Part I

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Neuroleptic-Induced Movement Disorders: Historical Perspective

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In February 1952, Laborit, Huguenard, and Alluaume published an article concerning the anesthetic properties of a new medication, chlorpromazine, mentioning therein the induction of a “psychic disinterest.” That same year, Delay, Deniker, and Harl (1952a,b), Delay et al. (1952c), and Hamon, Paraire, and Velluz (1952) first reported the effects of chlorpromazine in patients with various psychiatric conditions. A few months later, the effectiveness of the first neuroleptic was considered to have been demonstrated.

Initial Descriptions

The first description of an extrapyramidal syndrome during the course of neuroleptic treatment dates back to the 1953 Swiss symposium on chlorpromazine. The next year, Labhardt (1954) and Staehelin (1954) reported certain extrapyramidal complications caused by neuroleptics. It was Steck (1954, 1956), however, who vividly described such symptoms in a convincing manner. (Not until 1961 did Lambert and Broussolle note that it was not surprising that the Swiss authors had reported good results from their use of neuroleptics, given the high dosages used, which of course entailed a greater likelihood of developing extrapyramidal side effects.) Steck (1954) stated that “since the summer of 1953, we were impressed by the appearance of a well-developed parkinsonian syndrome in a chronic, cyclically agitated patient who also manifested schizophrenic symptomatology. This patient presented the well-known picture of post-encephalitic parkinsonism with psychomotor rigidity, tremors, facial seborrhea, marked salivation and akathisia.” Steck (1954) also reported the presence of extrapyramidal symptoms in 78 of 232 (34%) women and 33 of 77 (43%) men treated with neuroleptics. He claimed, as well, that this syndrome was completely reversible and that its occurrence depended on the dosage used. Comparing the symptoms of this syndrome
with those of encephalitis lethargica, Steck identified both an initial phase of somnolence, akin to the lethargic period of the encephalitis, and a parkinsonian syndrome similar to postencephalitic parkinsonism. That analogy prompted him to postulate an extrapyramidal and diencephalic localization for the actions of the neuroleptics.

A symposium on neuroleptic medications was held in Paris in October 1955; 5 of the 150 presentations discussed neuroleptic-induced extrapyramidal symptoms. Investigators reported that the “pseudoparkinsonian signs” of neurolepticized patients, which presented rarely as a typical parkinsonian syndrome, were more often seen as a forme fruste (Letailleur, Morin, & Monnerie 1956). Others reported that when compared with parkinsonian patients, the neurolepticized patients had more frequent tremors and different characteristic electromyographic tracings (Deniker, Bourguignon, & Lempérière, 1956). The positive effects of anticholinergic drugs were also noted (Letailleur et al., 1956).

In that same year, 1955, Delay and Deniker, on observing the similarities in therapeutic efficacy and extrapyramidal activity of two such seemingly different compounds as chlorpromazine and reserpine, used the term “neuroleptic” to characterize their combination of properties (Deniker, 1989).

In the following year, Flügel (1956) was the first to hypothesize the apparent necessity of inducing a parkinsonian state to obtain a therapeutic effect in the psychiatric condition. As concern with the extrapyramidal side effects grew, an international symposium on the subject was scheduled for Montreal in 1960, and there the questions regarding the efficacy of neuroleptics and their relationship to parkinsonism were fully discussed. Delay and Deniker (1961) reported that the percentage of patients who had experienced improvement when taking certain neuroleptics (perphenazine, trifluoperazine) seemed to be directly related to the appearance of extrapyramidal symptoms. Haase (1961) reported that it was only when extrapyramidal manifestations appeared that the neuroleptics led to improvements in the underlying psychiatric conditions. On the other hand, Lambert and Brousolle (1961) stated that some psychiatric patients had shown improvement without exhibiting extrapyramidal side effects, that others had exhibited extrapyramidal side effects without showing improvement, and that the addition of an anticholinergic did not affect the therapeutic outcome. Cole and Clyde (1961), in an efficacy comparison of thioridazine (which causes relatively fewer extrapyramidal side effects) and fluphenazine (which causes relatively more), found the two products equally effective.

