

# Monoaminergic Neurotransmission: The History of the Discovery of Antidepressants from 1950s Until Today

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**Abstract:** The 1950s saw the clinical introduction of the first two specifically antidepressant drugs: iproniazid, a monoamine-oxidase inhibitor that had been used in the treatment of tuberculosis, and imipramine, the first drug in the tricyclic antidepressant family. Iproniazid and imipramine made two fundamental contributions to the development of psychiatry: one of a social-health nature, consisting in an authentic change in the psychiatric care of depressive patients; and the other of a purely pharmacological nature, since these agents have constituted an indispensable research tool for neurobiology and psychopharmacology, permitting, among other things, the postulation of the first aetiopathogenic hypotheses of depressive disorders. The clinical introduction of fluoxetine, a selective serotonin reuptake inhibitor, in the late 1980s, once again revolutionized therapy for depression, opening the way for new families of antidepressants. The present work reviews, from a historical perspective, the entire process that led to the discovery of these drugs, as well as their contribution to the development of the neuroscientific disciplines. However, all of these antidepressants, like the rest of those currently available for clinical practice, share the same action mechanism, which involves the modulation of monoaminergic neurotransmission at a synaptic level, so that the future of antidepressant therapy would seem to revolve around the search for extraneuronal non-aminergic mechanisms or mechanisms that modulate the intraneuronal biochemical pathways.

**Key Words:** Depression, antidepressants, iproniazid, imipramine, fluoxetine, monoaminergic neurotransmission, history.

## 1. INTRODUCTION

Therapeutic approaches to affective disorders, from the perspective of current scientific pharmacology, date from the 1950s, with the introduction of imipramine and iproniazid. Prior to the clinical introduction of these first antidepressants, the therapeutic tools employed in dealing with mood disorders were extremely scarce [1]. In the early 20<sup>th</sup> century the agents used were chloral hydrate, barbiturates, amphetamines, and even opiate derivatives in agitated melancholic patients. During the first half of that century, and excluding biological treatments (insulin comas, chemical and electrical shock therapy, or the famous “sleep cures”), whose use was widespread, the only chemical preparations available to physicians were some non-specific ones, such as succinic dinitrite, malonic nitrite or lactic acid, whose antidepressant results were rather unsatisfactory.

It was in the 1950s that a veritable revolution took place in the fields of psychopharmacology and psychiatry, with the clinical introduction of the main groups of psychoactive drugs still used today. Although it is clear that in these early phases of psychopharmacology serendipity played an important role in the discovery of the majority of psychotropic drugs [2,3] –in addition, naturally, to large doses of wisdom and astute clinical observation [4]– what was truly important were the final results of these research processes. It suffices to highlight, apart from the discovery of imipramine and the

psychiatric use of iproniazid, the discovery of the antimanic action of lithium in 1949, the clinical introduction of chlorpromazine in 1952 and meprobamate in 1954, and the introduction, finally, of chlordiazepoxide in 1960. This is indeed why the 1950s is often considered the “golden decade” of psychopharmacology [5].

Thus, when we speak of a “revolution” in the area of psychoactive drugs during the 1950s, our intention is to highlight the crucial importance of the introduction of truly effective therapeutic tools for treating the different psychiatric disorders. And this is the case of iproniazid, and above all of imipramine, two drugs which not only marked a new era in the treatment of depression, but also relegated Ugo Cerletti’s electroconvulsive therapy, previously the only antidepressive treatment with significant rates of effectiveness, to use only in highly specific cases [1]. Even so, the clinical introduction of these drugs had many critics, since psychoanalytic currents, doctrinally dominant in the psychiatry of the time, considered depression as a symptomatological manifestation of certain internal personality conflicts. According to this view, such conditions were even deemed to have positive characteristics, in that they were a form of externalizing a whole series of subconscious and traumatic internal conflicts, supposedly processed by the patients themselves. In this framework, the pharmacological treatment of depressive symptoms (as would occur some years later in the case of anxiety disorders) was viewed by a large part of the psychiatric community as a real error, since it would prevent patients from discovering the “true” roots of their internal conflicts. In our opinion, iproniazid and imipramine made two fundamental contributions to the devel-

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opment of psychiatry: one of a social-health nature, consisting in an authentic change in the psychiatric care of depressive patients; and the other of a purely pharmacological nature, since these agents have constituted an indispensable research tool for neurobiology and psychopharmacology, permitting, among other things, the postulation of the first aetiopathogenic hypotheses of depressive disorders.

The introduction of the so-called atypical, heterocyclic or "second generation" antidepressants (maprotiline, nomifensine, trazodone, mianserine, among others) in the 1970s did not bring the heralded momentous progress, from either the therapeutic or safety perspective, except in individual cases, with respect to the classical antidepressants. On the other hand, the clinical introduction of selective serotonin reuptake inhibitors (SSRIs), in the late 1980s, once again revolutionized therapy for depression [1], opening the way for new families of antidepressants (see Table 1). Nevertheless, they all continue to employ the same action mechanism as the classical drugs, that is, the modulation of monoaminergic neurotransmission at a synaptic level.

## 2. IPRONIAZID AND MONOAMINE-OXIDASE INHIBITORS

### The Discovery of Hydrazone Compounds and of their Pharmacological Properties

Hydrazines have their origins in the research carried out by Emil Fischer in the 1870s. This father of organic chemistry discovered phenylhydrazine in 1874, accidentally, while he was working in the laboratory of Adolf von Baeyer in Strasbourg [6]. From hydrazine hydrate, a powerful reducing agent, Hans Meyer and Josef Malley, of the German Charles-Ferdinand University (Prague), synthesized isonicotinylhydrazine in 1912, as part of the work for their doctoral thesis [7]. However, forgotten for almost 40 years, it would not be until the early 1950s that it was resynthesized and that it

was discovered, by chance, that the compound had, at any experimental level, powerful antitubercular properties [8]. A decisive influence on this discovery were the large stocks of hydrazine discovered after World War II, having been used by the German army as fuel for their V2 rockets, and which were distributed to the chemical and pharmaceuticals industry at low cost [9].

The discovery of the antitubercular effects of this hydrazine derivative, which took place in 1951, is due to the research work carried out, independently, by two scientific teams, led by Herbert Hyman Fox of Hoffmann-La Roche Laboratories (Nutley, New Jersey) and Harry L. Yale of the Squibb Institute for Medical Research (Princeton, New Jersey), respectively [10]. In the framework of a research programme on anti-infectious drugs at the Squibb Institute in the 1940s, under the direction of Frederick Wiseloge, hundreds of compounds were synthesized and studied in mice previously infected with *Mycobacterium tuberculosis*. In 1951, one of the chemists in the group, Harry Yale, synthesized from a hydrazide intermediary (isonicotinyl-hydrazine), isonicotinyl-aldehyde-thiosemicarbazone, since researchers at the University of Indiana had already shown the tuberculostatic efficacy of thiosemicarbazones. However, there was enormous surprise when the synthetic intermediate employed was found to be much more active in the animal model than the final product. Almost at the same time, two weeks after the publication of the first Squibb report (10 January, 1952), Fox's team at Hoffmann-La Roche also announced the antitubercular properties of isonicotinylhydrazine [11]. Their research line started out from knowledge of the tuberculostatic effects of nicotinamide, a group B vitamin, so that their idea was to combine a pyridine derivative of this group with a thiosemicarbazone. As occurred with Yale, Fox's group found that the synthetic intermediary used, isonicotinyl-hydrazine, showed greater antitubercular power than the final product, isonicotinyl-aldehyde-thio-

**Table 1. Classification of Monoaminergic Antidepressants According to Action Mechanism and Historical Perspective on their Clinical Introduction**

Family	Acronym	Prototype Substance	Period
5-HT and NA reuptake inhibitors with blocking action of diverse receptors	TCA	Imipramine	1957-1980
Irreversible MAO inhibitors	MAOI	Phenelzine	1960-1965
NA reuptake inhibitors with blocking action of diverse receptors		Maprotiline	1970-1980
Antagonists of $\alpha_2$ auto-receptors		Mianserine	1970-1980
Selective DA reuptake inhibitors	SDRI	Bupropion	1980-1990
Selective 5-HT reuptake inhibitors	SSRI	Fluoxetine	1980-1990
Reversible MAO inhibitors	RIMA	Moclobemide	1980-1995
5-HT reuptake inhibitors and blockers of 5-HT <sub>2</sub> receptors		Nefazodone	1985-1995
Antagonists of $\alpha_2$ auto- and hetero-receptors and 5-HT <sub>2</sub> and 5-HT <sub>3</sub> receptors	NaSSA	Mirtazapine	1975-2000
NA and 5-HT reuptake inhibitors	NSRI	Venlafaxine	1975-2000
Selective NA reuptake inhibitors	SNRI	Reboxetine	1980-2000

Modified by López-Muñoz *et al.* [1].

semicarbazone [10]. Clinical trials were carried out with this compound almost immediately in different hospitals in New York State; its antitubercular effectiveness was demonstrated, and it became known as isoniazid. Subsequently, this line of research was continued by Herbert H. Fox himself and John T. Gibas, at the Hoffmann-La Roche Laboratories, and among different derivatives of isoniazid, these two scientists synthesized an isopropyl derivative called iproniazid (1-isonicotinyl-2-isopropyl-hydrazine), whose tuberculostatic activity was similar to that of isoniazid in lab animals, but superior in humans [12].

The enormous significance of the introduction of these drugs for the treatment of tuberculosis is reflected in the mortality data for this illness in the United States, which fell from 188 deaths per 100,000 inhabitants in 1904 to just 4 in 1952, one year after the introduction into the field of isonicotinyl-hydrazine or isoniazid [13].

### The Pharmacological Contributions of Iproniazid

Prior to the discovery of the antitubercular properties of hydrazines, Mary L. Hare (Mary Bernheim), a researcher at the University of Cambridge, described for the first time in 1928 how an enzyme (which she called tyramine-oxidase) was capable of bringing about oxidative disamination of the biogenic amines [14]. This enzyme was identified in 1937 by the groups led by Herman Blaschko and Derek Richter, at the Physiology Department of Cambridge University [15], and by those of Caecilia E. Pugh and Juda H. Quastel, at the Biochemical Laboratory of Cardiff City Mental Hospital [16], being given the name monoamine-oxidase (MAO). Blaschko's group showed that MAO, isolated from cells of the liver, kidney and small intestine, was capable of metabolizing adrenaline through oxidation, a process that could be inhibited by ephedrine [15]. These authors concluded that the MAO inhibitors would act in a very similar way to ephedrine, activating the adrenergic system. However, this theory was rapidly discarded in 1939 by Richter himself and Tigney, as described by Amat and Cuenca [17]. For their part, Quastel and Pugh also identified this enzyme in the brain, though its significance remained unclear [16]. It would later be definitively demonstrated that MAO constitutes a flavoprotein enzymatic system located at the level of the mitochondrial membrane, and whose function is to produce oxidative disamination not only of the biogenic amines (serotonin and catecholamines), but of other, sympathomimetic amines (tyramine, benzylamine,  $\beta$ -phenylethylamine, etc.).

In 1952, the team led by Ernst Albert Zeller (Fig. (1)) at Northwestern University Medical School (Chicago, Illinois) observed for the first time that iproniazid (and not isoniazid) was capable of inhibiting MAO [18]. Subsequent studies found that serotonin in the brain was converted into hydroxyindoleacetic acid by MAO; for a long period, indeed, this process was thought to be the only path for the metabolism of serotonin. In 1957, Sidney Udenfriend and colleagues, at the National Institutes of Health (NIH) (Bethesda, Maryland), observed that administration of iproniazid to experimental animals produced a rapid increase in brain levels of serotonin, similar to those resulting from the administration of 5-hydroxytryptophan, a substance capable of crossing the blood-brain barrier and producing serotonin through de-

carboxylation [19]. Simultaneously, Bernard B. Brodie (Fig. (2A)) and his colleagues at the Laboratory of Chemical Pharmacology of the National Heart Institute (a division of the NIH), Parkhurst Shore and Alfred Pletscher (the latter being Director of Research at Hoffmann-La Roche in Switzerland) (Fig. (2B)), confirmed that reserpine and other compounds produced a release of serotonin in brain, platelets and intestine [20,21].

