CHLORPROMAZINE: THE STORY OF PHENOTHIAZINE DERIVATIVES, THEIR CLINICAL INDICATIONS, THE INCIDENCE AND MANAGEMENT OF UNTOWARD EFFECTS, AND A PROPOSED RATIONALE OF ITS ACTION.

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My discussion will cover three aspects of the new pharmacological therapy of pathological changes in human behaviour. First, the story of the development of phenothiazine derivatives will be sketched out briefly. The second part will deal with the clinical indications for Chlorpromazine therapy which, to be sure, are often identical with those for Reserpine therapy. Untoward side-effects and clinical complications will be viewed with regard to their incidence and management, as well as certain new problems associated with pharmacological therapy. The last part of this discussion will attempt an integration of the neurophysiological action of Chlorpromazine with the goals of psychiatric therapy as a comprehensive approach to a human problem.

Phenothiazine, the parent substance of Chlorpromazine, is characterized by two six carbon rings joined by a sulphur atom on one side and a nitrogen atom on the other. The side chains in phenothiazine derivatives are attached to the nitrogen. It is interesting to note that methylene blue has a similar structure with side chains attached to two carbon atoms in symmetrical positions and a chloride atom attached to the sulphur. While methylene blue has an oxidizing action in the organism and phenothiazine is a reducing agent, both methylene blue and its reduction products and phenothiazine and its oxidation products comprise a reversible oxidation-reduction- system.

Phenothiazine itself has no definite pharmacological action in man except as an anthelmintic and it has also been used briefly as a urinary antiseptic. It has a toxic action on parasites but unfortunately also on red blood cells and because of the observation that large doses of phenothiazine may produce hemolytic anemia, phenothiazine is now only used in the treatment of helmintic infestations in domestic animals, according to Goodman and Gillman.

In the closing years of the Second World War, various phenothiazine derivatives were examined independently in the United States and in France. The hoped for anti-malarial properties of these phenothiazine derivatives, however, did not materialize and the study of these chemicals was discontinued in America. In France, the remarkable anti-histaminic properties of some of these compounds were discovered, in particular, of the compound promethazine (Phenergan).

Later the vagolytic properties of diethazine (Diparcol) were discovered and its excellent effect in the treatment of Parkinsonism.

It soon became evident that these products seem to have a direct action on the central nervous system although it was by no means easy to analyze this particular central action. Promethazine (Phenergan), for instance, has a strong hypnotic effect in humans but acts as a stimulant in small animals (rats).

Finally in 1950 Laborit, doing experimental work in anaesthesia in France, prompted a systematic study of the various phenothiazine amine derivatives with the aim of obtaining a product with the strongest action on the central nervous system regardless of its anti-histaminic activity.

In the course of this search, the product 3276 RP was developed in the Poulenc laboratories and observed to have a strong central activity and minimal anti-histaminic activity. This preparation under the name of promazine has recently been studied clinically in the United States. In the Poulenc laboratories, too, a chlorophenothiazine had been developed and the same side chain was attached to it resulting in chlorpromazine which proved to have a number of outstanding properties in the pharmacological laboratory as well as in the clinic.

While Laborit had prompted the development of chlorpromazine in his search for an anti-shock agent, to prevent and counteract surgical shock, Delay and Deniker applied the drug in the treatment of psychiatric conditions, particularly those characterized by psychomotor excitement and were soon able to report excellent therapeutic results.

It would be intriguing to speculate on the significance of the fact that three of the four most effective somatic therapies in psychiatry were shock treatments, namely, malaria fever therapy, insulin coma, and electroconvulsive shock treatment, while the fourth major development in the somatic therapy of psychiatric disorders is based on the application of a shock preventing agent.

The first clinical workers using chlorpromazine were impressed by its unique sedative action which reduced even the most severe psychomotor excitement without producing clouding of consciousness and/or emotional disinhibition. Psychomotor excitement as found in manic states, catatonic excitement, and acute panic states, has remained among the principal indications for chlorpromazine. Other indications comprise those emotional and mental disorders which are characterized by excessive anxiety or aggression even without accompanying motor excitement. More generally, all psychiatric conditions characterized by emotional turmoil would fall into the therapeutic spectrum of chlorpromazine.