Somewhat earlier, Delay and Deniker (1957) had outlined five characteristics by way of defining the new class of neuroleptics. Neuroleptics, they said,
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produced psychomotor indifference, a sedative effect, an antipsychotic effect, and vegetative and extrapyramidal effects and had a dominantly subcortical site of action. Those authors were criticized, however, by their American counterparts, as recounted by Deniker: “Naturally, this definition did not please everybody. In fact, Americans were horrified. It was a matter of defining a group of drugs by their adverse effects, and they preferred such terms as tranquilizers, later on using the expression ‘major tranquilizers’, and finally, using the expression ‘antipsychotic’. In 1970, Stille and Hippius announced that clozapine was a powerful antipsychotic without extrapyramidal effects: our theory was therefore seriously attacked. In reality, this was the exception which proved the rule” (Deniker, 1989).

By 1960, the sequence of appearance of neuroleptic-induced extrapyramidal side effects had been precisely described (Goldman, 1961; Lambert & Broussolle, 1961), as follows: For the first few days, dyskinetic or dystonic excitomotor crises occur; the next few weeks bring about an akinetohypertonic parkinsonian syndrome; during the following weeks, a tardive excitomotor syndrome with akathisia occurs; and finally, after several months of neuroleptic treatment, continuous oral or choreiform movements appear. At the Montreal symposium, Lambert and Broussolle (1961) proposed a classification of the neuroleptics based on their therapeutic efficacy and extrapyramidal side effects. Those researchers distinguished a sedative group, with levomepromazine as its main referent, and an antipsychotic group, with thiothixene and piperazine derivatives as examples of its products. It was that latter group, they said, that produced higher rates of extrapyramidal side effects. Goldman (1961), who stated that anticholinergic drugs could prevent the development of extrapyramidal side effects, also noted that parkinsonian manifestations could spontaneously disappear and that akathisia was difficult to treat. At that same symposium, epidemiologic (Ayd, 1961) and psychoanalytic (Sarwer-Foner, 1961) studies of neuroleptic-induced extrapyramidal side effects were presented.

Tardive Dyskinesia

The tardive complications of neuroleptic treatment were not mentioned in the literature until the late 1950s. Moreover, they were referred to only anecdotally at the Montreal symposium (Goldman, 1961; Lambert & Broussolle, 1961). In 1983, Tarsy reconstructed the early history of tardive dyskinesia as follows:

- In 1957, Matthias Schonecker, in Germany, reported on 3 women, ages 60 years and older, who presented with bucco-oral movements a few weeks
after beginning chlorpromazine treatment. Although the neuroleptic dosage was decreased for one patient and the drug was discontinued for the other two, the symptoms continued. Those patients suffered from depressive or anxiety symptoms, with cerebral arteriosclerosis. Schonecker concluded that those manifestations differed from acute extrapyramidal side effects.

• In 1959, a French group (Sigwald et al., 1959) described 4 women, ages 54 years and older, in whom involuntary movements of the tongue, lips, and facial muscles had appeared after several years of phenothiazine treatment. Calling those movements “facio-bucco-linguo-masticatory dyskinesias,” the group proposed a first classification of the dyskinesias into acute and chronic types.

• In 1960, the Danish authors Uhrbrand and Faurbye described 29 patients who exhibited buccolinguomasticatory movements, sometimes associated with trunk and foot movements, that still persisted in 50% of the patients after discontinuation of the neuroleptics. Those authors noted that whereas discontinuation of the neuroleptics aggravated the syndrome in some patients, it unmasked the condition in others. They also noted that the movements were more frequent for aged patients suffering from organic abnormalities. Faurbye et al. (1964) proposed the term “tardive dyskinesia” for this condition.