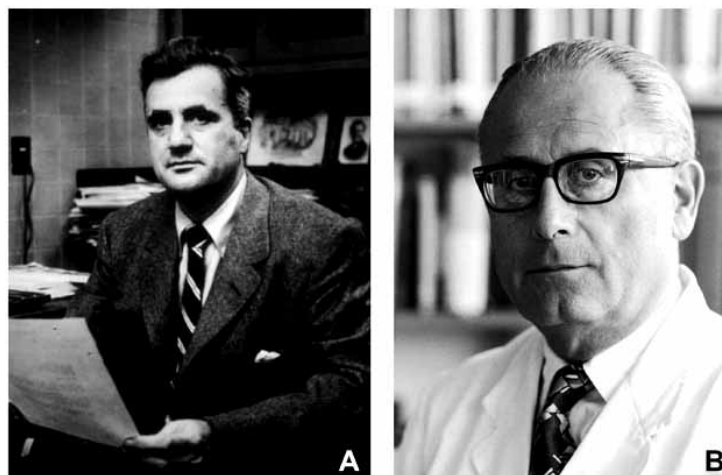


**Fig. (1).** Ernst Albert Zeller (1907-1987), biochemist at Northwestern University Medical School (Chicago, Illinois). His team demonstrated for the first time, in 1952, that iproniazid was an agent capable of inhibiting MAO.

All such work opened up an interesting research line on brain functions, in the framework of which are the contributions of Charles Scott at Warner-Lambert Research Laboratories (Morris Plains, New Jersey), who carried out certain animal experimentation studies that would be of great interest for the future characterization of these hydrazide drugs as antidepressants [22,23]. Scott believed that the tranquillizing effects observed in animals given reserpine, an alkaloid of *Rauwolfia serpentina*, were due to the release of serotonin caused by the reserpine. With this hypothesis, and knowing the results of Zeller's work, Scott administered iproniazid with the aim of limiting the enzymatic destruction of serotonin. However, the pre-treatment with iproniazid carried out by Scott before administering the reserpine had the opposite result to that expected by the researcher: a stimulant effect, rather than the predicted tranquillizing effect [24]. Similar results were obtained by Brodie's team at the NIH. In 1956, Scott's group described this effect of experimental alertization with iproniazid, which he called "marsilization", in reference to the trade name of this agent [24].

### Discovery of the Antidepressant Effects of Iproniazid: An Example of Serendipity

The origin of the first specifically antidepressant drugs, the MAO inhibitors (MAOIs), lies in the antitubercular hydrazide agents that had been used since the early 1950s



**Fig. (2).** Bernard B. Brodie (1901-1989) (A) and Alfred Pletscher (1917-2006) (B). The research work of Brodie (Director of the Laboratory of Chemical Pharmacology at the National Institutes of Health, Bethesda, United States) on serotonin and catecholamines in the 1950s contributed highly valuable data for the subsequent postulation of the neurobiological hypotheses of depression. In 1967, Brodie was awarded the Lasker Prize for Basic Medical Research “for his extraordinary contribution to biochemical pharmacology”. The works of Pletscher (Director of Research at F. Hoffmann-LaRoche, S.A. in its headquarters in Basle and Professor of Pharmacology at the city’s University) with serotonin-reserpine-iproniazid, initially in collaboration with Brodie, opened the way to an understanding of the biochemical bases of affective disorders.

[1,22,23]. It was precisely in 1952 that studies began, at the Sea View Hospital on Staten Island (New York), on the clinical effects of iproniazid, carried out by Irving J. Selikoff and Edward Robitzek, who observed that this drug possessed, compared to isoniazid, greater power to stimulate the Central Nervous System (CNS), an effect initially interpreted as a side effect [25]. The psychological changes observed in tuberculosis patients treated with iproniazid were especially striking [1,9,23,26]: these patients showed greater vitality, to the point in some cases of wanting to leave hospital, and a gradual increase in their social activity. A photograph by *Associated Press* from 1953 immortalized the effects of iproniazid. It shows several patients at the Sea View Hospital in party mood, even dancing. Under the picture it says: “A few months ago, the only sound here was the sound of victims of tuberculosis, coughing up their lives”. Other authors reported that patients were “dancing in the halls tho’ there were holes in their lungs” [9]. Similar psychostimulant effects were also observed in patients with other chronic illnesses, such as rheumatoid arthritis or cancer, treated with iproniazid [27].

However, the results of the first clinical trials with iproniazid indicated a safety profile, in the treatment of tuberculosis, inferior to that of isoniazid, so that it was practically abandoned, except in particular cases. For example, David M. Bosworth, Director of Orthopedics at St. Luke’s and Polyclinic Hospital in New York insisted on the superiority of iproniazid for treating bone tuberculosis [28]. But at this point in the story serendipity came into play [4], when a few very wise clinicians saw in the psychostimulant “side effect” –which had emerged by chance– a potential “primary effect” that could be useful in other types of patient, basically those of a psychiatric nature. These inspired individuals included Jackson A. Smith, of Baylor University, (Waco, Texas), who

in his analysis of iproniazid as a “tranquillizer” observed some improvement in two depressed patients from a group of 11 treated over a period of two weeks (increased appetite, weight gain, increased vitality and improved sleep) [29]; Gordon R. Kamman, of the University of Minnesota (Twin Cities) [30]; and Carlos Castilla del Pino, of the University of Córdoba (Spain), who described the euphoric and mood-raising effects of hydrazide therapy in tuberculosis patients [31]. Some studies were even published that assessed the mood-raising effect of isoniazid in psychiatric patients [32-34]. Indeed, it may even have been one of these authors, Max Lurie (a psychiatrist with a private practice in Cincinnati), who coined the term “antidepressant” to refer to the effect of isoniazid in depressed patients [35].

Finally, the year 1957 would be a key one for the future of hydrazide drugs as antidepressant agents, since it was at a meeting of the American Psychiatric Association (APA) in April of that year, in Syracuse, that the first data on the effects of iproniazid on depression were presented. Although it was much less widely used than isoniazid, George Crane, of New York’s Montefiore Hospital, reported improved mood in 11 out of 20 tuberculosis patients with concomitant depression [36] treated with iproniazid, while Frank Ayd, an assistant at the Taylor Manor Hospital in Baltimore [37], reported similar results. Nevertheless, these researchers never referred to iproniazid as an “antidepressant”. On the other hand, Nathan S. Kline (Fig. (3)) and colleagues (Harry P. Loomer and John C. Saunders), of Rockland State Hospital (Orangeburg, New York), who knew about Scott’s research, especially the capacity of iproniazid for preventing the immobility in mice induced by reserpine [24], were the first psychiatrists to assess the efficacy of iproniazid in non-tuberculosis depressed patients (chronic psychotic depression), carrying out the same procedures with humans as Scott

did with animals. For their study they recruited 17 highly inhibited subjects with severe schizophrenia and 7 with depression, all patients at Kline's private surgery; participants were given a 50 mg dose of iproniazid 3 times a day. Their results, also reported at the Syracuse Meeting but not published until the following year, indicated that iproniazid had a stimulant effect on depressed patients, and that 70% of the patients who received iproniazid had undergone a substantial improvement (raised mood, weight gain, better interpersonal capacity, increased interest in their surroundings and themselves, etc.) [38]. Such was the impact of the new drug that, in November of that same year, the Hoffmann-La Roche company sponsored the *Symposium on the Biochemical and Clinical Aspects of Marsilid and Other Monoamine Oxidase Inhibitors*, which discussed its effectiveness not only for depression, but also for other pathologies, such as hypertension or angina. Within the framework of this symposium eight studies were presented, covering a total of some 300 patients affected by different mental disorders, mainly depression.



**Fig. (3).** Nathan S. Kline (1916-1983), one of the great pioneers of psychopharmacology. In 1952 he set up the Research Unit at Rockland Psychiatric Center (later called Rockland State Hospital) in Orangeburg (New York). Kline was the man responsible for the clinical introduction in psychiatry of iproniazid and reserpine, and was twice awarded the prestigious Lasker Prize; first, in 1957, for his studies of the antipsychotic effect of reserpine, and again in 1964, for his contribution to the development of MAOIs.

In 1957, Kline, who combined his work in clinical research with the post of Assistant Professor of Psychiatry at the University of Columbia, published a report on the first neuropsychiatric experiences with iproniazid (previously presented at the annual meeting of the APA in Syracuse), during a Congress of the Committee on Appropriations of the United States Senate, held in May [39], proposing the term "psychic energizer" to refer to the drug's action [40]. Even two years later, at a symposium held in Montreal, Werner Janzarik proposed using the term "thymereitics", that is, substances that act through an increase in the stimulative

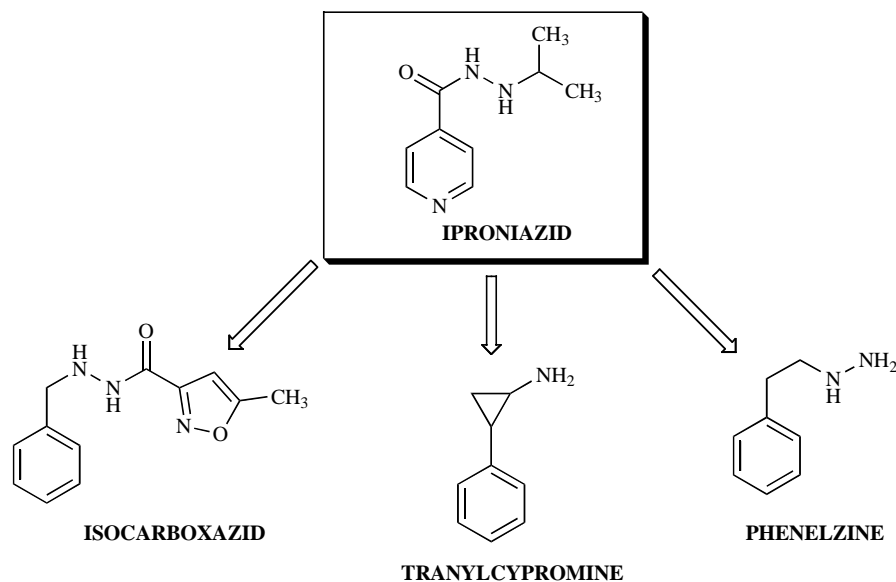
action of the impulse, to cover all the drugs that presented a spectrum of action similar to that of the incipient MAOIs. However, Kline's group ran into considerable difficulties for pushing further with the study of the antidepressant effect of iproniazid: in early 1957, when their clinical research project was already under way, they lost the explicit support of the doctors in charge at Hoffmann-La Roche, who judged the indication of their drug as an antidepressant to be subject to an uncertain and inadequate market [26]. Without losing hope, they managed, according to Kline [39] himself, to arrange a secret meeting with L. David Barney, President of the pharmaceutical company, at Theodore's Restaurant in New York. During the course of this meal, the researchers from Rockland State Hospital managed to interest Barney in their project, which was thus able to continue. Incidentally, the problems continued just after the APA meeting of April 1957, as the three members of the research group became involved in a serious conflict among themselves, carried on first through the pages of medical journals (*Journal of the American Medical Association*, 1965), and later even in the courts (Appellate Division of the Supreme Court, First Judicial County of New York, Index No. 7770, April 15, 1980; New York Court of Appeals, Decision of the Appellate Division of the Supreme Court, Upheld in *Saunders vs. Kline*, No. 141, March 26, 1981), over the attribution of the discovery of the antidepressant effect of iproniazid [9].

One year after the Syracuse meeting, and despite the fact that iproniazid was only marketed as an antitubercular agent, under the trade name Marsilid<sup>®</sup>, more than 400,000 patients affected by depression had been treated with the drug [10], which opened the way for the first group of specifically antidepressant drugs, later known as MAOIs. This great initial success of iproniazid was due, in part, to two important factors [1,23]: the good previous results obtained in the treatment of tuberculosis patients, and the lack at the time of truly useful therapeutic tools in the treatment of depression, so that the demand was enormous.

### The Saga Moves On

Iproniazid soon gave way to other agents with much greater power to inhibit MAO [41], such as isocarboxazid (Hoffman-LaRoche), tranylcypromine (Smith, Kline & French) [42,43] and phenelzine (Warner-Lambert) [44] (Fig. (4)), as well as other hydrazine derivatives (nylamide, mebanazine and pheniprazine) or indole derivatives (tryptamine) [45]. Standing out among all these MAOIs was tranylcypromine, a cyclopropylamine structurally unrelated to the hydrazines. This molecule had been synthesized in 1948 by Alfred Burger and William L. Yost, as an analogue of amphetamines (trans-dl-2-phenyl-cyclopropylamine sulphate) [46], but its MAOI action was not discovered until 1959, in Smith, Kline & French Laboratories [42,47]. Precisely because tranylcypromine was not, like iproniazid and iproniazid, a hydrazine derivative, its clinical interest increased enormously, as it was thought it might have a more acceptable safety profile than that of the previous MAOIs [48]. By the mid-1980s, tranylcypromine and phenelzine together accounted for over 90% of the market in MAOIs [49].

