Review

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The role of serendipity in the discovery of the clinical effects of psychotropic drugs: beyond of the myth

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The serendipity is the faculty for making a discovery through a combination of accident and sagacity. In psychopharmacology, the serendipity played a key role in the discovery of many psychotropic drugs, although there are marked disputes in this regard, possibly due to semantic differences in relation to the meaning of this term. We have implemented an operational definition of serendipity based on the discovery of something unexpected or not sought intentionally, irrespective of the systematic process leading to the accidental observation. The present paper analyses some representative examples of discoveries in the field of psychopharmacology according to different serendipitous intervention patterns. Following this approach there would be four different imputability patterns: pure serendipitous discoveries (valproic acid/valproate); serendipitous observation leading to a non-serendipitous discoveries (imipramine); non-serendipitous discoveries secondarily associated with serendipitous observation (barbiturates); non-serendipitous discoveries (haloperidol). We can conclude that pure serendipitous discoveries in this field are not very frequent, most common being a mixed pattern; an initial serendipitous observation which leads to a non-serendipitous discovery of clinical utility. This is the case of imipramine, lithium salts, chlorpromazine or meprobamate.

Key words:
Serendipity, Discoveries, Psychopharmacology, History of psychiatry

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El papel de la serendipia en el descubrimiento de los efectos clínicos de los psicofármacos: más allá del mito

La serendipia es la facultad de realizar un descubrimiento mediante una combinación de accidente y sagacidad. En el ámbito de la psicofarmacología, la serendipia jugó un papel fundamental en el descubrimiento de muchos agentes psicotrópicos, aunque existen marcadas controversias en este particular, posiblemente debido a divergencias semánticas en relación al significado de este término. Nosotros hemos aplicado una definición operativa de serendipia basada en el hallazgo de algo no esperado o no buscado intencionalmente, independientemente del proceso sistemático que condujo a la observación accidental. En el presente trabajo, se analizan algunos ejemplos representativos de descubrimientos en el campo de la psicofarmacología según diferentes patrones de intervención serendípica. De acuerdo con este criterio existirían cuatro patrones diferentes de imputabilidad serendípica: descubrimientos serendípicos puros (ácido valproico/valproato); descubrimientos serendípicos iniciales que conducen a descubrimientos no serendípicos (imipramina); descubrimientos no serendípicos asociados secundariamente a descubrimientos de caracter serendípico (barbitúricos); descubrimientos no serendípicos (haloperidol). Podemos concluir que los descubrimientos serendípicos puros en este campo no son muy frecuentes, siendo más habitual un patrón mixto, que parte de una observación inicial serendípica que conduce a un descubrimiento no serendípico de utilidad clínica. Este es el caso de la imipramina, las sales de litio, la clorpromazina o el meprobamato.

Palabras clave:
Serendipia, Descubrimientos, Psicofarmacología, Historia de la psiquiatría

INTRODUCTION

Randomly or accidently linked discoveries have made up a permanent constant over the history of science, a setting within which the use of the concept "serendipity" has become popular. This term is traditionally used by analysts to refer to those discoveries or findings having a fortunate or unexpected character, fortuitous events or accidental

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coincidences. In this sense, the discovery of most of the psychopharmacological agents which, during the decade of the 1950s, revolutionized psychiatric care,[1] has also not escaped this conceptualization. It is sufficient to remember the discovery of the antimanic action of lithium in 1949, the clinical introduction of chlorpromazine in 1952 and of meprobamate in 1954, the discovery of imipramine in 1955 and of the psychiatric use of iproniazide in 1957 or the introduction, finally, in 1960 of clordiazepóxide.[2]

