Experimental Neurological Syndromes and the New Drug Therapies in Psychiatry

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CONSIDERING the fact that encephalitis lethargica practically disappeared before its virus was identified, the disease would have been important only out of historical interest and also because of the progress in neurology which it led to. However, the illness developed fresh significance as result of the striking similarities which exist between the sequelae of the disease and the nervous syndromes induced, in reversible and almost experimental fashion, by those drugs which we call “neuroleptics.” Somnolence or changes of the sleep pattern, modifications of psychomotility and of the neuromuscular tonus, and production or reduction of abnormal mental phenomena are the three factors common to the action of neuroleptic agents and to the pathology of encephalitis which we will consider in their mutual relationship.

Ever since we first, in 1952, together with Jean Delay, experimented with Chlorpromazine, we have observed that this drug produces a very unique syndrome of psychomotor indifference which is today generally known. Since then we found in the literature a very similar condition, described under the name of “Syndrome akinetique sans hypertonic” (akinetic syndrome without hypertonia) by J. Lhermitte in his 1923 report on sequelae of encephalitis lethargica. If one compares this description with the one of the effects of chlorpromazine given by us, one might almost get the impression that one has been copied from the other. From the fact that this condition is not yet accompanied by hypertonia, the author infers that the akinesia of the patient suffering from parkinsonism is more than anything else a disorder of psychomotility. At the same time, he stresses the generalized slowing of motion (bradykinesia), the loss of natural associated movements, the condition of “dénervation musculaire” (difficulty of relaxation of antagonists), the micrography (again found in patients treated with neuroleptic drugs) and “fastrénie” (low energy level). Since, however, his patients were “turned into stone” in an attitude of complete indifference or stupor and had lost all initiative and all movement, the syndrome of Lhermitte appeared more intense and severe than the condition usually observed with neuroleptics. Today, of course, we possess new, more powerful neuroleptics which can, in a few hours, produce the akinetic syndrome in all its intensity.

The psychiatric application of reserpine, on the other hand, with indications almost overlapping those of chlorpromazine, became known in 1954. Although the administration of reserpine is followed by asthenia rather than indifference, its different and at times opposite autonomic actions have effects upon the same functions and are also important. Similarities between the two drugs

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seemed even more striking when H. Steck23 described the possibility of *therapeutic parkinsonism* with both these drugs and at the same time stressed that the clinical picture resembled that of postencephalitic parkinsonism. He remarked upon the frequency with which reserpine produced motor-instability syndromes, characterized by inability to remain motionless and by increased need for motion. This syndrome had already been described under the name of *Akathisia* (inability to sit still) and *Tasikinesia* (tendency to move) by A. Sicard24 in 1933, in patients suffering from postencephalitic parkinsonism. Sicard also stressed the high incidence of insomnia in these syndromes.

In 1955, together with Professor Delay,6 we placed chlorpromazine and reserpine, drugs of very different chemical constitution, under the common term of “neuroleptics.” We felt that, since their analogies of action, namely calming the agitated patient, restoring the awareness of the confused one, and facilitating the contact of the schizophrenic patient, were greater than their differences, they should not be regarded as simple tranquilizers.

The first international conferences concerned with reserpine and chlorpromazine were held in Italy and France in 1955. The electromyographic analysis of rigidity and tremor led H. Hoff,17 as well as J. Delay and myself,7 to interpret these symptoms as being somewhat different from those occurring with parkinsonism. Zambianchi,29 however, maintained that the neuroleptic symptoms and those associated with parkinsonism were identical, possibly because he had observed patients in a different stage of drug therapy. In general, the authors agreed with Belloni and Berlucchi1 that the therapeutic syndromes were closer to postencephalitic parkinsonism than to paralysis agitans of Parkinson. Freyhan,16 on the other hand, who made a special study of the incidence of these complications, concluded that they depended less on the dosage and the duration of treatment than on the individual response of the subject. The incidence of characteristic neurological syndromes, however, has greatly increased since the more potent phenothiazines became available. Finally, Fluegel,15 in an effort to obtain better therapeutic results, proposed his method of systematically producing the syndrome of parkinsonism by rapid increase of the dosage of chlorpromazine and reserpine.

After 1955, we witnessed the rapid multiplication of drugs called “ataraxics” and “tranquilizers,” whose efficacy in relieving psychosis was by no means comparable to that of the neuroleptics. This led us to establish clear distinctions between the two types of drugs and for this reason it was necessary to define exactly the meaning of the term neuroleptic. Of the distinctive criteria which we have specified,1 and which have been generally accepted, the characteristic neurological changes must be regarded as being most important.