The safety problems of MAOIs gave rise to a new research line on antidepressants in the 1970s. The existence of



**Fig. (4)**, Chemical structure of antidepressant drugs of the MAOI family.

two functional forms of MAO (MAO-A, located preferentially in the intestinal lining and associated with depressive disorders, and MAO-B) was revealed in 1968 by J.P. Johnston, at the Research Laboratory of May & Baker Ltd. (Dagenham, United Kingdom), in rat brain [50]. Subsequent studies confirmed that MAO-A preferentially disaminated adrenaline, noradrenaline and serotonin, whilst MAO-B metabolized benzylamine and  $\beta$ -phenylethylamine. Moreover, both isoenzymes had dopamine and tyramine as substrates. The classic MAOIs (iproniazid, phenelzine and tranylcypromine) irreversibly inhibited both isoenzymes, even though it was demonstrated that the functional form involved in antidepressant action was MAO-A [51]. These facts encouraged the development of new molecules with two important characteristics: a) the selective inhibition of MAO-A, permitting MAO-B to remain active and exercise its metabolizing action on certain substances, such as the tyramine ingested with food, and whose failure to disaminate could lead to hypertensive crises; and b) reversible and competitive inhibition of the isoenzyme, so that other substrates, such as tyramine, could move it from its enzymatic union. There thus appeared the reversible and selective inhibitors of MAO (RIMA). The first molecule of this family to be registered was moclobemide, developed at Hoffmann-La Roche by W. Wirkard and Moussa Youdim, though it always had to bear the reputation of limited clinical antidepressant effectiveness [52,53]. Later, brofaromine was registered, though for the same reason it did not come onto the market [54,55]. Also marketed, within the group of classic or irreversible MAOIs, was a selective inhibitor of MAO-B, deprenyl, prescribed for the treatment of Parkinson's disease, together with levodopa and peripheral inhibitors of dopa-decarboxylase.

### 3. IMPRAMINE AND TRICYCLIC ANTIDEPRESSANTS

#### Synthesis of Iminodibenzyl Derivatives

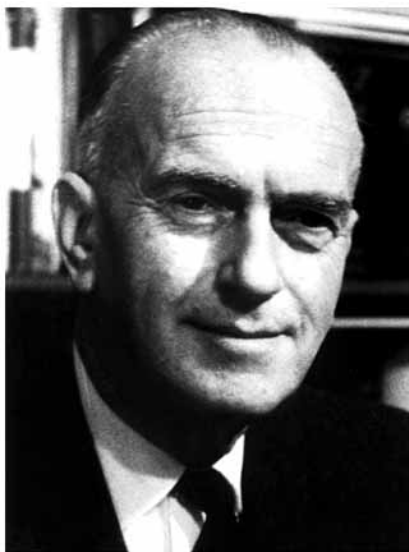
The history of tricyclic (TCAs) and tetracyclic antidepressants began in 1883, with the synthesis of the first phe-

nothiazine by Prof. Heinrich August Bernthsen, a 28-year-old laboratory chief at the Badische Anilin und Soda Fabrik (BASF) in the German city of Mannheim [56], who was commissioned to experiment with chemical dyes, particularly methylene blue [26,57]. In 1883 Bernthsen synthesized for the first time a phenothiazine that would serve as the basis for the subsequent synthesis, in 1899, of iminodibenzyl, by J. Thiele and O. Holzinger [58]. However, at the time, no use was found for this agent as a dye for the textile industry, so that it ended up gathering dust, so to speak, in a Basle warehouse, though remaining on the files of Swiss chemical company J.R. Geigy AG, which had used it at the end of the 19<sup>th</sup> century in the preparation of the Sky Blue dye [26].

Half a century later, the director of Geigy's Pharmacology Section, Robert Domenjoz (Fig. (5)), later to become director of the Pharmacology Institute at the University of Bonn, was impressed by data from the Paris company Rhône-Poulenc, which had developed, in close collaboration with the Institut Pasteur, some antihistamines that promised to be commercially successful as hypnotics or sedatives. Prof. Domenjoz encouraged his team to look into the effects of the phenothiazines, for which no important application had been found at that time, in the hope of their being useful as sedatives. In 1948, chemists Geigy F. Häflinger and W. Schindler used iminodibenzyl as the basis for synthesizing 42 derivatives [26,59]. The pharmacological tests carried out on these compounds revealed that the majority of them had, to a greater or lesser extent, antihistaminic effects, in addition to their sedative, analgesic and antispasmodic properties, and that the differences between them were related to the chemical structure of their lateral chain. Moreover, the basic toxicological and lethal dose 50 (DL<sub>50</sub>) studies carried out in mice revealed no significant adverse effects [60].

After these experiments in laboratory animals, and even some involving self-administration, these chemists contacted hospitals who might be interested in clinical research on these products, at a time when there were practically no bureaucratic restrictions on the implementation of these types

of study. One of these substances –known internally as G-22150– was sent to Roland Kuhn (Fig. (6A)), assistant medical director at the Thurgausische Heil- und Pflegeanstalt in Münsterlingen (close to Lake Constance) and pupil of Jakob Klaesi (who introduced the famous sleep cures), to see whether it could serve as a hypnotic. Kuhn discarded the possibility of using the substance in “pills for sleeping”, due to its irregular and rather unreliable results, but observed “a rather peculiar positive effect” [61]. However, interest in continuing the clinical development of this substance fell away.



**Fig. (5).** Robert Domenjoz (1908-2000). During his time as Director of the Pharmacology Section of the Swiss company J.R. Geigy AG, in the early 1950s, he carried out intensive psychopharmacological research, which would culminate in the clinical introduction of the first tricyclic antidepressant, imipramine.

Subsequently, in 1952, came the news that Pierre Deniker and Jean Delay had made an important discovery while testing a phenothiazine called chlorpromazine at the Saint-Anne university hospital in Paris [56,62], with thirty-eight psychotic patients showing spectacular improvements. These findings spurred an intensification of the search for substances with similar properties by the pharmaceutical companies, concerned that Rhône-Poulenc might corner the new market that was opening up. The result was that some long-forgotten antihistamines filed away by the Geigy company were dusted off, in the hope that they might prove useful to psychiatry [26,61,63,64].

At this time, the prevailing doctrine on the aetiology of depression was that it was the result of psychodynamic processes, despite the fact that the therapeutic effects of electroconvulsive therapy were obvious. Consequently, the thesis that drugs could have some effects on the symptoms of mood states but would not modify the course of the illness itself enjoyed the support of a majority of specialists. Even Roland Kuhn himself was scientifically committed in this philosophical field of psychoanalysis, despite being considered as

one of the pioneers of the new generation of “biologicist psychiatrists” by virtue of his extensive knowledge of organic chemistry and biochemistry [63], especially after February 1954, when he contacted Geigy (or *vice versa*, according to some authors) to study the possible antipsychotic effects of G-22150, which he had tested years before. Kuhn had to interrupt some treatments with this substance due to problems of tolerance [59,61], but asked Geigy to send him another phenothiazine, in the hope of finding another potent antipsychotic agent for his patients and avoiding a shortage of drugs at the Münsterlingen clinic. In early 1956, Kuhn received a compound called G-22355, a substance with the same lateral chain as chlorpromazine, which had been synthesized by Häflinger and Schindler, in 1948, from promethazine, replacing the sulphate bridge of phenothiazine with an ethylene bridge [13,64]. This substance had been registered in 1951 with US licence number 2554736 [65].

### Development and Clinical Introduction of Imipramine as an Antidepressant

The extensive clinical research that took place in 1956 at the Kantonsspital Münsterlingen (Fig. (6B)), near Basle, soon made it clear that agent G-22355 lacked any appreciable neuroleptic effect. Indeed, in some patients who had previously been treated with chlorpromazine their schizophrenic condition worsened, giving way to a state of agitation that gave cause for clinical concern. As a result, the clinic’s image was tarnished and relations between its directors and the pharmaceutical company became strained [60]. However, Kuhn observed that three patients diagnosed with depressive psychosis showed a marked improvement in their general state within just a few weeks. Consequently, in a letter to Geigy dated 4 February 1956 [3], Kuhn raised for the first time the possibility that this substance might have an antidepressant therapeutic effect. Subsequently, another 37 depressive patients were given this drug, thus demonstrating its special efficacy in the treatment of depressive disorders [61,66,67]. The antidepressant effect of imipramine was, therefore, totally unexpected, and its discovery completely accidental.

Kuhn’s impressions of the initial results, in a total of 40 depressive patients, were presented on 6 September 1957, at the II World Congress of Psychiatry in Zurich, to an audience of scarcely more than a dozen [66]: “The patients appear, in general, more animated; their voices, previously weak and depressed, now sound louder; they are more communicative, the lamentations and sobbing have disappeared. The depression, which had manifested itself through sadness, irritation and a sensation of dissatisfaction, now gave way to friendly, joyous and accessible feelings”. These results were published for the first time on 31 August 1957, in German, in the journal *Schweizerische Medizinische Wochenschrift* (“Über die Behandlung depressiver Zustände mit einem Imindibenzyl derivat (G 22355)”) [66]. Moreover, during the Zurich Congress, Paul Schmidlin introduced the term “timoleptic” to describe the new substances whose action was similar to that of Geigy’s compound [13].

Kuhn’s reports of the efficacy of this compound, now formally called imipramine, were received, as the author would later confess [68], with some scepticism by the medi-



**Fig. (6).** Roland Kuhn (1912-2005) (A), Medical Director at the Psychiatric Clinic of Thurgau Canton (B), in Münsterlingen, near Basle (Switzerland). Kuhn was one of the great pioneers of psychopharmacological research, and the discoverer of the antidepressant properties of imipramine.

cal community, since the view emerging from the numerous conferences on pharmaceutical and pharmacological disciplines held between 1953 and 1958 was based on the assumption that there could never exist a truly effective antidepressant substance, which went beyond reducing the symptoms of depression. The most widespread hypothesis at this time, as referred to above, was that depression as such emerged from intrapsychic conditions and conflicts [69], leading to the conviction that chemical tools merely masked the true symptoms of depressive conditions. Despite this clear opinion among experts, the antidepressant effects of imipramine were confirmed by such prestigious specialists as Paul Kielholz and Raymond Bategay, and imipramine was put onto the Swiss market by Geigy at the end of 1957, under the trade name Tofranil®. The drug came onto the market in the rest of Europe in the spring of 1958 [26,65], and represented a giant step in the treatment of depression, as the first example of a new family of drugs, known as imipraminic or tricyclic antidepressants (TCAs). As Kuhn [68] put it: “We have achieved a specific treatment of depressive states, not the ideal already going far in this direction. I emphasize ‘specific’, because the drug largely or completely restores what the illness has impaired –namely, the mental functions and capacity and what is of prime importance, the power to experience.”

In September 1958, at the I Congress of the recently founded Collegium Internationale Neuro-Psychopharmacologicum (CINP), held in Rome, an audience made up primarily of psychiatrists began to become aware of the positive effects of the new drug, though more than through the work of Kuhn, through that of other research teams. In fact, the year 1958 saw the publication of two new studies on imipramine in the *American Journal of Psychiatry*. One of these reproduced the lecture given by Roland Kuhn at Galesburg State Hospital in May of that year, and was published in the November issue. Although the article added nothing new

with respect what had appeared previously in the *Schweizerische Medizinische Wochenschrift*, it did have greater international repercussions. In it, Kuhn described at length the pharmacological effects of imipramine, reported its efficacy data and adverse effects, and offered recommendations for its clinical use and dosage and the duration of treatment. He recounted how “the patients got up in the morning voluntarily, they spoke in louder voices, with greater fluency, and their facial expression became more lively. They began to do some individual activities, they once more sought to make contact with other people, they began to train on their own, to participate in games, to become happier and to recover their ability to laugh” [67]. His observations were confirmed later through studies with larger samples [68]. The following year, 1959, saw the publication of more than 60 studies assessing the therapeutic effects and adverse reactions of imipramine in different groups of patients. The countries in which there was most expectation in relation to the new drug were Italy, France and Canada, though positive results were also reported in Russia, Poland, Sweden and South Africa.

The introduction of imipramine in North America was due largely to the work of one of the great pioneers of psychopharmacology and the man who had previously introduced chlorpromazine there [62,70], Heinz E. Lehmann, a psychiatrist from Berlin who had fled Nazi Germany and was working at the Verdun Protestant Hospital in Montreal (now the Douglas Hospital). At the II World Congress of Psychiatry in Zurich, Lehmann heard Kuhn’s lecture and immediately began treating groups of Canadian patients [26]. Lehmann designed and implemented a study on the efficacy of imipramine in a sample of 48 depressive patients, thus permitting the drug to be marketed in the United States [71]. The fact that Lehmann, an expert of great international prestige, put his faith in imipramine was of enormous importance for its acceptance worldwide.