Most of these discoveries have been considered, even by the investigators per se involved in them, as a consequence of a chance or serendipitous intervention. However, the use of the concept serendipity to characterize these discoveries is at least confusing and contradictory. So, Blackwell states that "...many important discoveries and most, if not all, of those related to biological psychiatry, were a result of this (thanks to the serendipity]" (p. 15)[3] and more recently Klein stresses that in "all these large families of psychopharmacological agents were discovered serendipitously" (p. 1063).[4] On the contrary, for Jeste et al., "it can never be stated that the discovery of the most relevant biological treatments of the psychiatry have been a consequence of serendipity" (p. 1173).[5] Many specific examples can also illustrate this contradictory attribution of serendipity. In relation to chlorpromazine, Pierre Deniker, one of those responsible for its clinical introduction, stated that "this advance could be, more accurately, to the synthesis of new compounds that support the hypothesis that treatment of mental disorders is possible from a strictly medical perspective. (p. 155)[6]. On the contrary, another member of the same research team, Jean Thuillier, states that the discovery of chlorpromazine was "by chance" (p. 543).[7] Another example can be obtained with the benzodiazepines. While Cohen defends that the discovery of this group of anxiolytic agents "was not a result of serendipity" (p. 140),[8] Valenstein states that "serendipity also played an outstanding role in the discovery of the benzodiazepinic agents" (p. 54).[9]

Figure 1 — Portrait of Horace Walpole (1717-1797), fourth Earl of Oxford, done in 1754 by John Giles Eccardt (1720-1779) (National Portrait Gallery, London).

The semantic ambiguity is precisely found in these differences of opinion on the role of the fortuitous or risky discoveries, as we will analyze in the following. In the present work, we will try to break down the true role played by of serendipity in the findings that make up the origin of modern psychopharmacology, according to an operational and categorical definition of serendipity that has recently been published by our group.[10]

BASED ON THE TERM "SERENDIPITY" AND THE FORMING OF ITS CONCEPT

Historic approach

The term serendipity originated from the writings of the English historian Horace Walpole, fourth Earl of Oxford (Figure 1), and in the correspondence with his friend Sir Horace Mann, a British diplomat posted in Italy who had sent Walpole a portrait of an Italian aristocrat of the XVI century, Bianca Cappello (subsequently converted into Grand Duke of Tuscany, after her marriage to Francesco de Médici). In a letter dated 28 January 1724, Walpole told Mann that because the canvas had no frame, he wanted to make one for him with the coat of arms of the Cappellos. In said epistle, Walpole speaks about how, looking for the Medici coat of arms in a Venetian book of heraldry he happened to find that of the Cappello's: "... this discovery is the type that I call serendipity, a very expressive word that I am going to try to explain to you ..., you will understand it better by means of its origin than by definitions. I once read a little story titled 'The three princes of Serendip.' In it, their Royal Highnesses made continuous discoveries in their travels, discoveries by accident and sagacity of things which, at first, they were in quest for. For example, one of them discovered that a mule that had recently covered the same road was blind in the right eye because the grass was more worn out on the left side - Do you understand serendipity now?" (p. 407-8).[11]

Thus, Walpole drew the inspiration for his neologism from a classical story, possibly of Persian origin, initially published in the West by the Italian author Cristoforo Armeno under the title of *Peregrinaggio di tre giovani figliuoli del re di Serendippo* (1557). In subsequent editions and versions, in several languages, it became *The three Princes of Serendip*, sometimes loosing or replacing the authorship, or forming a part of literary collections. In this narration, three princes (Figure 2) from the mythical country of Serendip (historically called Ceylon, nowadays Sri Lanka), made several deductions from the information they obtained, without having to deliberately look for it, during the pilgrimages they carried out by order of their father in order to know the world, thanks to their capacity for observations and their astuteness. [12]

The term serendipity first appeared in print in a 1875 publication, when the chemist and bibliophile Edward Solly replied to an anonymous investigation published a few weeks earlier in the journal *Notes and Queries* about the history of Walpole and the "Prínces of Serendip." In this reply, Solly wrote that "Horace Walpole used the word *serendipity* to express a special type of natural intelligence" (p. 51).[13] Finally, this term was incorporated into the 1909 edition of the dictionary *The Century Dictionary and Cyclopedia*, under the meaning of "accidental sagacity" to find interesting things and mixing the concepts of personal "happy faculty" and "luck."[13] After this moment, the use of the term, serendipity, was gradually extended, although very circumscript, in the beginning, to the field of literary scholars.