In 1957, when only drug-induced akinesia, the parkinsonism-like syndrome or the syndrome of parkinsonism, states of akathisic overactivity and oculo-gyrice crises were known, experimentation with a new phenothiazine containing the piperazine ring—prochlorperazine—gave rise to a peculiar complica-
tion: attacks of trismus, suggesting a diagnosis of tetanus and attacks called “hysterical” or “hysteria-like” by the early observers who had seen them either in neurotic patients or in subjects hardly suspected of hysteria. In view of our interest in these phenomena, we resumed a study at the University Hospital in Paris and quickly found that we were dealing with manifestations already described as part of the “syndrome excito-moteur” of postencephalitic patients by Pierre Marie and Miss Levy, and by Marinesco et al., in the perspective of “organic” hysteria. The trismus, sometimes violent, but always reducible by will power and suggestion, is part of the “syndrome linguo-facio-masticateur” of Pierre Marie and G. Levy, characterized by involuntary opening of the mouth, movements of the lower jaw and tongue and by various types of protrusion of the lips. These, moreover, have been described under the name of “oral syndrome” by Kulenkampff and by Eicke, the latter noticing the effect of suggestion upon these manifestations. The phenomenon of lingual protrusion seems relatively rare in neurology, but has been described by André Thomas, by J. Lhermitte and by others in patients who suffer from postencephalitic parkinsonism. With prochlorperazine, the oral syndrome is often associated with oculogyric crises, with attacks of spasmodic torticollis or retrocollis, which might extend to the spine and to the limbs in the form of attacks of opisthotonus. The “syndrome excito-moteur” also includes the various types of tremors, jerky movements, akathisia, tachikinesia and the choreoathetotic phenomena.

More unusual are the attacks of emprosthotonus and of “bradykinésies de salutation” (chorea salutans), manifestations which, alternating with those just cited, help to give the inexperienced observer the impression of conversion symptoms or of simulation. One notices veritable hysteriform attacks, with arching of the back, rolling movements of the eyes, with rigidity and muscle fasciculation of the limbs, phenomena which disappear temporarily under the influence of counter-suggestion but reappear later on, for as long as the drug action persists. It will, in fact, be noticed that these attacks, which can appear under the influence of emotional stress (in one case at the moment when the patient heard about her husband’s infidelity) or at the sight of other patients with similar attacks, occur only under the influence of the drug, if given in critical dosage, and disappear when the drug is withdrawn. Their authenticity is furthermore documented by accompanying, often asymmetrical, changes of reflexes and tonus. It is interesting to relate hysteriform attacks induced by Prochlorperazine to hypertonic paroxysmal attacks, with deviation of the head and of the eyes, with trismus, retrocollis, opisthotonus and rigidity of the limbs, described by Marinesco et al. in 1925 in patients suffering from postencephalitic parkinsonism. The Roumanian authors stressed the “wave-like mode of appearance,” and since they could be provoked and stopped by suggestion, related these attacks to organic hysteria. The mental condition of the patient during these attacks seems similar to what we have observed in our patients. Although suggestibility plays an important role, we could not find all the traits of the hysterical personality. Marinesco et al. described identical hysteriform attacks which
appeared as part of a familial disease in which they observed anatomical lesions located in the substantia nigra.

Other hysteria-like symptoms may be seen in patients treated with neuroleptics: forward flexions of the trunk or camptocormias were observed with chlorpromazine. With prochlorperazine we have noticed the distension of the abdomen similar to the "gros ventre hystérique" described in war neuroses, believed to be due to spasms of the diaphragm. There is much to be said about the differences between these hysteriform attacks and those of conversion hysteria. This has been the subject of a special study. The presence of autonomic manifestations, of suggestibility, of narrowing of the range of awareness and of impaired volition, as observed during the dyskinetic phase, thus produce a state of experimental neurosis.

In studying the excitomotor syndrome as induced by prochlorperazine, we observed that on the day following the attack, spectacular mental improvements occurred which led us to believe that the drugs with "hyperkinetic" action had therapeutic indications which differed from those of other neuroleptic compounds. In 1957, we began to establish separate indications for reserpine and chlorpromazine in the treatment of schizophrenia. In schizophrenic states characterized by deficit symptoms, reserpine seemed more effective than the phenothiazines. In contrast to chlorpromazine, reserpine produces tremor early, parkinsonism is apt to be more severe and akathisia more frequent.