The first imipramine-placebo controlled clinical trial was performed in 1959 by Ball and Kiloh [72], demonstrating the efficacy of this substance, especially in so-called endogenous depressions and in psychotic depressions. In March of that same year, at the *McGill Conference on Depression and Allied States*, an international event held in Montreal, all the data on imipramine accumulated up to that time from North American and European studies were presented. However, it would be another six years before Gerald L. Klerman and Jonathan O. Cole demonstrated that imipramine was significantly superior to placebo in the treatment of depression, thanks to an analysis with data from 23 published studies and a total of 1000 patients treated with imipramine (550 patients) or with placebo (459 patients). The results of this analysis confirmed the rate of improvement at 65% in the imipramine group, as against 31% in the placebo group [73]. Indeed, imipramine has maintained its status as one of the most effective antidepressants up to the present day.

### The Development of New Tricyclic Antidepressants

Despite the great success of imipramine, it was not until 1961 that a second TCA came onto the market. Three years earlier, the research team at the Merck and Co. Pharmaceutical had developed amitriptyline, initially intended as an antipsychotic, after modifications to the central ring of the thioxanthene family, constituting the first compound in the dibenzocycloheptadien group [74]. Merck appointed Frank J. Ayd Jr. to lead the clinical research on this new compound. Ayd, one of the most prolific biologicist psychiatrists of his time [75], had gained prestige years earlier as one of the pioneers in the US of the study of chlorpromazine (1952) and would later (1962-1965) be a regular guest on the *Religion and Science* series broadcast by Radio Vaticano. At the Baltimore Square Hospital, Ayd treated 130 patients with amitriptyline, finding the antidepressant effect to be similar to that of imipramine. On 7 April 1961, amitriptyline was approved as an antidepressant by the Food and Drugs Admini-

stration (FDA), under the trade name Elavil®. This substance would maintain some of the tranquillizing effects of the thioxanthenes, so that it supplanted imipramine in the treatment of patients with agitated or anxious depression. Simultaneously, European pharmaceutical firms Hoffmann-La Roche and, a little later, H. Lundbeck and Co. had succeeded in synthesizing amitriptyline, through the corresponding modification of the chemical structure of imipramine, though given the priority of its request, Roche received the European marketing rights under the name Saroten® [76].

During the 1960s a whole series of TCAs were developed (Fig. (7)) [64]. In 1963, nortriptyline was approved in the UK, as Allegron®, whilst in the USA it was approved by the FDA in November 1964, the year that also saw the approval of desipramine (J.R. Geigy), previously identified as the principal urinary metabolite of imipramine; trimipramine arrived in the UK and other European countries in 1966, under the trade name Surmontil®. Other TCAs soon followed: protriptyline (known as Concordin® in Europe and Vivactil® in the USA) in 1966, iprindol (Prondol®) in 1967, dothiepin (Prothiaden®) –not approved in the USA– and doxepine [77] –marketed in Europe by Boehringer subsidiary Galenus (Aponal®) and in the USA by Pfizer (Sinequan®) [78]– in 1969, and finally, clomipramine (Anafranil®), which was marketed in Europe from 1975 but was not approved in the USA. Moreover, the 1960s saw the dibenzazepine structure of imipramine undergo many modifications in order to obtain new antidepressants. Among the results of these were the so-called heterocyclic, tetracyclic or “second-generation” antidepressants [74], such as maprotiline, first sold by Ciba-Geigy in Europe and Japan in 1972 [26], or mianserine (Tolvin®).

### The Pharmacological Contributions of Imipramine

The efficacy of TCAs in the treatment of depression was indisputable by the end of the 1950s [79]. However, their

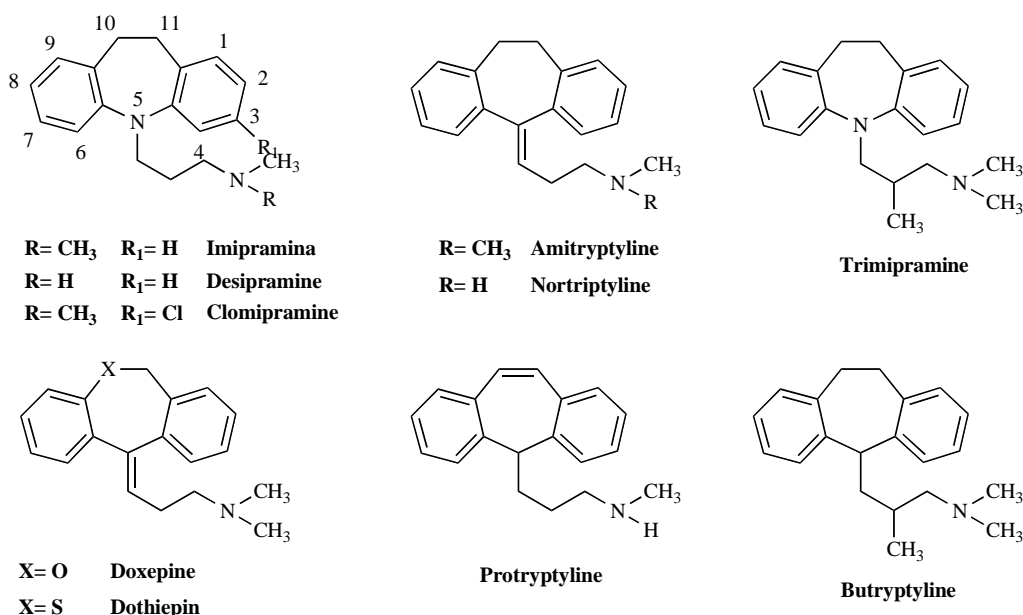


Fig. (7). Chemical structure of tricyclic antidepressants (6-7-6), with a “classic” lateral chain.

action mechanism was not well understood. The year 1952 saw the introduction in German-speaking countries of reserpine for the treatment of schizophrenia, but it soon became clear that this substance had pro-depressive properties. In 1959, Robert Domenjoz, director of the Pharmacology Section at J.R. Geigy AG, and W. Theobald confirmed that imipramine produced an antagonism of the effects of reserpine [80]. Two years later, Bernard Brodie's team at the NIH demonstrated the physiopathological role of biogenic amines in depression, on finding, in studies with laboratory animals, that imipramine inhibited the absorption of noradrenaline. Another NIH team, led by Julius Axelrod—who maintained a great rivalry with Brodie, despite having been his pupil—demonstrated a reduction in the uptake of noradrenaline in the synaptic nerve endings during treatment with TCAs [81]. But the fruits of this between Brodie and Axelrod finally served at least as the basis for the subsequent work of William Bunney Jr. and Joseph Schildkraut, who in 1965 proposed the catecholamine-deficit hypothesis of the aetiology of depression [82].

#### 4. BETWEEN THE DECLINE OF MAOIs AND THE RISE OF TCAs

Towards the end of the 1950s, the prevailing idea that depressive syndromes should not be treated solely and optionally with antidepressants began to change, with the pharmacological treatment option gaining more and more ground. First of all, and contrary to the postulates of Freudian doctrines, the new basic opinion of most psychiatrists was that depressive syndromes had not only psychodynamic but also biological causes, which could benefit from treatment with drugs [26,63]. Secondly, numerous clinical studies had demonstrated the superior efficacy and good tolerability of tricyclic agents. And finally, the pharmaceutical industry had discovered the enormous economic potential implied by the high prevalence of depression worldwide. The clinical introduction of diverse pharmacological agents with different action mechanisms (TCAs and MAOIs) intensified, in synergic fashion, competition and marketing strategies. As a consequence of such developments, depression ceased to be solely in the hands of "specialists", that is, hospital psychiatrists. However, in spite of the enormous commercial opportunities opening up for antidepressant drugs, the two great families of pharmacotherapeutic agents evolved in markedly different ways: while TCAs achieved a success unprecedented in the history of psychiatry, MAOIs began a rapid decline, leading to their virtual disappearance from the therapeutic arsenal [13].

The rise of TCAs was due in large part to Merck and Co., since 1919 a legally independent US firm with the same name as its German mother company, which, after the II World War, continued its activities in the field of psychiatry. Merck's introduction of amitriptyline, the second tricyclic agent, increased the confidence of general practitioners and specialists in these drugs. It was in this context that, in 1961, Frank Ayd—an arch example of the biologicist psychiatrist who advocated "treating not only the spirit but also the body" [75]—produced a book explaining depression and its treatment that made them easier to understand. For its part, Merck and Co., as a "typical" US company, had realized that what was most important was not selling drugs, but rather,

selling an idea. In this case, the central message was the ability to treat with antidepressants not only the rare disorder known as "vital depression", but all types of depressed mood [26]. Thanks to the commercial power of these two chemical multinationals and a marketing agreement between them (as Elavil® by Merck and as Tryptizol® by Roche) throughout the world, except in the USA, covered exclusively by Merck, amitriptyline soon became the most widely prescribed antidepressant of its time.

As this process of acceptance became consolidated, many highly prestigious scientists became involved in it, and antidepressant therapy with TCAs continued to grow. But the story for MAOIs was totally different. Towards the end of the 1950s, MAOIs constituted possibly the family of therapeutic agents most widely used in the treatment of depression [83]. However, the situation changed suddenly, and the decline in the use of these drugs was as rapid as was their clinical introduction. Indeed, the commercial life of iproniazid was really quite short, since it was withdrawn from the US market in 1961 after accusations of its having induced a series of cases of jaundice and nephrotoxicity. The imputability of these adverse effects was fiercely challenged, since no specific immunological studies were carried out to determine whether the small number of jaundice cases observed were induced by the drug or were simply cases of viral hepatitis [39]. These hepatotoxic adverse effects of iproniazid were also described for the rest of the MAOI drugs from the hydrazine group, such as nylamide, isocarboxazid and phenelzine. As regards the last of these, more than 50% of deaths during treatment were attributed to hepatic cell damage, and this led to the withdrawal from the market of the majority of MAOIs at an international level [13,23].

As occurred with iproniazid, tranylcypromine was withdrawn from the US market, though for different safety reasons, in 1964, after reports of an increase in the number of hypertensive crises related to the drug. These hypertensive crises, associated with intense headaches and in some cases with subarachnoid intracranial haemorrhages, were described from the very moment the drug was approved, in 1961, and according to Barry Blackwell, at Maudsley Hospital in London, it was traced to the ingestion of certain cheeses, so that these crises became referred to as the "cheese effect" [84]. A.M. Asatoor and colleagues [85], at the Westminster Medical School in London, showed that after the ingestion of cheese there was a considerable increase in the excretion of metabolites of tyramine. Later, it was confirmed that many other foods (products made with yeast, chicken liver, snails, pickled herrings, red wines, some types of beer, tinned figs, broad beans, chocolate, products including cream, and so on) contained amines with indirect action (chiefly tyramine), which could also provoke hypertensive episodes in patients treated with MAOIs.

Despite the dramatic nature of these reactions, their incidence was actually extremely low, and did not justify withdrawal of the product. However, these problems attributed to MAOIs, together with the results of some clinical trials, as the sponsored by the British Medical Research Council [86] (strongly questioned later on), that confirmed their lower efficacy for major depression *versus* TCAs, considerably limited their therapeutic use, especially in European coun-

tries [87], and favored a generalized loss of prestige. In fact, today, MAOIs are always considered a second-choice drug, potentially of great help in cases of intolerance or lack of response to other antidepressants (refractory depression) [45,88].

## 5. THE GREAT CONTRIBUTION OF IPRONIAZID AND IMPRAMINE TO THE HISTORY OF PSYCHIATRY: POSTULATE OF THE FIRST AETIOPATHOGENIC HYPOTHESES ON DEPRESSION

The clinical introduction of iproniazid and imipramine contributed, as we have seen, to revolutionizing therapy in the field of psychiatry. However, despite the importance of this contribution, it is not the only one of historical relevance for the progress of biological psychiatry. From the strictly scientific point of view, TCAs and MAOIs played a decisive role in the development of the first aetiopathogenic theories of affective disorders in the 1960s [82,89]. Thus, it could finally be demonstrated that psychotropic agents had the capacity to modify altered mental states, and that psychiatric disorders should no longer be filed under "Philosophy: alterations of the soul". Moreover, with specific regard to the area of psychopharmacology, the development of these drugs made it possible to introduce new methods for assessing the antidepressant activity of different substances [90]. This permitted, in turn, enlargement of the arsenal of antidepressant therapy over the following decades, always in search—in line with the postulates set down half a century before by Paul Ehrlich—of a kind of "magic bullet" that would eradicate the illness without harming the patient.

The clinical incorporation of the new psychoactive drugs in the 1950s gave rise to a Copernican shift in the way the origin of mental illness was understood. Although they had only a very slight effect on people with normal mood state, in depressed patients these drugs brought about a marked reduction of symptoms, especially after a period of two or three weeks. Thus, support began to grow among the scientific community for the notion that these drugs might be correcting a kind of specific "chemical imbalance", the underlying cause of the illness. Furthermore, this concept would be highly convenient and liberating for society in general, and for the mentally ill and their families in particular, since it would relieve patients of a heavy moral burden and allow the symptoms of the illness to be removed through administration of a series of chemical substances [91]. This concept of "chemical imbalance", then, revolutionized the view held by the most traditional sectors of society about mental illness, entrenched in pseudo-medieval conceptions such as states of possession, and even by psychiatrist themselves, some of whom continued to see psychiatric patients as deranged individuals with moral defects, needful of moral therapy.