The incorporation of the term "serendipity" into the scientific thinking began in the decade of the 1930's[13,14] thanks to, in a large degree, the works of the North American Physiologist Walter B. Cannon (see Cannon[15]). It achieved its final recognition during the decade of the 1950's, with the publication of an article in the Journal *Scientific American*. In this article, the microbiologist, of Italian origin. Salvador E. Luria, subsequently awarded the Nobel Price of Physiology and Medicine (1969), recovered this term for science on discovering the casual circumstances that concurred in the exploration of the so-called "Mystery T2" during his investigations in the University of Indiana. This "mystery" refers to a bacteriophage virus (called T2) that can infect a bacteria, is able to replicate itself and to finally destroy it: "Our story has as its critical episode one of those coincidences that show how discovery often depends on chance, or rather on what has been called 'serendipity' the chance observation falling on a receptive eye" (p. 92).[16]

Figure 2 — Detail of the page of a manuscript of the XVI century of the Safavid style, possible of Shiraz, showing King Bahram Gur in the Sandalwood Pavilion. The legend of the Three Princes seems to be inspired in the children of Bahram Gur or Bahram V of Persia (421-438).

What should we understand by serendipity and what is its real meaning?

Over time, the word "*serendipity*" has acquired multiple meanings in English, none of which exactly coincide with the original definition of Walpole. For example, the *Oxford English Dictionary Online* defines it as "the faculty of making happy and unexpected discoveries by accident." Furthermore, it designates the "event or circumstance in which this discovery occurs." In turn, the *Webster's Third New International Dictionary of the English Language* defines it as "the faculty of finding valuable or agreeable things not sought for."[17] Finally, the *Random House Webster's Dictionary* states that it is "an aptitude for making discoveries by accident."[18] In Spain, the term "serendipity" has still not been summed up by the Real Academia Española (Royal Spanish Academy) and the only dictionary in which it is included, under the meaning of "serendipidad," is in the *Diccionario de Español Actual* of Manuel Seco, Olimpia Andrés and Gabino Ramos. For them, it means "facultad de hacer un descubrimiento o un hallazgo afortunado de manera accidental"[19] (the faculty of accidently making a fortunate discovery or finding). All the definitions mentioned share a common characteristic: the ingredient of chance or accident. However, it is ironical if the use made by Walpole of this neologism is taken literally, that none of these definitions explicitly include the necessary ingredient of sagacity, understood as that cognitive capacity or capacity of mental discernment necessary to admit that a certain observation has a meaning and important significance. In this sense, the history of the science is full of stories about persons who made observations of great importance that do not make up important discoveries because they were not able to recognize the importance of that being observed. For example, we could obtain the words of Alexander Fleming in his Nobel speech, when he stressed the role of "luck, fortune, fate or destiny" in his transcendental discovery: "...I prefer to stress the truth, that [the discovery of penicillin] began with

a casual observation. My only merit is that I did not neglect the observation and I approached the problem with the view of a bacteriologist." (p. 83)[20]

Thus, sagacity marks the difference between serendipic discovery and absence of discovery in presence of relevant accidental information. However, on the other hand, although sagacity constitutes an essential element of serendipity, its usefulness when distinguishing between serendipic and non-serendipic discoveries is very limited inasmuch as sagacity should be a basic and essential component of the scientific mentality per se. However, there is an important baseline difference. In a non-serendipic discovery, sagacity precedes and leads to the observation while in a serendipic discovery, the manifestation of sagacity occurs after the unexpected observation. In any case, this observation is also not exempt of problems, since the scientists tend to explain, *a posteriori*, their discoveries as a consequence of some perfectly planned working hypotheses, even when these occur in a totally unforeseen way.

Considering the above, it seems clear that the first component of serendipity, "accident," marks the difference between a serendipic and non-serendipic discovery. The term "accident," in this context, may have two different meanings, that is, discovery due to chance or unforeseen discovery. However, chance is a deleterious concept, which entails the idea that natural phenomena are subjected to some randomization. From our point of view, the concept of accident as the appearance of something unforeseen adapts more to the phenomenon of serendipity. In this sense, we could categorize the serendipic discovery as that discovery of something not looked for, independently of the systematic process that lead to the accidental observation.