It therefore seemed feasible that neuroleptics which produce hyperkinesia might have different therapeutic indications from those which produce akinesthesia. To test this assumption more thoroughly, we requested that a new neuroleptic drug, a phenothiazine containing the piperazine ring and the sulfamide group (preparation R.P. 7843)* be placed at our disposal.

Investigation of this drug in the laboratory showed that it had almost no effect upon conditioned reflexes, but produced, with utmost frequency and intensity in minimal doses, animal catalepsy, tremor and even hypertonia, phenomena indicative of drugs which are liable to produce neurological syndromes in men. Furthermore, though reproduction of parkinsonism in monkeys is difficult to achieve, phenothiazine sulfamide produced in the macaca excitement states associated with incessant chewing, a condition related to the "syndrome excito-moteur linguo-facio-masticateur."

It seems that our expectations have been fulfilled. Phenothiazine sulfamide represents a major neuroleptic since it produces with great rapidity and intensity the syndromes which we consider to be characteristic of the action of this type of neuroleptic drugs. It should prove therapeutically advantageous because of the power and speed of its action and because of its efficacy in certain cases which have not responded to previously used neurolep-

*Editor's note: This compound is known in the United States as SKF 5883, or Vontil. It has been made available by the Smith, Kline and French Laboratories to various clinical investigators. Preliminary reports have already been published in this country.
tics.\textsuperscript{11} But to stay within the limits of the scope of this report, we will not go beyond a discussion of the neuroleptic manifestations of the drug.

\textit{Syndrome of akinesia without hypertonia.---}The new compound reproduces quite promptly the akinetic syndrome of Lhermitte and with maximal intensity as compared to chlorpromazine. The patients look as if they had been turned into stone, they are usually indifferent towards themselves and their environment, they are stuporous or prostrate, even before the clinical symptom of hypertonia appears. Lhermitte has commented on the "aptitude catatonique" of patients thrown into this state. Nobody has ever been able to reproduce, in men, with neuroleptics alone, experimental catatonia, but under the influence of phenothiazine sulfaamide, we have witnessed the reinforcement of catatonic states and the appearance of catatonic symptoms in schizophrenics who did not show them before.

\textit{Excitomotor syndrome.---}The various types of dyskinetic and hyperkinetic manifestations which are part of the excitomotor syndrome of P. Marie are seen with utmost frequency. Whereas one may observe them in only one out of six or seven patients treated with prochlorperazine, they are found in almost 50 per cent of cases treated with phenothiazine sulfaamide. However, by virtue of their very intensity, they give a truly "neurological" picture and there is, in spite of the fact that these attacks remain responsive to counter suggestion, no further danger of confusing them with hysterical disorders. The neurologic syndromes which the drug produces develop in a more or less constant order: the excitomotor period usually denotes the transition from the akinetic into the hyperkinetic phase. Neurologists who have described the sequelae of encephalitis have already noticed that excitomotor phenomena occur frequently as the prodromes of the syndrome of parkinsonism.

\textit{Akinetic-hyperkinetic syndrome.---}Parkinsonism appears very early, usually a few days after the initiation of therapy. The first sign of hypertonia is the exaggeration of the tonic biceps reflex. Then the syndrome develops rapidly and reaches an intensity comparable with that of the most severe forms of postencephalitic parkinsonism. The subject looks as if he had been welded together and is no longer able to get out of bed. In many instances, hypertonia is most marked in the muscles of mastication, and feeding, already impeded by the excessive salivation, is greatly interfered with. It is then necessary to withdraw the drug and this permits us to convince ourselves of the complete reversibility of the symptoms and to observe the therapeutic effects which now appear. Treatment may be repeated several times, according to the technique of \textit{interrupted neuroleptic therapy} which we have proposed for this drug.\textsuperscript{12}

\textit{Hyperkinetic hypertonic syndrome.---}In the course of the state of parkinsonism, we frequently observe the appearance of intense taskinesia (need for movement). This gives the subjects a very peculiar appearance because of their extreme rigidity. One can see them on the ward walking incessantly and with short steps, and following each other like a group of automatons arranged in a circle. This syndrome is very characteristic of the new drug.