Thus, one of the main consequences of the discovery of the new psychoactive drugs in the 1950s, together with the simultaneous advances in knowledge of the neurochemical aspects of brain functioning—as in the case of neurotransmitters—, was the possibility of postulating the first biological hypotheses on the genesis of mental illnesses, and laying the bases of so-called "biological psychiatry" [92]. In this way, psychoactive drugs have helped to define the neurochemical process underlying mental illness and generate a physiopa-

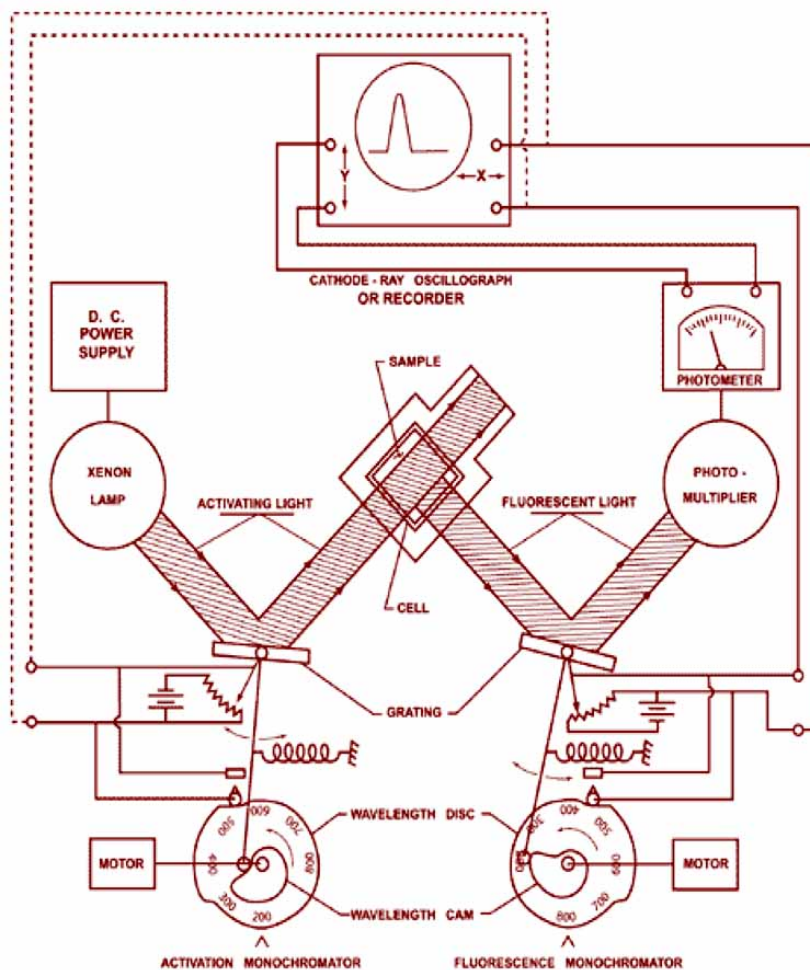
thological theory of it, in an eminently "pharmacocentric" approach, as some authors put it [93].

### The Role of Iproniazid and MAOIs

The action mechanism of iproniazid as a MAO inhibitor was described, as already mentioned, by E. Albert Zeller's group in 1952. Initially, this action mechanism was interpreted as being closer to that of the psychostimulants than that of the other antidepressants. However, it was observed that acute administration of MAOIs to experimental animals or to healthy individuals provoked practically no modification of their behaviour, except in the case of tranylcypromine, which has stimulative effects similar to those of amphetamines. On the other hand, as occurred with TCAs, the MAOIs antagonized, at an experimental level, the effects of reserpine and the tetrabenazine, and boosted the effects of amphetamine, of hexobarbital, of 5-hydroxytryptophan and of DOPA [82].

Coinciding with the clinical introduction of iproniazid, the mid-1950s saw the introduction, in the context of neuropharmacological research, of an analytical technique that greatly contributed to speeding up our understanding of how psychoactive drugs work, and in turn of the pathophysiology of mental disorders: spectrophotofluorimetry (Fig. (8)) [3]. Thanks to this technique, it was possible to begin detecting changes in the levels of monoamines in the brain and of their metabolites through direct research. Furthermore, the observations carried out with reserpine between 1955 and 1957 (depletion of serotonin in the nervous system, or modifications in levels of noradrenaline in different tissues) in countries such as the United States, Britain, Switzerland, Spain or Sweden, permitted considerable progress in knowledge of the physiology of the autonomic and central nervous systems [94]. Bernard Brodie's group at the NIH, using spectrophotofluorimetry, as developed in the same laboratory by Robert Bowman and Sidney Udenfriend [95], discovered that the administration of reserpine to rabbits brought about a depletion of brain levels of serotonin, and more importantly, that the sedative and other effects of this substance remitted as the serotonin returned to its normal levels [96]. Two years later, this same team correlated the appearance of depressive symptoms with the depletion of serotonin deposits after administration of reserpine [21]. Moreover, when the animals were given a MAOI (iproniazid) after the administration of reserpine, there was no modification of the sedative effect induced by this agent [97], whereas if administration of iproniazid preceded that of reserpine, there was neither depletion of serotonin nor the effects of the reserpine, though the animals displayed hyperactivity and signs of increased sympathetic nerve activity [98]. In the words of Pletscher [99], "these experiments with the iproniazid-reserpine combination also supported the hypothesis that the action of the psychotropic drugs is mediated by biogenic amines, and that biogenic amines play a role in the functioning of the brain".

Thus, it could be confirmed that the administration of reserpine reduced the levels of serotonin [100] and noradrenaline [101] in the brain, while the administration of iproniazid increased them. This, combined with the clinical observations that iproniazid induced euphoric conditions in



**Fig. (8).** Schematic drawing of the Aminco-Bowman spectrophotofluorometer.

some tuberculosis patients [36], and reserpine induced depression in some hypertensive patients [102], allowed the postulation of the initial hypothesis that inhibition of MAO and the resulting increase in serotonin and noradrenaline in the brain was responsible for the stimulant effect on mood (antidepressant effect) of iproniazid [103]; these factors also lent support to the theory that alterations of mood were mediated by modifications of the levels of serotonin, noradrenaline, or both [20]. This theoretical approach, eminently pharmacocentric, opened the door for the first time to an understanding of the neurobiological bases of depressive disorders. But it would be during the 1960s that monoaminergic theories of depression flourished – theories that postulated a functional deficiency of noradrenergic or serotonergic neurotransmission in certain brain areas as the essential cause of these pathologies [89].

### The Role of Imipramine and TCAs

In the 1960s, the precise mechanism through which imipramine and other TCAs worked as antidepressants remained unclear. While the initial studies carried out with

imipramine showed that the drug had multiple pharmacological actions, it could not be determined which of them was responsible for the positive effect on mood alterations. Among these actions, it was observed how imipramine antagonized and reversed the sedation, hypothermia, ptosis and diarrhoea induced by reserpine in rats, but how, in turn, the pharmacological actions of reserpine were not confined to the depletion of noradrenaline and serotonin, but rather included parasympathomimetic effects, the effect of imipramine on the disorders induced by reserpine did not provide the key to unlocking the mysteries of the way this antidepressant drug functioned [3,82].

However, such studies did help to produce a series of pharmacological models of the antagonism of reserpine, which in turn helped in the quest for new antidepressant agents with imipraminic effects [45]. One of those developed was desipramine, the demethylated metabolite of imipramine itself. This imipramine metabolite did indeed make a greater contribution to forming the hypothesis that the effect of imipraminic antidepressants was mediated by their action at the level of noradrenergic neurotransmission, thanks to the dis-

covery that the reversal of the effects of reserpine by desipramine did not occur in those animals in which a selective depletion of catecholamines had been induced through administration of  $\alpha$ -methylparatyrosine (AMPT), a selective antagonist of tyrosine-hydroxylase [94]. But this model also increased confusion about the action mechanism of antidepressants and the pathogenic mechanism of the illness, since the notion that depression was the result of a chemical imbalance, in which noradrenaline deficiency played a certain role, was called into question after it was demonstrated that administration of AMPT did not produce relapses in patients treated successfully with imipramine, or that it is tryptophan, precursor to serotonin, and not phenylalanine, precursor of noradrenaline, that triggers the antidepressant effect of MAOIs [104].

In Spain, the group led by Francisco G. Valdecasas at the University of Barcelona also studied this topic. A series of experiments with guanethidine, bretylium, amphetamine and tyramine suggested an inhibiting effect of noradrenaline uptake by demethylimipramine [105], which has been one of the basic mechanisms employed over the last 50 years for the study of new antidepressants. Subsequently, it was demonstrated that demethylimipramine was capable of antagonizing the response to tyramine, at the vascular level and in the deferent behaviour of the rat, indicating that TCAs also inhibited the reuptake of this indirect sympathicomimetic amine [106].

### Monoaminergic Theories of Depression

Thanks to the discovery and subsequent therapeutic use of TCAs and MAOs, the 1960s saw the flourishing of monoaminergic theories of depression [107], which postulated a functional deficiency of noradrenergic or serotonergic neurotransmission in certain brain areas as a primary cause of these pathologies [89], as we shall discuss presently. These findings equipped psychiatry, for the first time in its history, with a series of biological bases similar to those available in other areas of internal medicine.

#### Catecholaminergic Hypothesis

The “catecholaminergic hypothesis” was the first to be postulated, based on the observations mentioned above about the effects of the antidepressants recently discovered: the inhibitory action of iproniazid on MAO [18], the blocking of synaptic reuptake of noradrenaline by imipramine [108], and the fact that reserpine, an alkaloid that produces an emptying of noradrenaline in nerve endings, caused depressive symptoms in a high percentage of patients on being used as an antihypertensive [109]. This hypothesis on the biological mechanism of depression, presented by Joseph J. Schildkraut (Fig. (9)) of the Massachusetts Mental Health Center (Boston) in a classic work published in 1965, suggested that this pathology was due to a fall in noradrenaline level in the intersynaptic cleft: “some depressions, if not all, are associated with an absolute or relative deficit of catecholamines, particularly noradrenaline, in important adrenergic receptors in the brain. Contrariwise, elation may be associated with an excess of such amines” [110]. To date, Schildkraut’s article is still the most cited in the entire history of the *American Journal of Psychiatry*. In support of this theory, Schildkraut *et al.* [111] also highlighted the fact that lithium salts, effec-

tive in the treatment of the manic phases of bipolar disorders, reduced cerebral levels of noradrenaline, an effect opposite to that observed with TCAs.

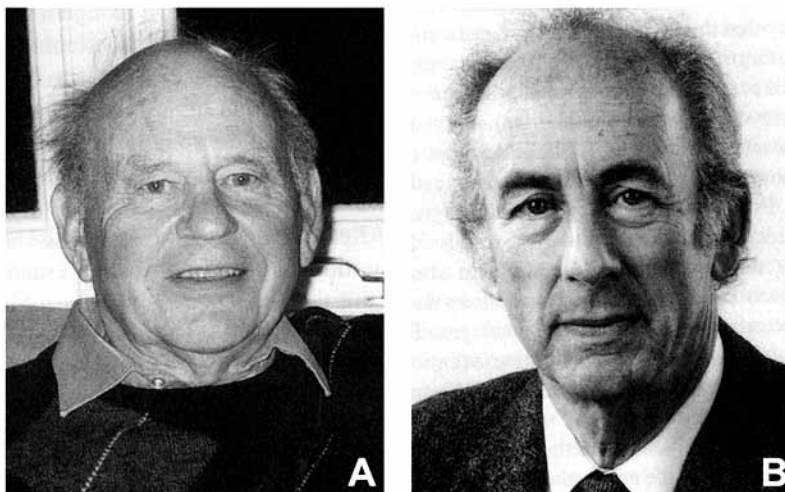
This so-called “noradrenergic hypothesis of depression” set off an avalanche of studies on the role of the noradrenergic system in the genesis of affective and other psychiatric disorders.



**Fig. (9).** Joseph Jacob Schildkraut (1934-), Professor of Psychiatry at the University of Harvard and Director of the Neuropsychopharmacology Laboratory at the Massachusetts Mental Health Centre (Boston). In his article entitled *The Catecholamine Hypothesis of Affective Disorders*, published in 1965, he postulated the noradrenergic hypothesis of depression.