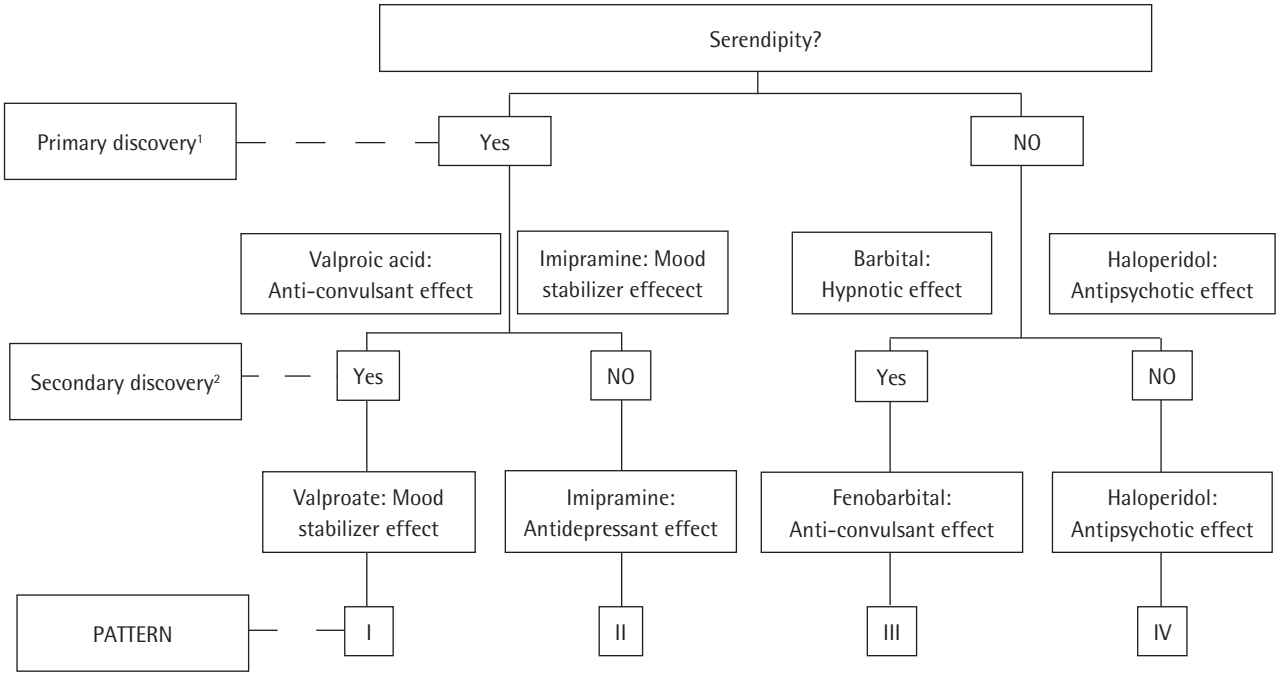
SERENDIPITY IN THE ORIGIN OF PSYCHOPHARMACOLOGY: CRITERIA AND PATTERNS OF ATTRIBUTION

The previously commented apparent differences in opinion found in the scientific literature on the role of serendipic discovery in the development of modern psychopharmacology may attribute to the degree of importance allotted by each author to sagacity and unforeseen accident. In fact, the statements that the most important discoveries of psychopharmacology were fortuitous generally imply that chance was a necessary and sufficient condition in these events. However, chance would rarely, if this were possible, be a sufficient condition.

