Serendipitous Discovery of First Two Antidepressants

In this editorial, we would like to recount how serendipity played a rôle in discovering the antidepressant activity of iproniazid, first monoamine-oxidate inhibitor (MAOI), and imipramine, prototype of tricyclic antidepressant (TCA).

Definition of Serendipity

The term "serendipity" was first coined by the British writer and historian Horace Walpole, fourth Earl of Oxford when he wrote to his friend Sir Horace Mann, a British diplomat posted in Italy. Walpole found the inspiration for his neologism in a classic story, possibly of Persian origin, tittled *The Three Princes of Serendip*, describing that three princes from Serendip (present day Sri Lanka) travelled by order of their father to know the world. This term appeared in print for the first time in a publication in 1875, when the chemist and bibliophile Edward Solly responded to an article published anonymously some weeks before in the a journal *Notes and Queries* about the story of Walpole. Thus, serendipity as a concept in science traditionally has been associated with fortuitous or accidental discoveries that are unexpected.

The rôle of serendipitous discovery in the development of modern psychopharmacology is often contradictory. In many instances these differences of opinion can be traced to the relative degree of importance that is attributed to sagacity and to unforeseen occurrence. We have proposed in previous publications [1, 2] that while sagacity is an essential element of a serendipitous discovery it is not a useful concept in distinguishing such discoveries from non-serendipitous ones. That is, sagacity is an essential element of all discoveries. In the absence of sagacious discernment the significance of an observation would not be recognized and a "discovery" would not occur. We have stressed, therefore, that it is the unforeseen nature of an observation that is key in defining a discovery as serendipitous; the discovery of something not sought. As a solution, we have proposed an operational definition of serendipity to classify discoveries as serendipitous and non-serendipitous [1, 2]. In regard to the stages of discovery we have present four patterns. The second pattern includes those initial serendipitous discoveries (frequently in laboratory animals) that led secondarily to non-serendipitous discoveries. This category comprises many of the most important findings of the decade of the 1950s, among them the discovery of the antidepressive effects of iproniazid and imipramine [3, 5].

Serendipity in Discovering Iproniazid

The first specifically antidepressant family drugs are MAOIs, which belong to the antitubercular hydrazide agents that had been used since the early 1950s (Figure 1) [3]. In 1952, studies began at the Sea View Hospital on Staten Island, New York City, on the clinical effects of iproniazid, carried out by Irving J. Selikoff and Edward Robitzek, who observed that this drug had, compared to isoniazid, greater power to stimulate the

編者評論：最初兩種抗憂鬱劑的偶然發現

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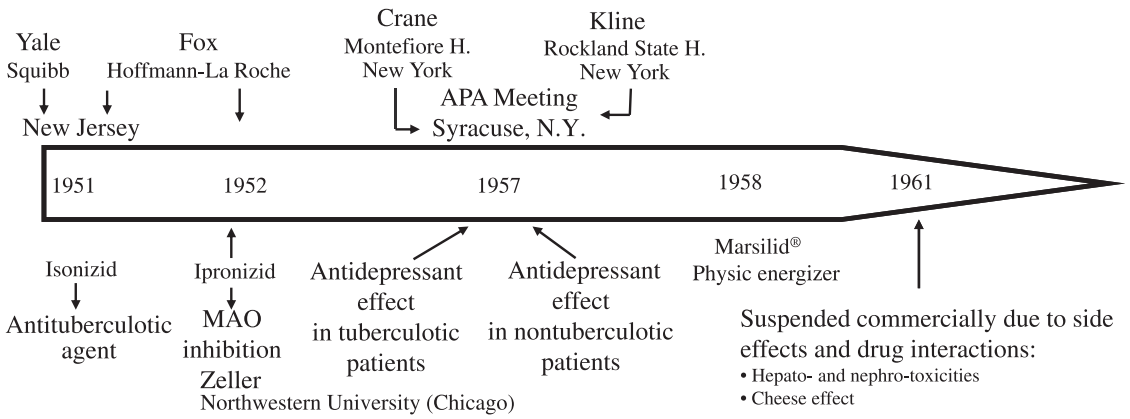

Figure 1. Dates and key milestones in the discovery of iproniazid: from antituberculotic drugs to monoamine oxidase inhibitors. APA, American Pschiatric Association

central nervous system, an effect initially interpreted as a side effect [5]. Finally, Nathan S. Kline and colleagues (Harry P. Loomer and John C. Saunders), of Rockland State Hospital, were the first psychiatrists to assess the efficacy of iproniazid, marketed as an antitubercular agent, under the trade name Marsilid®, in non-tuberculotic depressed patients (chronic psychotic depression). For their study, they recruited 17 highly inhibited subjects with severe schizophrenia and 7 with depression. Their results showed that iproniazid has a stimulant effect on depressed patients, and that 70% of the patients who received iproniazid improve substantially (in lifted mood, weight gain, better interpersonal capacity, increased interest in their surroundings and themselves, etc.) [6]. In 1957, Kline published a report on iproniazid, proposing the term "psychic energizer" to refer to the drug's action [7].