#### Serotonergic Hypothesis

At the same time, there began to develop a “serotonergic hypothesis” of depression. Since 1952, thanks to the work of Betty Twarog, a researcher in Professor John Welsh’s laboratory at Harvard, it had been known that serotonin was a brain neurotransmitter [112]. For their part, the efforts of Brodie’s group, mentioned above, in relation to reserpine and the tissular depletion of serotonin, including in the brain [20], were complemented by those of other groups, such as that led by Alec J. Coppen (Fig. (10A)) of the Neuropsychiatric Research Institute, which belonged to the Medical Research Council of London. Coppen’s group demonstrated that the administration of tryptophan, a precursor of serotonin, to depressed animals boosted the therapeutic effects of MAOIs [104]. Another important group was that of Dutch psychiatrist Herman M. van Praag (Fig. (10B)), of the Department of Biological Psychiatry at Groningen University. Van Praag, working initially with the biochemist Bart Leijne, concluded that there were reasons to acknowledge a relationship between MAO inhibition and antidepressant action, and between serotonergic dysfunctions and the appearance of certain types of depression [113].



**Fig. (10).** The serotonergic hypothesis of depression is based largely on the pioneering work of Alec James Coppen (1923-) (A), at the Neuropsychiatric Research Unit of the UK Medical Research Council (MRC), and Herman M. van Praag (1929-) (B), at the Department of Biological Psychiatry of the University of Groningen (The Netherlands).

However, this serotonergic hypothesis was postulated without a clear demonstration of neurobiochemical correlates at a central level [89], but rather on the basis of studies of variables related to peripheral serotonergic dysfunction, basically at platelet level [107]. The definitive extrapolation of these hypotheses to CNS functioning did not take place until the introduction of more modern techniques. Thus, in 1968, Arvid Carlsson and colleagues at the University of Gothenburg (Sweden) described for the first time how TCAs blocked the reuptake of serotonin at a brain level [114], permitting Izyaslav P. Lapin and Gregory F. Oxenkrug to postulate, in 1970, the serotonergic theory of depression, as opposed to the catecholaminergic hypothesis, based on a deficit of serotonin at an inter-synaptic level in certain brain regions [115]. Finally, it would be confirmed that TCAs (and electroconvulsive therapy) improved the efficiency of serotonergic transmission, above all that which was mediated by 5-HT<sub>1A</sub> receptors, either through sensitization of post-synaptic receptors or through desensitization of pre-synaptic receptors, which usually reduce the release of serotonin in the synaptic cleft or inhibit the frequency of discharge of serotonergic neurones [116]. With all of these experimental observations it could also be concluded that a fall in synaptic levels of serotonin, in certain brain areas, was one of the biochemical causes of depressive disorders.

## 6. FLUOXETINE AND SELECTIVE SEROTONIN REUPTAKE INHIBITORS

As already mentioned, the incorporation of TCAs and MAOIs into the antidepressant arsenal was the fruit of coincidence and of the observational skills of some researchers, both basic and clinical. However, the scientific value of these drugs, in the framework of the pharmacology of mental disorders, is of crucial importance, since they provide highly relevant data on the action mechanisms of pharmacological agents at the synaptic transmission level and, by extension, throw light on the aetiology of the antidepressant effect,

opening the way for the development of new, much more specific drugs.

In contrast to the case of the way these substances were introduced into the clinical context, the selective serotonin reuptake inhibitors (SSRIs) constitute the first family of psychoactive drugs developed in line with a procedure of rational and directed design [117], that is, following a strategy planned in advance, which involved seeking a drug capable of acting on a specific *locus* of action (the serotonin reuptake pump, in this case), avoiding, moreover, other non-essential *loci* (e.g., different neuroreceptors) and the associated potential undesirable effects.

Fluoxetine was the first SSRI to be synthesized and developed, by the US firm Eli Lilly (Indianapolis, Indiana), and is considered the prototypical molecule of this family of antidepressants, becoming, indeed, the world's most widely prescribed antidepressant. The first publication on fluoxetine dates from 1974. The 15 August issue of the prestigious journal *Life Sciences* included the article by Wong *et al.* entitled "A selective inhibitor of serotonin uptake: Lilly 110140, 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine", which described the actions of the new molecule on amine reuptake systems and postulated its potential utility for the study of the serotonergic function and of certain mental disorders [118]. Twelve years later, the drug came onto the pharmaceutical market in Belgium, and in 1987 (12 December) it was approved for sale as an antidepressant by the FDA. Fluoxetine is, moreover, the most written-about drug – together with chlorpromazine – in the history of pharmacology, being the subject of well over 25,000 scientific publications.

### A Triumph for the Policy of the Rational Design of Psychoactive Drugs: The Discovery of Fluoxetine

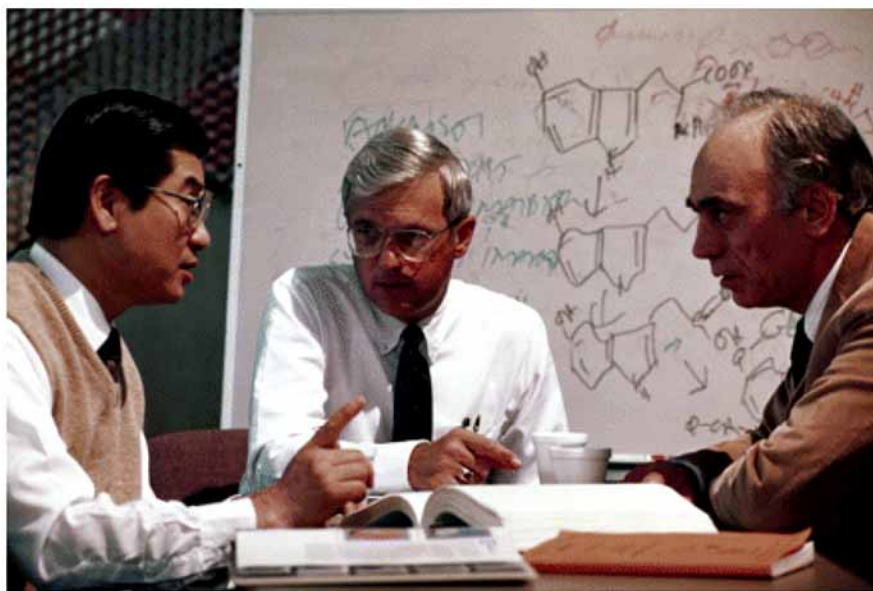
The story of the synthesis and development of fluoxetine [119] begins with the studies carried out in the 1960s on the

action mechanisms of TCAs. At the end of that decade, the serotonergic hypothesis of depression began gaining momentum among researchers after studies demonstrated the powerful inhibition of cerebral reuptake of serotonin exercised by imipramine and other, tertiary derivatives [120] –an inhibition that was much more powerful in the case of clomipramine (a molecule with a chloride group added to the triple ring of imipramine). Clinical evidence also supported this serotonergic hypothesis, such as a decrease in levels of serotonin and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in the rhombencephalon of depressive patients who had committed suicide [121] and reduced concentration of 5-HIAA in the cerebrospinal fluid of depressive patients [122]. Moreover, treatments with precursors of serotonin, such as tryptophan or 5-hydroxytryptophan, showed antidepressant effects [89], while the incorporation of new technologies, such as preparations of rat brain synaptosomes, enabled Lilly Research Laboratories, among other things, to determine the high-affinity kinetics in the uptake of serotonin [123].

The development of fluoxetine, from a historical perspective, can be dated from 1971, when a prestigious pharmacologist with experience in serotonin research, Ray W. Fuller (Fig. (11)) joined Lilly. Fuller soon began trying to make the directors of the company aware of the importance of these new neurotransmitters in the genesis of affective disorders, though there was some initial reluctance from Lilly to embark upon research in this direction. That same year, Solomon H. Snyder from Johns Hopkins University –one of the founding fathers of modern biological psychiatry–, was honoured by Lilly Research Laboratories and invited to give a lecture. The theme he chose was neurotransmission, and his lecture highlighted the great utility for biological research of so-called brain “synaptosomes”, procedure that he himself

developed, which would subsequently be applied in the development of fluoxetine [119]. The insistence of Fuller, supported by the biochemist David T. Wong (Fig. (11)) resulted in the formation of a “serotonin-depression study team”, made up of Fuller, Wong, the organic chemist Bryan B. Molloy (Fig. (11)) and Robert Rathbun, and which would be the driving force behind the development of the new antidepressant [1,124].

This group, led by Wong, devoted its research efforts in the early 1970s to obtaining molecules capable of selectively inhibiting the reuptake of serotonin, as potential antidepressant agents, and which would lack the cardiotoxicity and anticholinergic properties of TCAs. The work of Molloy and Rathbun was pioneering in this regard. Having observed that diphenhydramine and other antihistamines were capable of inhibiting the reuptake of monoamines [125] and of blocking, to the same extent as imipramine and amitriptyline, the ptosis induced by tetrabenazine in mice [126] –a standard test of antidepressant activity–, Molloy synthesized a series of phenoxyphenylpropylamines as analogues of diphenhydramine. One of these substances, LY-14939 (later known as nisoxetine), was studied by Rathbun and Richard Kattau, who observed that it was as powerful as TCAs in reversing hypothermia induced by apomorphine in mice. Moreover, both nisoxetine and desipramine antagonized the hypothermia induced by reserpine in mice [127], and were powerful inhibitors of noradrenaline reuptake in brain synaptosomes, though nisoxetine scarcely blocked the reuptake of serotonin and dopamine [128]. Wong considered that small chemical modifications of the phenoxyphenylpropylamine compounds could provide selective serotonin reuptake inhibitors, and hence chose 55 derivatives of this series and 2 naphthalenoxide analogues to test the power of reuptake inhibition in the



**Fig. (11).** David T. Wong (1936-) (left), biochemist at Lilly Research Laboratories and leader of the research group that developed and introduced fluoxetine, seen here at his laboratory in Indianapolis (USA). Bryan B. Molloy (1939-2004) (right), research chemist at Lilly Research Laboratories and responsible for the synthesis, among other phenoxyphenylpropylamine derivatives, of fluoxetine, in 1972. In the centre, Ray W. Fuller (1935-1996).

three monoamines *in vitro*. On 8 May 1972 a member of Wong's team, Jon-Sin Horng, tested fluoxetine oxalate (LY-82816), and on 24 July of that same year it was found that fluoxetine chlorhydrate (LY-110140) was the most powerful and selective inhibitor of serotonin uptake in the entire series [118], with a potency for inhibiting the uptake of serotonin 6 times greater than N-methyl-phenoxyphenylpropylamine, the father compound of the series, while its potency was 100 times smaller in the uptake of noradrenaline. Precisely the p-trifluoromethyl radical of the phenoxy ring of fluoxetine chlorhydrate was confirmed as the key element in the great potency and selectiveness of this drug for serotonin reuptake. Moreover, the affinity of fluoxetine for different neuroreceptors was seen to be very low [129], which explained the scarcity of adverse effects associated with it, especially compared to the range of side effects typical of TCAs (constipation, urine retention, blurred vision, orthostatic hypotension, sedation, memory disorders, dizziness, etc.).

### The Clinical Introduction of Fluoxetine

In relation to the clinical development of fluoxetine, it should be mentioned that after the synthesis of the SSRIs and the corresponding experimental safety studies, there began in Indianapolis and Chicago a series of clinical trials which, despite promising results, were never published, perhaps because of the company's commercial policies. Moreover, the first clinical publication on this drug was of a negative nature, since it reported the appearance of a severe dystonic condition in a patient treated with this antidepressant [130].

Nevertheless, in 1980 Lilly decided to commit themselves definitively to the new molecule, entrusting the clinical research task to John Feighner, who carried out his studies at his private psychiatric clinic in La Mesa (California). In 1983, the first positive results began to appear: fluoxetine was as effective an antidepressant as the classical tricyclic drugs, and moreover, showed far fewer adverse effects [124]. Feighner [131] began talking of a "New Generation of Antidepressants". Between 1984 and 1987 clinical trials with fluoxetine multiplied, and finally, in December 1987, the FDA definitively approved its clinical use, under the trade name Prozac®.

Numerous clinical trials subsequently confirmed that the antidepressive efficacy of fluoxetine was similar to that of TCAs in outpatient major depression and superior to that of placebo [132]. The efficacy of fluoxetine was also confirmed in patients with major depression and melancholia [133], dysthymias [134] and different degrees of inpatient depression [135]. All such conditions were included, in the early 1990s, by two researchers at the McLean Hospital, in a category called "Disorders of the Affective Sphere" [136]. Thus, perspectives for the use of fluoxetine were highly promising. Indeed, growth of fluoxetine use has been the most rapid in the history of psychotropic drugs: in 1990, three years after its introduction in the USA, it was already the most widely prescribed drug by North American psychiatrists, and in 1994 it sold more than any other drug worldwide, except Zantac® [63]. Furthermore, as occurred with Miltown®, Prozac® became established within the cultural scene of the nineties, making the front pages of popular newspapers and periodicals, such as the *New York Times* ("With Millions

Taking Prozac, A Legal Drug Culture Arises", 1993), or *Newsweek* ("How A Treatment For Depression Became As Familiar As Kleenex And As Socially Acceptable As Spring Water", 1994), and becoming the main protagonist of a best seller (*Listening to Prozac*, 1993) by Peter D. Kramer [137], Professor of Psychiatry at Brown University.