It is generally agreed, however, that in depressive states, chlorpromazine is of limited value. It sometimes seems to increase the depression although associated motor agitation may be improved.

Since most acute psychotic breakdowns are characterized by emotional turmoil, it was not too surprising to discover that acute schizophrenic episodes would respond to chlorpromazine. It was hard to believe, though, that the drug would have an effect on long established paranoid states, that it could "dissolve" fixed delusional systems, and it was least of all expected that the drug might have any effect in long standing quiet and apparently apathetic schizophrenics. Nevertheless, within the last three years, countless clinical observations in all parts of the globe have confirmed the therapeutic effectiveness of chlorpromazine in many paranoid conditions and its unexpected therapeutic action in a number of inert chronic "back ward" cases.

This may be the time to ask ourselves which are the essential new clinical results that chlorpromazine - and almost simultaneously, Reserpine - has brought into psychiatry. There are four such new results which could not previously be obtained by means of physical therapy: the first result is the shortening of the time required for the hospitalization of a number of psychotic patients. Whether chlorpromazine is used by itself or in combination with other physical therapies, we have been able to show in a statistical analysis of cases with histories of previous hospitalizations that chlorpromazine often shortens the time of hospitalization by 50%. The second new result appears in the fact that acutely psychotic patients can now be rendered accessible to psychotherapy and responsive to constructive influences emanating from the therapeutic milieu within a much shorter time than was previously possible. The third new result appears in the remissions of some deteriorated long term psychotics who had remained refractory to the shock therapies.

The fourth new result can be found in the possibility of establishing maintenance therapy with a pharmacological agent for psychotics whose social remission and adjustment to the community can be maintained as long as they continue to take the drug.

None of these results could be obtained with other physical treatment methods but we should not forget that all of them could have been produced by psychotherapy. The shortening of the patient's time in the hospital, making him more rapidly accessible, producing remissions in long standing deteriorated psychotics, and maintenance therapy of precarious border-line cases in the community - all this could be achieved by an experienced, skillful, and devoted psychotherapist given unlimited time and almost inexhaustible financial resources.

The hitch, of course, lies in these qualifications. There are very few highly experienced, skillful and devoted psychotherapists and even fewer patients with unlimited time and financial resources. There are, however, hundreds of thousands of psychotics who require these therapeutic results. The principal advantage of the new drugs in psychiatric treatment consists in a saving of some of the excessive demands on human time and labour which made psychotherapy in psychotics almost impossible in practice. It cannot be stated strongly enough that the resources of psychotherapy, occupational therapy, recreational activities and of the whole therapeutic milieu are needed more than ever if we want to take full advantage of this new pharmacological aid in psychiatry. Yet it is no longer necessary to spend many days, weeks or months at the expense of tremendous personal effort on the part of the therapist in order to produce small improvements in the patient's behaviour or emotional responsiveness. One might say that the new drugs have enabled us to establish a bridge head deep in the territory of the psychosis from where we can deploy our other therapeutic weapons.

The experience of most psychiatrists has been that chlorpromazine and reserpine seem to produce more spectacular results in the hospitalized patient than in the ambulatory patient. Therapeutic results with stimulating drugs such as the amphetamines, meratran, etc. are as a rule more effective in ambulatory patients than in those who are hospitalized. In this connection, we may remember, that the restraining influence of the tranquillizing drugs is more compatible with the situation of confinement in a hospital with limited outlets for contact and communication while the exciting action of stimulating drugs finds more appropriate expression in a setting where the patient is in no way confined.

Chlorpromazine is often very effective in the treatment of anxiety states in private psychiatric practice but one cannot rely on its action as a substitute for psychotherapy.

We have learned a great deal during the past four years about untoward side-effects and complications associated with the administration of chlorpromazine. Orthostatic hypotension and drowsiness are undesirable side-effects which usually disappear after the drug has been given for several days. Parkinsonism - or as some investigators claim - a pseudo-Parkinsonism develops in 10 to 15% of patients who receive large doses over several weeks or longer. Jaundice due to bile stasis but without hepato-cellular damage may occur in 1 to 1.5% of cases while the incidence of agranulocytosis is estimated at 1 in 50,000. Perhaps the most bothersome side-effects are sensitivity reactions which usually appear as a variety of skin manifestations, rashes, edema, itching, photo sensitization, etc. Their incidence is probably in the order of 10 to 15%.