\textit{Autonomic syndrome.---}Pulse, arterial blood pressure and temperature are
not much affected. Sweating, on the other hand, is very profuse, and can become as intense as in Sakel's insulin coma therapy. It is accompanied by oliguria without signs of renal dysfunction. One also sees marked salivation, a very intense seborrhoea and edema of the face. All this together with the previously mentioned rigidity gives the patient's face a very characteristic appearance.

Psychic syndrome.—Regardless of the kind of mental state prior to treatment, phenothiazine sulfaamide produces specific modifications which, *grosso modo*, parallel the development of the psychomotor syndromes as shown in table 1.

From the therapeutic point of view, the first results which we published are interesting because the improvements were obtained in chronic cases resistive to other therapies, and more particularly in very longstanding cases of schizophrenia with pronounced deficit symptoms. They responded very favorably. We furthermore found that the drug effectively and with remarkable speed terminated excitement states.

Finally, we found that, for the first time, a neuroleptic drug produced true

| Table 1 |
|-----------------|-----------------|
| **First 48 hours** | **After 48 hours** | **Throughout the course of therapy.** | **Following discontinuation of therapy (2 to 6 days).** |
| Subject "petrified." Loss of initiative. No sign of hypertonia. | Parkinsonism of increasing intensity | Excessive perspiration and salivation, seborrhoea, mild bradycardia and hypotension. | Progressive disappearance of symptoms |
| 2. *Hyperkinetic syndrome.* | 4. *Hyperkinetic-hypertonic syndrome.* | **Indifference syndrome with mutism,** which can progress towards sudden emotional "sideration" (accentuation of pre-existing catatonia). | Syndrome of *euphoria,* usually mild, |
| Exitomotor crises of mouth, neck, generalized, etc. | Overpowering need to walk combined with the rigidity of an automaton. | Severe uneasiness with anxiety attacks. Responsiveness of the motor disorders to counter suggestion. | in depressed patients may even lead to inversion of the mood level. Maximum therapeutic effects. |
| (in one half of all cases) | | | |
reversals of the mood level in depressive states with post-therapeutic hypomania (can be the case with ECT).

The similarities between those syndromes induced by neuroleptics and those of von Economo's disease are found mainly in those manifestations which have just been considered. Convulsions may occur with reserpine or chlorpromazine, but their similarity to postencephalitic epilepsy remains obscure in the absence of comparable EEG findings. Paralyses, and more specifically ocular paralyses, have never been caused by neuroleptic agents. Autonomic changes, on the other hand, and endocrine-metabolic disorders present definite similarities. While the respiratory rhythm is not changed by neuroleptic drugs, pulse changes, arterial hypotension and obesity, for instance, constitute secondary manifestations in both encephalitis and neuroleptic treatment.

From the psychic point of view, one may consider as diametrically opposed encephalitis which produces mental disorders, and the neuroleptic agents which reduce psychotic syndromes. We may recall that lethargic encephalitis caused confusional and hallucinatory syndromes which are specifically mitigated by neuroleptics. Catatonic and hebephrenic-like states and actual postencephalitic dementia praecox have also been described. Whereas neuroleptic treatment has been more effective in paranoid than in catatonic and hebephrenic states, phenothiazine sulphamide, which tends to aggravate the catatonic state during the therapeutic course, may lead to an improvement after termination. We may recall in this connection the observation by Steck that schizophrenics improved after they had contracted lethargic encephalitis.

Von Economo's disease also produced mood disturbances characterized by manic excitement and various degrees of depression. Neuroleptic drugs, which actually represent the best therapy available for excitement states, are only of limited use in the treatment of melancholic states. Reserpine, as is known, can induce depressive states. As already mentioned, phenothiazine sulphamid is induces quite regularly a state of "moroseness," indeed melancholic sadness during the akinetic-hypertonic syndrome, whereas a true reversal of the mood level with hypomania can occur at the cessation of therapy. It seems, therefore, that in neuroleptic treatment we work with drugs which act upon the same centers and functional systems as does the encephalitis virus. Fortunately, the disorders of memory of the Korsakoff type as well as the sexual and behavioral disturbances which are observed in postencephalitic patients, do not have their counterpart among the effects of neuroleptic drugs, except, perhaps, for some favorable action in the treatment of certain antisocial psychopaths.