### The Incorporation of New SSRIs

In the wake of the article by Wong *et al.* [118], a large quantity of selective serotonin reuptake inhibitors, of highly diverse chemical origin, began appearing in the scientific literature. Six of them, including fluoxetine (duloxetine, to-moxetine, nisoxetine, dapoxetine, fluoxetine and norfluoxetine), owed their existence to the research efforts of Wong's group [119]. The first SSRI to be marketed was zimelidine, in 1982, by Astra Pharmaceuticals (Södertälje, Sweden). However, this drug was rapidly withdrawn from the market (just the following year) due to problems of hypersensitivity (fever, myalgias, increased levels of aminotransferases and, above all, various cases of neurological complications) [138]. Subsequently, and within a relatively short period, four more drugs from this family (Fig. (12)) were made available to physicians, each one developed by a different pharmaceutical company; citalopram (Lundbeck), fluvoxamine (Solvay), paroxetine (AS Ferrosan, Novo Nordisk) and sertraline (Pfizer). Fluvoxamine was first marketed in 1983 in Switzerland, citalopram in 1989 in Denmark, sertraline in 1990 in the UK and paroxetine in 1991 in Sweden.

### Pharmacological Contributions of Fluoxetine

*In vivo* neurochemical studies also confirmed the specificity of fluoxetine in the inhibition of serotonin reuptake, thus reinforcing the serotonergic hypothesis of depression. Among the results of research in this context it is also important to highlight the reduction of serotonin reuptake *ex vivo* by rat brain synaptosomes treated with fluoxetine [128] or the blocking of toxicity induced by neurotoxics, such as p-chloroamphetamine (p-CA), at the level of the membrane transporter responsible for the reuptake [139]. Despite the lack of techniques for determining serotonin concentration in the synaptic cleft, various indirect tests permitted confirmation of an increase in extraneuronal concentrations of this neurotransmitter, such as a cytofluorimetric technique called "fading", which reveals that fluoxetine increases the extracellular serotonin concentration in areas of the brain raphe area in rats [140], or *in vivo* voltimetric techniques, confirming a slight and prolonged increase of the signal in the corpus striatum of the rat as a result of fluoxetine, as well as its prevention of a rapid and intense increase in the signal after administration of p-CA, a competitor for the transporter of the reuptake pump of this amine [141]. Finally, through push-pull cannulation in the nucleus accumbens of the rat, a seven-fold increase in serotonin concentration was observed in the first hour after intraperitoneal injection of fluoxetine [142].

However, despite the excellent results obtained at a biochemical level, fluoxetine was not effective in some models of tests carried out on experimental animals and used in pre-clinical screening of potential antidepressants, such as those related to avoidance of hypothermia induced by reserpine or



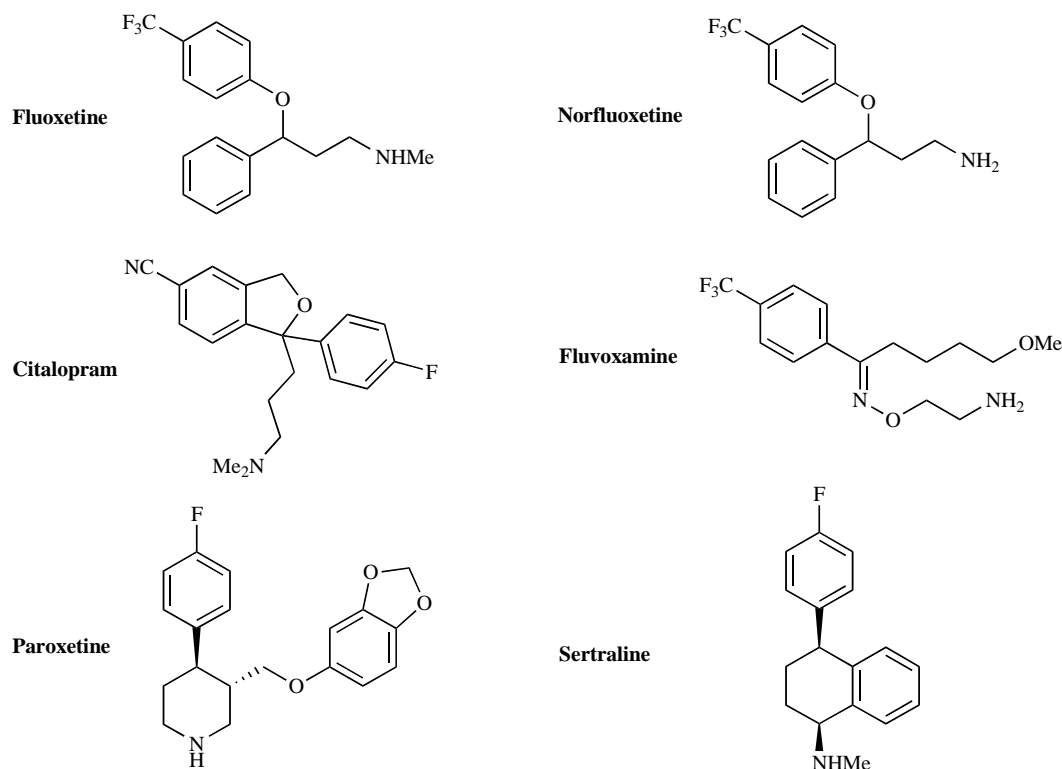


Fig. (12). Chemical structure of selective serotonin reuptake inhibitors (SSRIs).

apomorphine, whose result was negative with fluoxetine [127], or to the incapacity to reduce mobility, in the forced swimming test in rats [143].

In any case, all the data mentioned here indicate that fluoxetine has not only constituted an extremely important therapeutic tool for treating different mental disorders, but indeed, as Fuller and Wong [144] rightly claim, it “has represented a valuable pharmacological instrument for the study of serotonergic transmission mechanisms and the physiological functions of serotonergic brain neurones”.

## 7. NEW LINES OF ANTIDEPRESSANT DRUGS DEVELOPMENT

Currently, a priority goal for psychopharmacology is to discover the precise nature of the circuits responsible for the modifications of neuronal functioning that lead to depression, as well as the adaptation mechanisms triggered by antidepressants, for correcting and normalizing the behavioural, cognitive, affective and neurovegetative alterations observed in these conditions. For this purpose, research should not be limited to the classical aminergic mechanisms (reuptake and metabolism) or the more modern ones (receptor mechanisms), but should rather explore other sources of knowledge constantly being provided by biochemistry, molecular biology and genomics. In line with this approach, and despite the fact that the latest antidepressants introduced into clinical practice maintain the same aminergic action mechanism, the future of antidepressant therapy appears to be trying to turn towards extraneuronal non-aminergic mechanisms or mechanisms that modulate the intraneuronal biochemical pathways.

## The Most Recent Additions to the Antidepressant Therapeutic Arsenal

Despite the considerable clinical advantages of SSRIs, based largely on their better tolerance and safety profile and greater convenience, there are a series of problems encountered in antidepressant therapy that have yet to be resolved. It suffices to mention the delay in the onset of antidepressant response or the percentage, estimated at around 30%, of patients who do not respond to treatment [145]. Such problems, among others, have justified research efforts in the quest for new antidepressants, and which have led, in the last 15 years, to the clinical introduction of new drugs, with different pharmacodynamic properties. Notable among these are venlafaxine, duloxetine, nefazodone, mirtazapine and reboxetine. However, these drugs, despite belonging to four new families of antidepressants [146], continue to share an action mechanism that revolves around the enhancement of aminergic functioning: inhibitors of noradrenaline and serotonin reuptake (venlafaxine, duloxetine, milnacipram), antagonists of serotonergic 5-HT<sub>2</sub> receptors (nefazodone), specific noradrenergic and serotonergic antidepressants –NaSSA (mirtazapine)– and selective inhibitors of noradrenaline reuptake (reboxetine, atomoxetine) (see Table 1).

The incorporation into the antidepressant arsenal of these new families of drugs has brought progress in some cases, and in others disappointment, with regard to the treatment of depression. As positive events we can consider the introduction of venlafaxine, mirtazapine and reboxetine. On the other hand, nefazodone –actually withdrawn from the market due to safety issues– and the selective and reversible inhibitors of MAO (RIMA) have not had the desired results [147].

**New Integrated Approaches in Aetiopathogenic Theories of Depression**

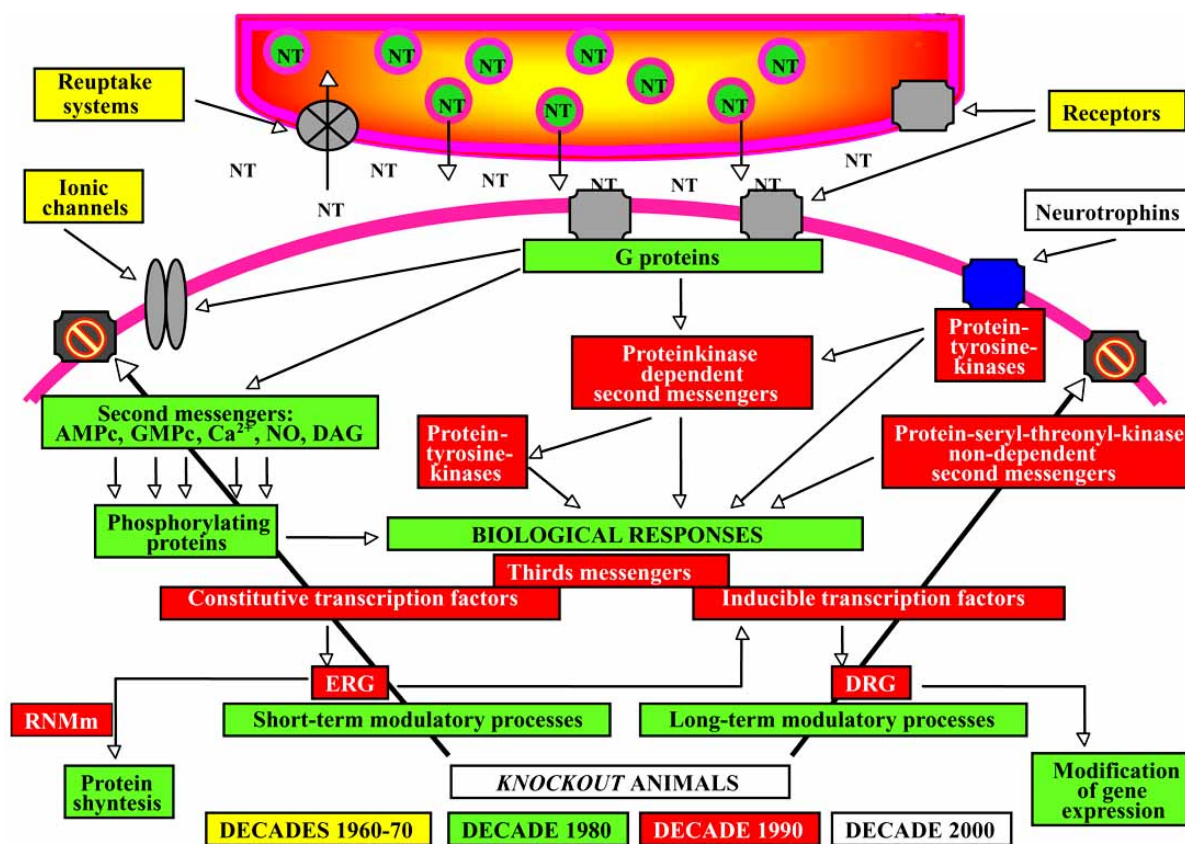
Despite the important advance represented by the monoaminergic hypotheses in relation to the aetiopathogeny of mental disorders and the action mechanism of antidepressants, a feeling soon emerged that these theories reflected only a small part, probably an initial part, of this action mechanism [1]. This realization led, in the 1980s, to the theory of receptor adaptation. According to this theory, the persistent activation of receptors, as a consequence of the increase in serotonin and noradrenaline in the synaptic cleft, led them (adrenergic 5HT<sub>2</sub> and β) to downregulate, a phenomenon that coincided in time with the onset of the therapeutic effect of the antidepressant [148]. However, the fact that this regulation phenomenon was not universal to antidepressants and that, furthermore, the blockers of these receptors lacked antidepressant effect –and could even induce depression in some people [149]– called into question the possibility that this receptor-adaptation mechanism was not the sole factor responsible for the therapeutic effect of antidepressants.