Fortunately, most of these complications are not dangerous and easily reversed. The extrapyramidal syndrome with Parkinsonian symptoms usually disappears within a week after the drug has been discontinued although in a few cases, symptoms have been observed for as long as two months. We have found that reduction of the dosage and simultaneous administration of an anti-Parkinsonian agent such as diparcol, are often helpful.

If jaundice occurs, the drug should be discontinued immediately and no other specific therapy is required. Sometimes bile in the urine or a rapidly rising alkaline phosphatase level in the serum are warnings of the threatening impairment of liver function.

We have been fortunate in not having seen any case of agranulocytosis. This complication, if not discovered early and treated energetically with antibiotics, may be fatal. Several workers have reported good results with the addition of ACTH or cortisone to the antibiotics. Most important is the early diagnosis of agranulocytosis which means that any sore throat in patients who have been receiving the drug for some time should be carefully investigated. It is not practical, as has been pointed out by several authors, to do regular blood counts on all patients who receive chlorpromazine since the incidence of this complication is so low and blood counts would have to be done almost daily if they were to be used as an effective safeguard.

The various skin manifestations usually respond to anti-histaminics and discontinuation of the drug. Strangely enough, they often disappear spontaneously even when the drug is continued.

It is probably best to reduce the dosage for a few days if sensitization symptoms appear and if there is no improvement, the drug should be discontinued completely until all symptoms have disappeared. It may then be started again and in many cases, there will be no repetition of the skin manifestations. In one very stubborn case where the patient reacted with sensitization symptoms to almost any drug including anti-histaminics, and at the same time was in great need of chlorpromazine therapy, we were successful in suppressing all skin manifestations by giving 50 mgms of cortisone twice daily during the time of chlorpromazine administration.

Chlorpromazine lowers the convulsive threshhold and this has to be taken into consideration when the drug is given to epileptics. It may be necessary to increase the anti-convulsant medication but in many cases, this is not necessary. The need for anti-convulsant medication may even be decreased. This latter effect may be explained by the fact that the convulsive threshhold depends not only on physiological and pharmacological factors but also on the patient's emotional state. The dampening of emotional excitement by chlorpromazine and the resulting rise of the convulsive threshhold may outweigh the pharmacological lowering of the threshhold due to the drug.

Some new and special problems have arisen with the widespread use of chlorpromazine and drugs which are related to it in their action. One problem is our peculiar indecision to settle on a generic name for these drugs. They have been referred to as ganglioplegic, neuroplegic, neuroleptic, neurotropic, phrenotropic, antipsychotic, ataraxic, and tranquillizing drugs (I am sure this list is not complete!). All of the drugs belonging to this particular pharmacological class have in common their sedative action and the absence of clouding of consciousness and emotional disinhibition.

Since chlorpromazine was the first drug which was systematically studied in this respect, one could conceivably speak of drugs with chlorpromazine-like action just as we speak of drugs with atropine-like or muscarine-like action, etc. (and now I have added another name!).

A minor problem is developing among some psychiatrists and psychiatric nursing personnel who, since the advent of the new drugs, have become "spoiled" and are no longer able to tolerate any kind of acute excitement or emotional tension in their patients. We witnessed a similar phenomenon when after a few years of convulsive therapy our young psychiatrists and psychiatric aides found it extremely difficult to deal with a deeply depressed patient for longer than a day or two.

A sociological phenomenon which now is observed more frequently than before presents a more serious problem. I am referring to the difficulties faced by families who have been accustomed for years to consider their relative as chronically and incurably mentally ill, and who now, sometimes after ten or fifteen years, are asked to take the patient home after he has improved considerably, sometimes to the point of almost complete remission following chemotherapy. Here again we can find a parallel in the problems that arose when prefrontal lobotomies restored a number of chronic patients to the point where they could function in the community.

Another problem facing the clinician at present is the choice of the drug to use in the treatment of his patients. New drugs for psychiatric chemotherapy are constantly being developed and advertised and the psychiatrist has to decide whether he should choose his drug on the basis of pharmacological action, clinical reports, or the economic status of his patient.