In an attempt to clarify these controversies, we have recently proposed a standardization of the meaning of serendipity in relation to the scientific discoveries.[10] Using this working definition, focused on the discovery of something not intentionally looked for and unexpected by the investigator, in the present work, we have classified the psychopharmacological agents into four groups, in accordance with the serendipic attribution pattern (Figure 3). A first pattern would correspond to pure serendipic discoveries. Of these, we will discuss the discovery of the anti-seizure and mood stabilizing effects of valproic acid and valproate, respectively. Another example of this pattern is made up of the discovery of the psychotropic effects of lysergic acid diethylamide (LSD). A second pattern, a variant of the previous one, would correspond to those initial serendipic discoveries (in some cases made in laboratory animals) that secondarily lead to non-serendipic discoveries. In this category, we will comment on, as an example, the discovery of the antidepressive effect of imipramine, the first tricyclic antidepressive agent. Furthermore, in this group, the discovery of the lethargic effect in the guinea pigs of lithium salts and its subsequent antimanic effect in humans, the discovery of the antipsychotic properties of chlorpromazine and of clozapine, the mood stabilizer and antidepressant effect of the monoamine oxidase inhibitors (MAIO) or the experimental tranquilizing properties of meprobamate and its subsequent anxiolytic effect on the symptoms are included. The works of our group can be consulted to extend on the data on the historic development of these drugs.[21-30] The third pattern we will mention corresponds to the non-serendipic discoveries associated secondarily to serendipic-type discoveries. The most representative example of this group would correspond to barbiturates[31] and to their sought hypnotic effect, which made possible the subsequent serendipic discovery of their anti-seizure and anti-epileptic effects. Finally, there would be a fourth pattern of non-serendipic discoveries, in accordance with our working definition of non-sought finding. In this group, we could include the anxiolytic effect of chlordiazepoxide, the first benzodiazepines agent, or the antipsychotic effect of reserpine and haloperidol. The latter would serve as an illustrative example. The works of our group on the historic development of these drugs can also be consulted.[32-34] In the last pattern, the drugs arose, apart from serendipity, from the systematic research programs designed specifically for the development of drugs that are effective in different psychiatric disorders.

Pattern I: the case of valproic acid and valproate

A clear example of pure serendipity is found in the discovery of the anticonvulsant effect of valproic acid, a substance synthesized in 1881 by the American chemists Beverly S. Burton as organic solvent analog of valeric acid.[35] In the middle of the last century, valproic acid was a very popular organic solvent in the industry of Western countries and the pharmaceutical industry began to use it frequently as a solvent. [36] In 1963, Georg Carraz, an investigator in the Laboratoire Berthier (Grenoble), tried to evaluate the experimental anticonvulsant activity of a series of compounds of khelline[37] and, in agreement



[1] Usually, although not always, they correspond to discoveries in laboratory animal.

[2] Discoveries regarding the clinical efficacy.

Figure 3 | Outline of the four patterns of serendipic attribution in the discovery of the psychopharmacological agents, using four illustrative examples

with the common practice in this period, used valproic acid as a solvent agent. Using the pentylenetetrazole model,[38] Carraz discovered, by chance, that all the solutions that contained valproic acid, regardless of the khelline evaluated, had anticonvulsant activity, and that the mentioned substance was responsible for the effect.[39]

After this discovery, Carraz synthesized valpromide, a derivate of valproic acid, which, in theory, would have greater liposolubility and would cross the brain-blood barrier more easily.[38] For his study in humans, Carraz contacted Sergio Borselli, a psychiatrist who studied with Pierre A. Lambert in the Hôpital Psychiatrique of Bassens (Rhône-Alpes). This made it possible for him to initiate a series of clinical trials in patients with epilepsy.[40,41] In the beginning, Borselli and Lambert observed that valpromide had a sedative effect, above all when administered with other anti-epileptic agents available at that time, such as phenobarbitone. However, after the administration of valpromide and valproate separately, these investigators also observed, serendipitously, that the patients not only experienced improvement in their neurological picture but also mood state stabilization.[42] The latter finding was described by Lambert in the following way: "... the patients felt themselves more; the mental stickiness, viscosity that had sometimes been the standard with the older agents, was less. We saw the disappearance of the tendency to depression, sometimes even a mild euphoria" (p. 47).[43] Valproate was authorized as an anti-epileptic in 1967 (France) and as an antimanic agent in 1993 (the United States).

Both examples are illustrative of non-sought scientific observations and as manifestations of clear serendipity.

