in drug interaction, involving not only monoamine oxidase inhibitors but also many others drugs.

Almost simultaneously with the introduction of the monoamine oxidase inhibitors, another new type of antidepressant appeared. In the quest for new antihistamines, many compounds were synthesized in the laboratories of the pharmaceutical industry. Most of them were found to have too little of the desired effect and were stored unused on some shelves. So it was with the compound G 22355 in the Swiss firm Geigy, but in animal experiments it was found to have a weak neuroleptic effect. In the middle of the 1950s many neuroleptics had rather pronounced extrapyramidal side-effects, while some of the weaker ones seemed to have less. Therefore G 22355 was submitted to a clinical trial by the Swiss psychiatrist Ronald Kuhn. His results were highly unexpected. The substance had no effect as a neuroleptic, but it dramatically improved symptoms of endogenous depression (Kuhn 1957). This observation was soon confirmed. G 22355 was named imipramine, and many new drugs with the same principal effect followed, such as amitriptyline. For the antidepressants the name "thymoleptic" has been introduced, from Greek thúmos: passion, mood, courage and again, lepto: make fine. Because of the 6-7-6 three ring structure of these compounds, they became better known as tricyclic antidepressants.

The biochemical background of tricyclic antidepressants was different from that of the monoamine oxidase inhibitors. The tricyclics had no effect on the amino-oxidases, but they were shown to inhibit the uptake of the amines into tissues (Axelrod et al. 1961), including the brain (Glowinski and Axelrod 1964). This fact showed the connection between the effects of the two types of antidepressants. Both increased the concentration of neurotransmitters at the synapse. Monoamine oxidase inhibitors prevented their presynaptic inactivation, presumably allowing more transmitters to be released. Tricyclics prevented their reuptake presynaptically, a major method for termination of synaptic transmission. It became clear that the amines in some way or another played a role in the pathogenesis of endogenous depression.

Other well-known compounds, such as cocaine, turned out to have the same inhibiting effect as tricyclics on the uptake of the amines. It is interesting to note that Sigmund Freud at the end of the nineteenth century used cocaine in the treatment of depression. Theoretically, he might have succeeded, but he wisely gave up the treatment as cocaine use led to addiction.

The anxiolytics

Up to about 1950, sedatives were the only known anxiolytic drugs. Phenobarbital was preferred, but many attempts were made to find other and better anxiolytics, although with little success. The first clue to a new approach came through mephenesin, an accidentally-discovered muscle relaxant. Mephenesin was a phenyl glycerol ether that was too short-lived to be of much clinical use. In an attempt to protect it against too rapid metabolism, the structure was modified to 2-methyl-2-propyl-1,3-propanediol. This change was not successful, but coupling of carbamic acid residues to the free hydroxyl groups produced meprobamate. For a long while the principle mode of action of meprobamate was thought to be connected in some way to its muscle-relaxant action. It ultimately proved to have a pharmacological profile not much different from the barbiturates, which had preceded it (Berger 1954).

Inspired by the commercial success of meprobamate, many new substances were made and analysed pharmacologically in order to obtain similar drugs that were not barbiturates. In the Roche Laboratories some benzodiazapines were found especially effective. The first one was chlordiazepoxide, effective in about one tenth the dose of meprobamate. Moreover it seemed to have an even more pronounced taming effect in doses that caused little or no ataxia (Randall et al. 1960; Henschule 1961).

Another benzodiazepine, diazepam, soon followed. This drug became enormously popular, and has probably been the most widely used sedative in medical history. Benzodiazepines had two distinct clinical advantages over phenobarbital. First, they were only mild respiratory depressants, so that overdoses were unlikely to be fatal. Second, they did not stimulate drug-metabolizing enzymes, as phenobarbital did, with ensuing drug-drug interactions. Their arrival soon made phenobarbital and meprobamate obsolete.

Chlordiazepoxide and diazepam were followed by many other benzodiazepines. More than 20 such compounds are

marketed throughout the US and Europe. The majority are promoted primarily as sedatives or anxiolytics, but some are promoted as hypnotics or anticonvulsants. On the whole, all have similar pharmacological properties but they differ greatly in their pharmacokinetics. Their enormous popularity has evoked many concerns about their overuse but, in general, they have been one of the safest groups of drugs ever introduced into medical practice. A major concern is about psychic and physical dependence, in which they resemble the barbiturates and meprobamate, but with a greater therapeutic margin.

A major advance in understanding the biochemical basis for the effect of benzodiazepines was the discovery of sites in the central nervous system that strongly and specifically bind benzodiazepines (Squires and Braestrup 1977; Mohler and Okada 1977). It now seems to be experimentally well supported that benzodiazepines bound to their specific sites facilitate the effect of gamma aminobutyric acid (GABA) (Olsen 1982). This fact reasonably explains at least the strong anticonvulsive effect of the benzodiazepines, but it remains uncertain whether or not this effect plays a role in their anxiolytic action. Neither meprobamate nor phenobarbital is bound to benzodiazepine binding sites, indicating that benzodiazepines act through a distinctive mechanism.

Lithium

Lithium holds a special position among psychotherapeutic drugs. The lithium salts were the first to be used clinically and among the last to be generally acknowledged. While the hitherto described group of psychotherapeutic drugs were received with enthusiasm, the therapeutic use of lithium achieved its current status only with difficulty. This is reflected in the number of publications on lithium. In 1950 less than 20 appeared, in 1960 about 30, in 1970 more than 200, and in 1980 over 600 (Schou 1983).