More recent theories [150] defend a “dysregulation” model, which would involve not just a single neurotransmit-

ter pathway; rather, there would be alteration of several, including the noradrenergic, the serotonergic and even the dopaminergic pathway. In line with these postulates, Delgado and Moreno [151] proposed an aetiological model in which depression would result from a dysfunction of different brain areas, notably the frontal cortex, the hippocampus, the amygdala and the basal ganglia, which, in turn, would be modulated by different monoaminergic neurotransmission systems. According to this theory, numerous factors, notably stress, could influence the correct functioning of these areas, in either a selective or a generalized way, which concurs with the classic postulates of a heterogeneous aetiology of depressive disorders. Appended to this hypothesis should be the possible existence of marked alterations in the intraneuronal pathways of signal transduction, which would also situate the source of depressive disorders in the sphere of molecular dysfunctions.

**New Targets in the Quest for Antidepressants: From Synaptic Pharmacology to Intraneuronal Pharmacology**

As pointed out earlier, in the 1960s and 70s the majority of studies that set out to demonstrate the effects of drugs on the CNS focused on extracellular aspects of synaptic transmission (Fig. (13)), basically involving the interaction of the



**Fig. (13).** Historic advances in the understanding of the neurobiology of neurotransmission systems and of the action mechanisms of psychotropic drugs, including the intracellular systems of transduction of external signals.

NT (neurotransmitter); NO (nitric oxide); DAG (diacylglycerol); ERG (early response genes); DRG (delayed response genes).

neurotransmitter with its receptor. This interaction was the consequence of acting on the inhibition of the systems of reuptake (TCAs and SSRIs) and metabolism (MAOIs), which increased the levels of monoamines in the synaptic cleft, thus facilitating their action on the receptor. However, these events occur rapidly, and are detectable from the first administration of the antidepressant drug, though the therapeutic effect does not begin until after a few weeks of treatment. These correlates suggested that the cited antidepressant effect occurs after a series of adaptations at a neuronal level, as a consequence of the chronic administration of these drugs [152] (Table 2).

**Table 2. Pre- and Post-Receptor Mechanisms in the Central Nervous System Modified by Chronic Administration of Monoaminergic Antidepressants**

• Synaptophysin
• Proteins G
• cAMP
• Protein-kinase A (PKA)
• Protein-kinase C (PKC)
• Protein-kinase dependent on Ca <sup>2+</sup> and calmodulin
• cAMP-dependent protein associated with microtubules (MAP <sub>2</sub> )
• CREB Protein
• Fos RNAm protein
• Neurotrophins (BDNF)

CREB (cAMP response element binding protein); BDNF (brain derived neurotrophic factor).

Thus, it became more and more obvious that the union of the neurotransmitter and the receptor represented only the beginning of the effects of neurotransmitters on their neuronal targets. In fact, it became clear over the last decade that these neurotransmitter substances regulated cell functioning (downregulation of receptors, protein synthesis, release of neurotransmitters, etc.), through the activation of biochemical pathways of intraneuronal messengers (G proteins, second messengers, such as AMPc or intracellular calcium and phosphorylating proteins), which eventually induced modifications in the gene expression of neurones, responsible for a wide range of biological responses (Fig. (13)) [152]. Moreover, though, neurones possess a high quantity of tyrosine-kinase proteins encrusted in their cell membrane, which act as receptors for neurotrophins and other growth factors (Fig. (13)), and this complicates even further the understanding of the diffusion of nerve information.

Thus, the increase of monoamines in the synaptic cleft triggers a series of intracellular neurochemical changes which, as recently postulated, have a decisive influence on the therapeutic effect of antidepressants. The intracellular effects of antidepressants have made it possible to propose the hypothesis that these drugs, after increasing the action of monoamines, the first messengers, on their corresponding receptors, and regardless of the transduction pathway of the

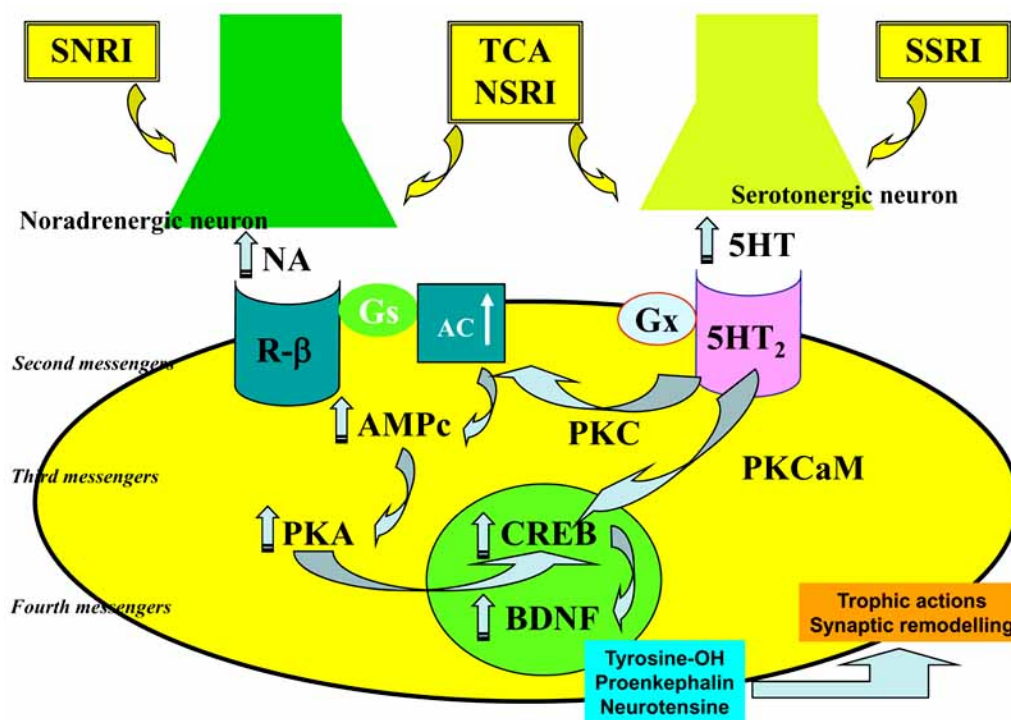
second messengers triggered (AMPc, diacylglycerol –DAG-, etc.), would have a point of convergence in the protein-kinases (PKA, PKC, PKCaM), considered as third messengers, which would control the genetic expression, through the phosphorylation of transcription factors that could be considered as fourth messengers (Fig. (14)) [152,153]. According to this hypothesis, SSRIs, TCAs and selective noradrenaline reuptake inhibitors (SNRI) would have a common intracellular mechanism widely removed from the point of action in the synaptic cleft, which would modulate, through modifications of gene expression, the synthesis of certain substances, such as proenkephalin, neurotensine, BDNF (brain-derived neurotrophic factor) or enzymes, such as tyrosine-hydroxylase, which, in sum, would provoke changes of functional adaptation, trophic actions or synaptic remodelling, tending to offset the possible anomalies present in depression. All of this unquestionably constitutes an enormous advance for our understanding of what could be the beginning of the psychopharmacology of this new millennium, capable of moving on from a superficial and synaptic psychopharmacology, until could be called intracellular psychopharmacology [152].

In any case, the scientific evidence accumulated over the last decade appears to confirm that there is no unitary biochemical mechanism to explain the antidepressant effect of all the substances currently available. Hence the movement of research on the action mechanism of antidepressants in other directions, as well as efforts to find new *loci* of antidepressant action. Thus, research is in progress on the role of neurotrophic factors (neurotrophins and BDNF), of corticotropine releasing hormone (CRH) and glucocorticoids, of excitatory amino acids and of the NMDA (N-methyl-D-aspartate) receptor, as well as on other possible targets (opiod system, interleukins, P substance, somatostatin, neuro-peptide Y, melatonin, nitric oxide, and so on).

## 8. CONCLUSIONS

The clinical introduction of psychotropic drugs in the 1950s constitutes one of the great medical advances of the 20<sup>th</sup> century, and the importance of the event has been compared with the discovery of antibiotics and vaccines. Gayral [154] refers to the “revolution of psychopharmacology” as the second revolution of psychiatry, arguing that the introduction of psychoanalysis was the first. For his part, J. Allan Hobson, neurophysiologist at the University of Harvard, remarks in his book *The chemistry of conscious states*, in reference to the introduction of psychoactive drugs in the 1950s, that “... the development of drugs that interacted with the brain’s chemical systems is the most important advance in the history of modern psychiatry” [155]. Moreover, from the clinical and public health points of view, the net result of this introduction was a “powerful social change in the conceptualisation and acceptance of mental illness, including through the media, in the organization of mental health services, in the development of the specialty and nosology of psychiatry, in the dynamics of high technology economies” [91].

Iproniazid, in spite of its short psychiatric life, and imipramine deserve a privileged place in the history of psychopharmacology and psychiatry, since not only did they open



**Fig. (14).** Effect of the different families of antidepressants on intraneuronal molecular mechanisms and end point of convergence at the genetic level.

TCA (tricyclic antidepressants); NSRI (noradrenaline and serotonin reuptake inhibitors); SNRI (selective noradrenaline reuptake inhibitors); SSRI (selective serotonin reuptake inhibitors); NA (noradrenaline); 5HT (serotonin); G (G proteins); AC (adenylate-cyclase); PKA (protein-kinase A); PKC (protein-kinase C); PKCaM (kinase dependent on calcium and calmodulin); CREB (cAMP response element binding protein); BDNF (brain derived neurotrophic factor).

the door to the specific treatment of mood disorders –lending great prestige to the psychiatry of the time, improving everyday clinical practice and increasing patients’ quality of life–, they also made it possible to develop the first serious hypotheses on the biological nature of these affective disorders [1,22,27,79,82,99], the monoaminergic theories of depression, around which scientific discussion revolved in the specialized journals in the 1960s and 1970s [89]. Psychoactive drugs in general, and iproniazid and imipramine in the particular case that concerns us here, thus permitted the gradual definition of the neurochemical process underlying mental illness, and the generation of a physiopathological theory on it, permitting the advent of so-called “biological psychiatry”. We are talking, then, about an approach that could be considered “pharmacocentric”, with far-reaching heuristic implications for psychiatry [3]. This situation emerged as unique in the history of medicine, since a large quantity of aetiological hypotheses were based on the action of a series of drugs whose application to psychiatric pathologies resulted, in many cases, as today, from the intervention of chance. With iproniazid and imipramine, depression ceased to be an illness of the mind to become an illness of the brain [82].

Even so, and excluding the clinical introduction of fluoxetine and the rest of the SSRIs in the 1990s, there have been scarcely any substantial advances in the pharmacology

of depressive disorders over the last 50 years. In this regard, it should be borne in mind that one of the most important challenges facing research today, in the field of Neurosciences, is an understanding of the molecular mechanisms responsible for intraneuronal communication and those through which cells manifest their phenotype in response to environmental signals. Detailed knowledge of these mechanisms could provide us, in the future, with much more specific and safer pharmacological tools for treating different neurological and psychiatric conditions, among the depressive disorders.

#### ABBREVIATIONS

AC	=	Adenylate-cyclase
AMPT	=	$\alpha$ -Methylparatyrosine
APA	=	American Psychiatric Association
BASF	=	Badische Anilin und Soda Fabrik
BDNF	=	Brain derived neurotrophic factor
CINP	=	Collegium Internationale Neuro-Psychopharmacologicum
CNS	=	Central Nervous System
CREB	=	cAMP response element binding protein

CRH	=	Corticotropine releasing hormone
DAG	=	Diacylglycerol
DOPA	=	3,4-Dihydroxy-phenylalanine
DRG	=	Delayed response genes
ERG	=	Early response genes
FDA	=	Food and Drugs Administration
5-HIAA	=	5-Hydroxyindole acetic acid
5-HT	=	Serotonin
MAO	=	Monoamine-oxidase
MAOIs	=	Monoamine-oxidase inhibitors
NA	=	Noradrenaline
NaSSA	=	Specific noradrenergic and serotonergic antidepressants
NIH	=	National Institutes of Health
NMDA	=	N-methyl-D-aspartate
NO	=	Nitric oxide
NSRI	=	Noradrenaline and serotonin reuptake inhibitors
NT	=	Neurotransmitter
p-CA	=	p-Chloroamphetamine
PKA	=	Protein-kinase A
PKC	=	Protein-kinase C
PKCaM	=	Kinase dependent on calcium and calmodulin
RIMA	=	Reversible and selective inhibitors of MAO
SNRI	=	Selective noradrenaline reuptake inhibitors
SSRI	=	Selective serotonin reuptake inhibitors
TCA	=	Tricyclic antidepressants

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