At this point, I should like to emphasize that we need to have considerable respect for the clinical experience we have gained over a period of time with a particular therapeutic agent, in this case, a particular drug. A clinician who has two years extensive experience with one drug will usually be able to succeed better with it than with another drug which may have certain advantages but lacks the advantage of being intimately known to the clinician. In the complex field of psychiatry, we have to draw on all our resources that enable us to individualize with regard to dosage, subjective and objective management of side-effects, evaluation of therapeutic timing of therapy, etc.

Let us now turn to the questions which have haunted all of us since these intriguing new drugs have appeared in the field. What is the rationale of this therapy? What is the mechanism or the dynamics of their action? One can be surer about some negative aspects of these questions. We know that the therapeutic effect of chlorpromazine in psychiatric patients is not due to shock nor sleep nor hibernation, although like all of these, the action of chlorpromazine is almost certainly an unspecific one. Some have been tempted to speculate on a specific chemotherapeutic action of chlorpromazine and similar drugs, thinking that they might counteract or compensate for certain metabolic deviations which were considered to be the cause of the psychotic symptoms. However, the drug's effectiveness in a wide range of mental and emotional pathology comprising a great variety of diagnostic entities seems to rule out such a specific action of chlorpromazine. It is specific only with regard to its psychological effects.

One wonders if the very pronounced adrenolytic action of chlorpromazine is essential for its therapeutic effect. Some of the other tranquillizing drugs do not have this property and it remains to be seen whether they will be as effective as chlorpromazine over a period of time and in severe mental disturbances. In conditions where anxiety plays an important role, an excessive output of adrenalin with its corresponding physiological and psychological disturbances may be expected so that an agent that can counteract these disturbances would appear desirable.

The arousal reaction, that is the diffuse and sustained mobilization of the whole cerebrum following any particular stimulus, is suppressed by chlorpromazine which allows the stimulus to pass and be registered, but dampens any subsequent reverberations at the cortical level. This action has been demonstrated in animal experiments and is probably also taking place in human subjects.

We may conceive of emotional and mental abnormalities as the results of disordered cerebral reverberations which are self-perpetuating and periodically reinforced by external stimuli of a disturbing nature. Such neurophysiological disorder would necessarily interfere with the smooth functioning of those cerebral processes that we assume to be the physiological substrate of ego functions.

Chlorpromazine has been shown to suppress the activity of the reticular activating system and more particularly, the hypothalamus without significantly interfering with cortical processes. By reducing the overwhelming influx of disturbing stimuli from the reticular activating system which plays a strategic role in the regulation of affective and motor impulses,

chlorpromazine stabilizes those neurophysiological processes which are essential for the functions of the ego. As anxiety is diminished, the need for defense against anxiety (is also reduced. This concept of a reduction of the need for defense against anxiety) can be considered as a key stone in a theoretical rationale of the action of chlorpromazine, and other drugs which are similar in their action. In this manner the often dramatically rapid action of chlorpromazine in acute psychotic states may be explained but also its effect in chronic, apparently apathetic, psychotics.

We have recently become very cautious in designating the emotional state of certain chronic schizophrenic patients as apathy. The unexpected therapeutic results after several months of chlorpromazine medication in some of these cases have led us to believe in retrospect that what we thought to be indifference was really a defensive withdrawal from anxiety producing situations - an active defense and not a passive defect.

I have no doubt that there exists such an entity as schizophrenic defect but I very much doubt that it is easy to distinguish such a state from that of an ongoing active schizophrenic defense. Chlorpromazine and similar drugs may have enabled us to refine our diagnosis of some chronic psychotic patients through therapeutic trial with the drug.

In neurophysiological terms, it can be stated that chlorpromazine inhibits the desynchronization of cerebral rhythms. In clinical language, the action of the new drugs is described as tension-reducing and sedative without interfering with emotional control or rational functioning. Using the terminology of psychoanalysis, we may describe the action of chlorpromazine as ego supportive, and we may compare its effect on human behaviour to the effect of one particular dynamic defense, namely, isolation,

which enables an individual to maintain full ego control under stressful conditions through the blocking of threatening or otherwise disintegrating impulses.

During the next few years, we will be faced with the task of working out a system of concepts that will allow us to bring together physiological facts, clinical observations, and psychodynamic theory, as they refer to the action of any drug which is studied for its effect on human behaviour.