Pattern II: the example of imipramine

The history of the clinical introduction of the first antidepressant (of the tricyclic agent family), imipramine, is within the frame of a process or search for antipsychotic drugs[27,29] after the therapeutic success reported with the clinical introduction, in 1952, of chlorpromazine[44] and reserpine, an alkaloid of the *Rauwolfia serpentina*.[45] These advances led to an increase in the search for substances with similar properties by the pharmaceutical companies. In this way, the pharmaceutical firm J.R. Geigy (Basel) revived some phenothiazine substances that they had tried to develop, unsuccessfully, with the hope that they might have some other psychiatric utility.[46] In this context, the psychiatrist Roland Kuhn, staff medical director in the Cantonal

Psychiatric Clinic of Münsterlingen (near Lake Constance), who had already studied the hypnotic and neuroleptic properties of some phenothiazine agents of Geigy,[46,47] requested that the Swiss company send them another phenothiazine, with the hope of finding a potent antipsychotic agent for their patients. At the beginning of 1956, Kuhn received a preparation called G-22355, a substance with the same side chain as chlorpromazine, that had been synthesized by Franz Häfliger and Walter Schindler, in 1948, from prometazine, replacing the sulphate bridge of the phenothiazine with the ethylene bridge.

The extensive clinical research developed during 1956 by Kuhn soon manifested that the agent G-22355 lacked noticeable neuroleptic activity. Some patients who had previously been treated with chlorpromazine even showed a deterioration in their schizophrenic picture, passing to a state of clinically concerning agitation. [48] However, Kuhn observed that three patients diagnosed of depressive psychosis experienced a significant improvement in their general state in only a few weeks. The antidepressive effect of this substance, later called imipramine, was therefore completely unexpected and its discovery was totally accidental. In this sense, the possibility that this substance could have an antidepressive therapeutic effect was proposed by Kuhn, for the first time, in a written report to Geigy, dated 4 February 1956.[49] After, 37 more depressive patients received this drug, thus demonstrating its special efficacy in the treatment of depressive disorder: "The patients generally seem to be more cheerful, their voices, previously weak and depressed, now sounded louder. They were more communicative, their grumblings and sobbing had disappeared. The depression, which had been manifested through sadness, irritation and the sensation of lack of satisfaction, now gave way to a friendly, happy and accessible feeling" (p. 1138).[50] With the data obtained from the clinical follow-up of 40 depressed patients, Kuhn presented his results in the II International Congress of Psychiatry, held in Zurich, in September 1957, to an audience of hardly 12 persons. The minutes of the conference were published in the August issue of the *Swiss Medical Journal*.[50] However, the following year, Kuhn republished his data (with a larger sample of patients) in the *American Journal of Psychiatry,*[51] thus being able to disseminate his discovery internationally.

Kuhn had the sagacity of recognizing an antidepressive drug when he was looking for an antipsychotic one. Kuhn himself commented in this regards: "It is supposed that casualty had something to do with the discovery of imipramine. Chance, however, was not decisive..... One part of intellectual deed with the capacity of "inventing" something completely new, something unknown up to the present, that is, a new disease....., must be added to this. Goethe, in few words, described this question: « Discovery needs luck, invention, intellect - none can do without the other »" (p. 216-7).[52]

The discovery of the antidepressive properties of imipramine constitutes a representative sample of how a serendipic finding, the observation that treatment of schizophrenic patients with this drug while seeking an antipsychotic effect, leads to a planned and non-serendipic discovery, as was the antidepressant effect. It is possible that this pattern in which serendipic findings were mixed with other non-serendipic ones was the most common during the first stages of modern psychopharmacology. However it is precisely this dual quality that has been an important reason for debate when attributing the serendipic character to the psychopharmacological discoveries.

Pattern III: Barbiturates

The synthesis of the barbiturates, a closed chain ureic compound whose core nuclear is malonylurea, occurred in 1864 by the German chemist Adolf von Baeyer (Normal Prize winner of Chemistry in 1905),[53] the diethyl-barbituric acid (also known as barbital, malonal and gardenal) being the first agent of this family being marketed (see López-Muñoz et al.[31]). Synthesized in 1881 by M. Conrad and M. Guthzeit, on treating argentic salt of barbituric acid with ethyl iodine, it was introduced clinically as a hypnotic in 1904, thanks to the works of Josef F. von Mering and Emil Fischer (Nobel Prize winner of Chemistry in 1902). Von Mering, Professor of Pharmacology at the University of Halle, had observed that some of the synthesis compounds obtained during the last two decades of the XIX century and marketed as hypnotics, such as sulfonal, contained a carbon atom with two ethyl groups in its molecular structure. Thus, he proposed analyzing the properties of the 5.5-diethyl-barbituric acid. To do so, he went to Fischer, head professor of Chemistry of the University of Berlin and knowledgeable about the chemistry of malonylurea since he had been the assistant of von Baeyer for 8 years in Munich. These investigators tested the new resynthetisized product, observing in the dog that its hypnotic potency was much greater than the diethyl-barbituric of von Mering.[54] This new hypnotic drug was patented by Fischer in January 1903, and two months later, the first scientific data of the barbiturics were published in a brief communication. [55]