• The first North American observations date to 1960. First, Kruse (1960) reported on 3 women, ages 50 years and older, who developed akathisia accompanied by abnormal movements of the legs, arms, and mouth that continued for several months after neuroleptics were discontinued. Then Druckman, Seelinger, and Thulin (1962) described severe dystonia of the neck and trunk in a 46-year-old man whose manifestations had not changed during 20 months following discontinuation of neuroleptics. It was Keegan and Rajput (1973) who first used the term “tardive dystonia.”

• The first British observations were reported by Hunter, Earl, and Janz (1964a) and Hunter, Earl, and Thornicroft (1964b), who described the different manifestations of tardive dyskinesia as bucco-oral, choreiform movements of the limbs, along with respiratory dyskinesia. Comparing that condition to encephalitis lethargica, with its viral origin, they suggested the presence of a chemical encephalitis.

As shown by those historical vignettes, the patients described in the early literature were mainly of advanced age, a time when organic involvement is common. It was not until the late 1960s that serious epidemiologic studies were undertaken, showing prevalences varying between 0.5% and 65% (Wolf & Gautier, 1987). Indeed, most of the predisposing factors suspected in the
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early studies (cerebral lesions, lobotomy, electroconvulsive treatment) have never been decisively confirmed by more recent studies, whereas such factors as older age and female gender were confirmed only later (Tarsy, 1983).

Deniker (1989) showed that interest in tardive dyskinesia varied widely from one country to another. French researchers, for example, were less concerned about this side effect than were their American counterparts. Perhaps dyskinesia was a more severe problem in the United States because of the Americans’ more liberal use of neuroleptics, at higher dosages, and because fewer such medications had been approved for use in the United States (Deniker, 1989). Medicolegal concerns in the United States had also increased the apprehension of American physicians (Wolf, Grunberg, & Garneau, 1988). Periodically the American College of Neuropsychopharmacology (1973) and the American Psychiatric Association (1980, 1992) have published reports by various “task forces” synthesizing the current knowledge concerning tardive dyskinesia. Yassa and Jeste (1988) have speculated that the new antipsychotic molecules that are devoid of neurological side effects may lead to the disappearance of tardive dyskinesia.

**Conclusion**

Tardive dyskinesia remains an enigmatic phenomenon, not only because of its paradoxical clinical aspects but also from a scientific viewpoint. It will constitute a challenge for basic and clinical researchers for generations to come.

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Clinical Aspects of Tardive Dyskinesia
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Aging and Tardive Dyskinesia

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Tardive dyskinesia, a syndrome of abnormal, involuntary body movements, is produced by administration of antipsychotic drugs. The movements can involve the face, lips, jaw, tongue, neck, trunk, upper extremities, and lower extremities. Less obvious internal body regions can also be involved, such as the muscles of respiration. “Dyskinesia” is a generic term, referring to excessive or abnormal movements of any etiology or character. Historically, it has been used predominantly to refer to choreoathetoid-type movements; more recently it has also been used to include tics, dystonia, akathisia, myoclonus, and ballismus. Although tremors are also, by definition, abnormal movements, they have traditionally been recorded as a separate form of movement disorder. When an antipsychotic drug is believed to be the cause of the dyskinesia, the term “tardive” is employed. When an antipsychotic drug is implicated in the appearance of tremors, the term “drug-induced parkinsonism” is used. In general, it has been the rule that at least 3 months of neuroleptic treatment should precede any attribution of these drugs as causative agents in the development of tardive dyskinesia (Schooler & Kane, 1982), although recent work with older individuals suggests that shorter exposure times may be sufficient. The abnormal movements themselves can be distinguished phenomenologically by their rhythmicity, speed, and repetition, as well as by the presence or absence of sustained postures at the termination of the movement. Combinations of different movements are frequently seen, with parkinsonism, choreiform dyskinesia, and akathisia being among the most common in elderly patients. Generally, the movements do not occur during sleep, and frequently they are exacerbated by anxiety and stress.

Many different rating systems have been used to document the location and character of abnormal involuntary movements; none, however, can be diagnostic without a family history and concurrent medical, neurological, physi-