Serendipity in Discovering Imipramine

The history of tricyclic and tetracyclic antidepressants began in 1930s, when antihistamines were pursuited as potential hypnotics or sedatives by the Swiss chemical company J. R. Geigy (Figure 2). Robert Domenjoz, director of Pharmacology Section of Geigy, encouraged his team to look into the effects of the phenothiazines, because no important application had been found at that time, in the hope of their being useful as sedatives [4]. In 1952, Deniker and Delay as well as Hamon et al. had made an important discovery while testing chlorpromazine, at the Saint-Anne University Hospital as well as Val de Grâce Military Hospital in Paris, respectively [8-10]. These findings intensified the search for substances with similar properties. 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 in psychiatry [4, 11, 12]. One of these substances – known internally as G-22355 – which had been synthesized in 1948, was sent to Roland Kuhn, at the Thurgausiche Heil- und Pflegeanstalt in Münsterlingen (close to Lake Constance), Switzerland, in early 1956, to see whether it could be used as an antipsychotic drug [4]. The extensive clinical research that took place in 1956 at the Kantonsspital Münsterlingen,

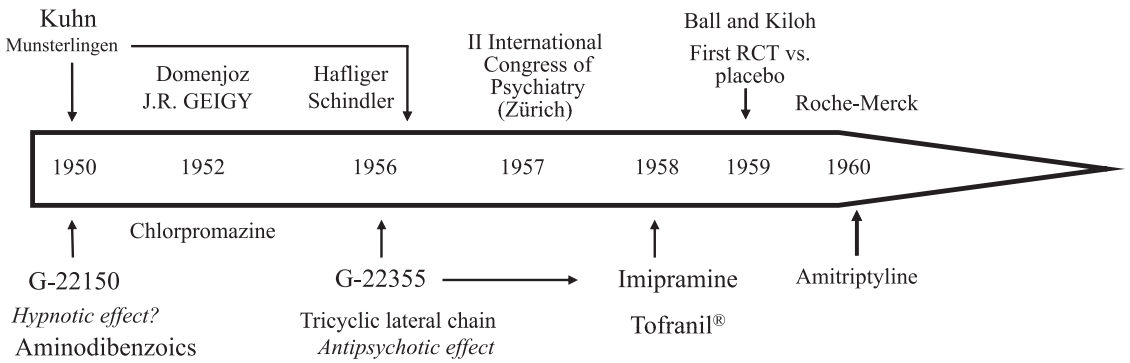

Figure 2. Dates and key milestones in the discovery of imipramine: from antihistamines to tricyclic antidepressants. RCT, randomized contolled trial.

near Basle, found that agent G-22355 lacked any appreciable neuroleptic effect. But Kuhn observed that three patients with depressive psychosis improved remarkedly in their general state within just a few weeks. Subsequently, another 37 depressive patients received this drug, formally called imipramine, thus showing its special efficacy in treating depressive disorders [13, 14]. The antidepressant effect of imipramine was, totally unexpected, and its discovery was done accidentally. But Kuhn had the sagacity to recognize an antidepressant drug while searching for a substituted antipsychotic drug.

Kuhn himself commented: "Chance admittedly had something to do with the discovery of imipramine. Chance was not decisive, however... to this had to be added a measure of intellectual achievement that was able to "invent" something completely new, something hitherto unknown, namely a new disease... Göthe put the sense of the matter in a nutshell when he wrote: "Discovery needs luck, invention, intellect – neither can do without the other [15]."

Conclusion

The clinical introduction of psychotropic drugs in the 1950s is a great medical advance of the 20th century, and the importance of the event has been compared with the discovery of antibiotics and vaccines. Although in these early phases of psychopharmacology, serendipity played an important rôle in the discovery of many psychotropic drugs [16], the final results of these research are truly important.

Drug discovery is often a multi-stage process, and that serendipity may play a rôle in some but not other stages [1]. In the area of psychopharmacology, purely serendipitous discoveries are rather rare. The majority of discovery presents a mixed pattern, a combination of serendipitous and non-serendipitous finds. (The authors declare no potential conflict of interests.)

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