The first barbital analogs, numbering around 18, were synthesized and tested by the group made up of von Mering and Fischer. One of them, and perhaps that used most afterwards, was phenobarbital, synthesized by the chemist of the F. Bayer Company and Co., Heinrich Hörlein in 1911, when one of the ethyl groups was replaced with a radical phenyl. Phenobarbital was used in therapy as a hypnotic for the first time in 1912 by Loewe, Juliusburger and Impens, and was marketed this same year by Bayer, under the name of Luminal®. Phenobarbital, a drug with a longer drug action than its predecessor, soon became "the king of the barbiturics," both within the setting of hospital care and

outpatient care.[56] It opened the doors to another important therapeutic indication of the barbiturics, as was epilepsy.

This discovery took place in 1912, the same years as its marketing, thanks to the perceptiveness of Alfred Hauptmann, a resident physician in psychiatry in Freiburg, who was responsible for the medical care of a series of hospitalized epileptic patients. Because he found it impossible to be able to get adequate sleep because of the continuous seizures of his patients, Hauptmann decided to administer them some of the new hypnotics introduced into the market, among them phenobarbital. Surprisingly, Hauptmann observed that the seizure incidence in patients treated with low doses of phenobarbital was clearly reduced, not only during the night but also during the daytime.[57] Among the conclusions contributed by Hauptmann, it stands out that phenobarbital did not only cause a mere reduction in the number of seizures but also that they lead to a decrease in their intensity. This made it possible for many of the patients to be desinstitutionalized and to even return to the work activity. However, the international diffusion of phenobarbital as an antiepileptic agent was clearly delayed because, in the first place, of the limited repercussion, outside of his borders, of the German journal in which Hauptmann published his experience (*Münchener Medizinische Wochenschrift*), and in the second place, to the advent of the First World War.

The discovery of the anti-seizure properties of barbiturics represents a clear example of serendipity secondary to a non-serendipic discovery since the barbiturics were specifically developed as hypnotic agents. However, the finding of their anti-seizure efficacy was totally accidental within the frame of their use as hypnotic agents in epileptic patients.

Pattern IV: based on haloperidol

Haloperidol was also discovered under the trail of therapeutic success of chlorpromazine.[34] In the middle of the 1950's, the hypothesis that related the clinical manifestations of paranoid schizophrenia with abusive consumption of amphetamines (hallucinations, delusional ideas, motor stereotypes, etc.) was in force. This was a commonly observed phenomenon in professional cyclists, who consumed amphetamines to improve their sports performance. With this base, Paul A. Janssen (Janssen Pharmaceutical, Beerse) initiated an ambitious research program based on the hypothesis that the agents capable of antagonizing the effects of amphetamine had antipsychotic properties. In this way, a study was made of the antagonist properties of amphetamine on the part of a series of butyrophenone compounds previously synthesized by the Belgium company, confirming them for the first time.[58] These facts motivated Janssen to synthesize many derivates of this family, in order to find an agent having greater potency and neuroleptic specificity. On 11 February 1956 and among 438 synthesized derivates, the 45th butyrophenone of these series and the most potent of the tranquilizers up to date (coded as R-1625 on 15 February 1958) came into being. This was a derivative of the 4-fluorobutyrophenone, synthesized by Bert Hermans that was given the generic name of haloperidol due to the two halogenate substitutes incorporated into the molecule.[59] This substance was endowed with a great antagonist potency of the amphetamine (only 0.02 mg/Kg of haloperidol decreased the agitation induced by a standard dose of amphetamine in the rat) and it showed an antipsychotic activity that was 50 times greater to that of chlorpromazine.[60]