Before concluding, we must comment on the practical and theoretical implications of the analogies which have been elaborated. First of all, we can say that the occurrence of the various types of psychomotor disturbances, according to the drug employed, contributes to a classification of the different neuroleptic compounds. Thus, one can distinguish between those substances which, like chlorpromazine, produce mainly akinesia and bradykinesia, and
those which, like phenothiazine sulfamide, produce maximal incidence of excitomotor symptoms. The distinction between two types of secondary action makes it possible to arrange the available neuroleptic drugs into the following groups: phenothiazines which produce akinesia and have mainly sedative effects, like chlorpromazine and levomepromazine; phenothiazines which produce hyperkinesia and stimulation, like prochlorperazine and phenothiazine sulfamide; reserpine occupies an intermediate position.

This classification is useful in as far as therapeutic indications are concerned. For a long time, we simply tried one neuroleptic drug after the other to find those to which each patient responded best. Today, one may logically choose drugs which produce akinesia for patients in whom excitement, agitation, and delirious and hallucinatory episodes predominate, whereas drugs which produce hyperkinesia will be preferable for withdrawn and underactive patients.

Can we explain the action of neuroleptics on the basis of an analogy with the encephalitis virus? This, of course, would not be tenable. The various compounds are chemically very different, but their mode of action seems to involve the same nervous structures. In the case of lethargic encephalitis, one finds: (a) extensive minimal lesions through the gray matter of the brainstem and especially the cortex; and (b) a special predilection for lesions in the meso-diencephalic centers.

We still have very little information about the histopathologic changes which are undoubtedly produced by neuroleptic drugs. However, the experiments of Waze et al., concerning the cerebral distribution of labeled chlorpromazine, indicate that the substance at first diffuses into the whole brain, then accumulates selectively in the hypothalamic area. We are indebted to Cazzullo for the first pathologic-anatomic investigations of the action of reserpine and chlorpromazine. In animals which receive rapidly increasing doses of these drugs, he localizes lesions for the former drug predominantly in the diencephalon, for the latter drug predominantly in the mesencephalon.

Can one, on the basis of these still very fragmentary anatomic findings, return to “localization” hypotheses of psychiatry to find an explanation of the therapeutic action? We do not think so. With the advancing knowledge of the physiology of the subcortical systems and the reticular substance, knowledge which has accumulated since the beginning of this century, we are compelled to admit that certain neuropsychic functions are mediated by these systems: the functions of sleep and of wakefulness and, no doubt, the equilibrium of mood and temperament, functions which have been referred to as “regulation thymique.” The level of wakefulness and the basic instinctive tendencies seem to play a significant role in what Delay, after P. Janet, calls the mental tonus. When, as the result of prolonged neuroleptic medication, we see a change in a previously rigid system of delusions, it is really the patient’s increasing lack of interest and his loss of feeling for his delusional fantasies which account for the improvement.

Is the production of neurologic symptoms harmful or unimportant or is it, on the contrary, necessary for the efficacy of therapy? On the one hand, we
know that the therapeutic effects of neuroleptic drugs were confirmed already before the neurologic phenomena, which I referred to, were known. The secondary effects could, therefore, be considered as injurious since by virtue of being neurologic, they refer to a tissue substratum, assuming a more or less organic nature.

However, those of us who, like Fluegel, resolutely and systematically aim to produce neurological syndromes to get better results than can be obtained when neuroleptic drugs are given at less effective doses, find supportive evidence in our observations with this major neuroleptic drug, the effect of which, when given in small dosage, cannot be compared with its proven efficacy following the appearance of characteristic neurologic syndromes. If this can be confirmed, another aspect of the therapeutic action may have to be considered. The question arises whether, aside from the drug action on certain brain structures, a particular effect is achieved by the introduction of the experimental neurologic "disease." We know, for example, that the efficacy of malaria therapy, that is to say of experimental malaria, is different and generally superior to that of other pyretotherapies, limited to the production of artificial fever. Thus, one may ask whether the somatic disease may be necessary to cure the mental illness and, with J. Delay, reflect upon the fact that most successfully used biologic therapies in psychiatry produce artificial somatic diseases. Here belong insulin therapy, which induces repeated comas, Metrazol and electroshock which provoke "epilepsy," and finally the neuroleptic agents with their two varieties of reactions, akinesia or hyperkinesia.

Based on the extensive work with new chemotherapies since 1952, it can be said in conclusion that aside from laboratory investigation, simple clinical psychiatry and neurology are in a position to provide objective data, and that the classical neurological literature can illuminate pertinent problems in contemporary psychopharmacological research.

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