Only a few decades after the discovery of lithium in 1817–1819, it was shown that lithium urate was easily soluble in water, and the use of lithium salts became recommended first against urinary calculi and later against gout. Based on several large and comprehensive monographs on gout by the highly esteemed English physician, Sir Alfred Garrod, the concept of gout in the latter half of the 19th century was enlarged to the extent that it comprised not only the well-known manifestations in the joints, but also a range of other, sometimes rather undefined syndromes such as gastric complaints, headache, and mental depression, which were named "irregular gout" or "uric acid diathesis." They were treated with lithium salts, of which many were on the market, or with mineral water containing lithium, found in various spas. A Danish psychiatrist, Carl Lange, at the end of the former century described a syndrome that he called "periodic depression" and apparently treated successfully with lithium. His work and the whole idea of uric acid diathesis vanished into oblivion during the first decades of this century, and with this the therapeutic use of lithium. The early history of lithium is described by Johnson and Amdisen (1983).

During an investigation on the toxicity of urea, which lithium seemed to diminish, the Australian physician John Cade observed that lithium carbonate injected into guinea pigs induced a peculiar lethargy. Inspired by this observation, he tested lithium carbonate in the treatment of patients with mania. His good results were convincingly described. Some patients were normalized but relapsed to their previous state if the lithium treatment was discontinued (Cade 1949).

At the same time, lithium chloride was introduced commercially in the US as a substitute for sodium chloride. Shortly after, cases of severe lithium intoxication were reported among patients kept on a salt-free diet (Hanlon et al. 1949). In spite of the fact that a sodium-free diet strongly enhances the toxicity of lithium, these incidents presumably caused a reluctance among psychiatrists to use lithium in therapy. In a review published 10 years after Cade's first publication, Schou (1959) found published results of lithium treatment from only 17 departments with a total of 370 patients, of whom about half were from Schou's own material. All the publications were favourable and confirmed Cade's results. Lithium salts were effective in cases of acute and chronic mania and often worked better than the neuroleptics.

Further investigations on patients with affective disorders indicated that chronic lithium intake has a prophylactic effect, not only on the occurrence of mania attacks, but also on the occurrence of periodic depressive episodes, even if lithium was found ineffective in the treatment of a developed endogenous depression. For a rather long time this effect of lithium was questioned by many, until it was definitely confirmed by Baastrup et al. (1970) in a sophisticated double-blind trial.

In spite of much intensive biochemical work, it has not yet been possible to demonstrate any effect at the cellular level that can yield a reasonable explanation of the peculiar and specific effect of the lithium ion.

Some comments

The saga of the psychotherapeutic drugs is in principle more or less similar to that of the other new drugs that appeared in the middle of the 20th century, based on a mixture of ideas, hypotheses – which often even proved to be erroneous – luck, serendipity, followed up with hard, systematic work. There is little doubt that the many important drugs that were introduced during this period, such as antibiotics and corticosteroids, raised the hope that a similar development also could be possible in psychiatry. Derivatives of sedating antihistamines were already marketed as psychotherapeutic drugs before chlorpromazine. Some of them had a reasonable effect as minor tranquillizers, but they are not mentioned as none of them has opened a gateway to further research or exploitation comparable to those described here.

The interval between the first neuroleptic and the appearance of the benzodiazapines was less than 10 years. During this short span, not only did three extremely useful new types of psychotherapeutic drugs appear, but the study of their action contributed much to the understanding of important aspects of the biochemical background of the brain function.

The history of the now generally used groups of psychotherapeutic drugs is a result of an intimate collaboration among psychiatrists, biochemists, pharmacologists, neurophysiologists, and not least the pharmaceutical industry. However, it is noteworthy that the most important discoveries have been made by clinicians who used weapons forged by the industry for other purposes. Rhône-Poulenc

had no intention to develop an antischizophrenic drug, nor had Geigy planned to make an antidepressant.

The "great period" in psychiatric pharmacotherapy covers so short a time that the historical description should specify not only the years, but also, like the French revolution, months or even days. For several reasons this is impossible here. In too many cases the date of the first publication is uncertain, it may have been at a congress or at a special meeting of experts, and the printed publication may have appeared several months later, if ever. Moreover, it has been a policy of many pharmaceutical firms to postpone publication of many relevant biological facts obtained in their laboratories until a drug has been marketed. The same idea may have originated in different groups at the same time, and many authors may have their names on the same publication. All this often makes it impossible to name one single investigator as an initiator of a new idea. My very limited list of references includes the contributions I have found the most important. If some are missing, please understand that this is not due to prejudice or ill-will.

Development during the last 20 years has been steadier and much less dramatic. Still, there has been considerable progress. Clinicians have learned to use the drugs more effectively. New congeners with some differences in the effect have been added to the old drugs. Some of these congeners will perhaps prove more useful than the old ones. In the field of neurophysiology, important new knowledge has been obtained, including the elaboration of an ever-growing number of putative neurotransmitters and receptors. The discovery of the two types of dopamine receptors and the demonstration of the receptor sites for the benzodiazepines may provide further keys to understanding the pathophysiology of schizophrenia and anxiety. However, no break-through has occurred compared with the introduction of the neuroleptics or of the antidepressants.

The discovery of the clinical effect of the drugs combined with the acquired knowledge of their biochemical action has had a great influence on the concept of the aetiology of the mental diseases. A large proportion of psychiatrists now regard many, if not all, symptoms of both cognitive and affective diseases as caused by a dysfunction of the neuronal transmitter system by analogy with many diseases in the peripheral neuro-endocrine system. In any case, it must be emphasized that all known psychotherapeutic drugs have a symptomatic effect only. The symptoms will sooner or later return if the medication is discontinued or if the disorder does not spontaneously remit. It is therefore necessary to assume that under the layer that has been made accessible for pharmacological treatment are found deeper layers the nature of which we do not know. Whether or not such layers ever can be found and whether or not they can be treated pharmacologically are questions that belong to a future history.

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