Rapidly, Jean Bobon et al., of the Psychiatric Clinic of the University of Leige, studied the efficacy of haloperidol in psychotic patients using a dose 50 to 100 times lower than that which had been used with chlorpromazine. They confirmed that butyrophenone caused a rapid (5-15 min) and prolonged (3-5 h) decrease of psychomotor agitation in 18 patients diagnosed of several psychotic-type psychiatric disorders.[61]

Serendipity did not intervene in the discovery of haloperidol and the verification of its antipsychotic effect, as its development was a consequence of a working hypothesis to achieve, precisely, a drug that was effective in the treatment of schizophrenia. Furthermore, in the first place, these tests made it possible to obtain the design of new experimental models of prediction of the antipsychotic effect (antagonism of the stereotypes induced by amphetamine substances). This lead to the considerable advance of the basic research of psychotropic agents. In the second place, these tests made it possible to initiate the basic systemic investigation that led to the opening of successive doors in the setting of biological and neurological psychiatry.[34] In fact, an outstanding role in the origin of the dopaminergic hypothesis of schizophrenia is attributable to haloperidol, thanks to, among others, the works of Arvid Carlsson (University of de Göteborg), since he found that the cerebral levels of dopamine, in the experimental animal, varied when haloperidol was administered (as occurred with chlorpromazine).[62] After, Solomon H. Snyder, of the John Hopkins University, could confirm that the antipsychotics, as haloperidol, were capable of blocking the dopamine receptors.[63] All these advances were based on rational working hypotheses, that successively lead to new empiric theories. This converted the surroundings of haloperidol into an example of rationality in the pharmacological discoveries, where the role of serendipity is practically null.

DISCUSSION AND CONCLUSIONS

As we have stressed, the participation of serendipity in the process of discovery of the drugs, widely mentioned in

the specific case of modern psychopharmacology, is an extremely controversial fact based on the authors who have approached this subject. Possibly, these differences of opinion are due to the semantic ambiguity of the term "serendipity," that has been used based on a large variety of meanings. [13] For this reason, we, in line with the original proposal of the meaning, defend that this term refers to the discovery of something unexpected or not intentionally sought.[10] In other words, it refers to that finding that occurs without the expectation of the observer of finding it. In fact, during recent years, the meaning of the term serendipity has shifted towards the original interpretation of Walpole, including the cases of scientific discoveries that occur "by chance" and that are found without searching for them, but also incorporating the fact that they would not have occurred if not for the astute vision of the investigator, attentive to the unexpected and not at all indulgent with the apparently unexplainable. As Louis Pasteur very accurately explained more than one century ago, "in the realm of scientific observation, luck is granted only to those who are prepared." (cit. Hofmann, p. 1)[64]. Proof of this new orientation is the edition in Spanish of the book by Royston M. Roberts, *Serendipity. Accidental discoveries in Science* (1989), in which the term "*serendipity*" was translated as that condition of discovery that is made thanks to the combination of accident and sagacity.[65] Therefore, the meanings "fortuitous discovery" and "serendipity" cannot be considered as synonymous since the latter, besides chance, makes an additional reference to the sagacity of the investigator.

In the scope of psychopharmacology, it seems clear that serendipity, to a greater or lesser degree, played a fundamental role in the discovery of psychotropic agents during the 1950's, although, of course, it is also necessary to keep in mind the dynamics of the systematic and rational search for results, a phenomenon inherent to the scientific research per se and that was consolidated in successive decades. In this sense, some authors have reindicated the role of serendipity in the current process of scientific research, as Donald Klein in his recent article *The Loss of Serendipity in Psychopharmacology.*[4]

However, in the first moments of the modern psychopharmacological era, pure serendipic discoveries, on the contrary to that which has been postulated, are rather scarce. Most of them have a mixed character, in which serendipic and non-serendipic findings are mixed and they generally follow a consistent pattern that begins with an initial serendipic observation, as occurred in our example of imipramine. These facts may favor the existence of the previously mentioned contradictions among authors, some of which only interpret them from the random perspective, since they consider that the results of the clinical trials are a mere *continuum* of the initial serendipic findings and that everything should be considered as a single discovery and not as separate events. In any event, and excluding the comprehensive examples in the type IV pattern, we are always faced with a cocktail of change and ingenuity, of scientific accident and perceptiveness.

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