nitrite Cholografin would enable the physician to look for functional disturbances in disease of the hepatobiliary system, such as biliary dyskinesia.²

When Cholografin fails to visualize the biliary ducts, one should look for the following points: (1) Hepatic disease, or a biliary obstruction which is complete or nearly complete; in such a case the agent is excreted through the kidneys (2 of our cases). (2) Radiological technical deficiencies. Sometimes we have been unable to demonstrate why the opacification did not occur. In such a case we kept in mind the possibility that the contrast agent did not remain in the biliary tract but went directly into the duodenum through an open sphincter of Oddi.

SUMMARY

A new contrast agent (Cholografin) for the opacification of the biliary tract presents the following advantages:
1. Opacification of the hepatic and the common duct, even in cholecystectomized patients.
2. Good tolerance and low toxicity.

3. Elimination of all factors in administration and absorption leading to uncertainty.
4. Opacification of the gall-bladder, of which the concentration capacity is poor.
5. Possibility of information on biliary dyskinesia.

REFERENCES

85 rue Ste-Anne, Quebec.

RéSUMÉ
Les auteurs rapportent les résultats obtenus dans une série de 21 cas où ils ont utilisé une nouvelle substance de contraste permettant de montrer les voies biliaires à la radiographie. Cette préparation, le Cholografin de E. R. Squibb & Sons, est administrée par voie intraveineuse et offre les avantages suivants:
(1) faible toxicité et bonne tolérance;
(2) opacification des voies biliaires, même chez les patients cholecystectomisés;
(3) possibilité d'opacification d'une vésicule biliaire perméable mais qui a perdu son pouvoir de concentration;
(4) possibilité d'étudier le fonctionnement pathologique des voies biliaires en associant ce procédé d'opacification avec l'emploi d'agents pharmacodynamiques. M.R.D.

THERAPEUTIC RESULTS WITH CHLORPROMAZINE (LARGACTIL) IN PSYCHIATRIC CONDITIONS

H. E. LEHMANN, M.D., Montreal

A number of reports on the therapeutic effects of chlorpromazine (Largactil) have been published in the last three years. The drug has only recently been introduced into Canada from France where the original experimental work on its action was carried out. We started using chlorpromazine at the Verdun Protestant Hospital in May 1953, and our first clinical results in 71 cases have been reported in a previous publication¹ where further references to the pertinent literature and an analysis of its psychological action can be found. Our material has now increased considerably and the following is a report on our experience with the first 283 cases treated with the new drug. Winkelmann² and Kinross-Wright³ have recently reported their results with chlorpromazine therapy in neuropsychiatric patients from two centres in the United States. In a recent issue of this Journal, Azima and Ogle⁴ published their experiences with the drug in the treatment of mental syndromes.

Chlorpromazine is a phenothiazine derivative which is chemically closely related to the antihistaminic Phenergan (promethazine B.P.) and to Diparcol (dithazine) which is employed in the treatment of Parkinsonism. Chlorpromazine is known under the proprietary name of Largactil¹ in Canada. It is called Thorazine in the United States and Megaphen in Germany. Discovered in France, it was first studied by French investigators who noted its remarkable potentiating action when given in combination with anaesthetics, analgesics, narcotics or sedatives. Laborit⁶ worked out a technique of "hibernation treatment" in which chlorpromazine in combination with sedatives and physical cooling methods produces a state of anaesthesia characterized by lowered body temperature and decreased metabolism.

PHARMACOLOGICAL EFFECTS

Chlorpromazine has mild antihistaminic properties, a moderate parasympatholytic action and pronounced sympatholytic effects. In human subjects, it lowers the sympathetic and diastolic blood pressure, which is in keeping with its hypothermic effect. It lowers the systolic and diastolic blood pressure, which is in keeping with its hypothermic effect.
pressure. It acts on the central nervous system in a specific manner by producing inhibition of motor, autonomic and affective functions without clouding of the sensorium or gross reduction of intellectual efficiency. A patient under the influence of chlorpromazine will be drowsy and may sleep lightly most of the time but he can be easily awakened, engage in rational conversation and will fall asleep again when not stimulated.

It is this selective inhibitory action on the central nervous system, in particular in the sphere of motor and emotional functions, that makes the drug interesting to the psychiatrist. In contrast to most of the other commonly used sedatives, chlorpromazine causes little depression of higher cortical functions, and it also differs in action from other sedatives in the absence of emotional disinhibition when small doses are administered. One practically never sees a patient who appears "drunk" after receiving chlorpromazine in the sense of presenting lack of emotional control. Chlorpromazine does not give rise to euphoria. Psychological tests demonstrated that reaction time and test performance based on the functions of memory and learning are usually not impaired by chlorpromazine, while the same functions tend to show pronounced impairment with barbiturates.

An analysis of the effects of chlorpromazine on the autonomic and central nervous system leads one to believe that at least one principal site of action is the reticular activating system of the brainstem. This system has recently been shown to be responsible for the regulation of wakefulness, attention, and motor initiative. Although Azima and Ogle point out that the cortical action potentials are left intact by the drug and interpret this as indirect evidence that the reticular activating system cannot be affected by it, we remain convinced that chlorpromazine becomes effective at the level of the mesencephalon and diencephalon, which are also the strategic structures for the regulation of autonomic responses and affective discharge.

**Symptomatic Effect in States of Psychomotor Excitement**

The drug is of great clinical value for the symptomatic control of virtually any state of psychomotor excitement. It is equally effective in manic states, catatonic excitement, depressive agitation, toxic delirium, epileptic clouded states, or hysterical excitement. In the latter it possesses distinct advantages over other sedatives, for instance, the barbiturates, because it does not produce affective disinhibition. Such disinhibition would reduce the patient's emotional control further with the apparently paradoxical effect of exciting instead of depressing the patient's psychomotor activity. We have found in chlorpromazine an almost foolproof pharmacological control of those states of violent excitement which sometimes prove refractory even to heroic doses of barbiturates, paraldehyde, or hyoscine. Since we have started to use chlorpromazine, it has not been necessary in a single case to resort to electroconvulsive therapy as an emergency measure for the control of acute excitement.

Because of the fact that the drug does not tend to increase mental confusion but often seems to counteract it, it is particularly useful in agitated conditions associated with organic cerebral disturbances. Although we agree with Azima and Ogle that no immediate beneficial effects on the expected confusion following single electroconvulsive treatments are produced by chlorpromazine, we have employed it to good advantage in patients who become unmanageable and aggressive during a course of electroconvulsive treatment. It gave excellent results in the treatment of lobotomized patients who became uncontrollably excited. In senile psychoses, both in senile dementia and cerebral arteriosclerosis, it has given most gratifying results when other methods of pharmacological sedation have failed.

The drug is also valuable in the management of behaviour problems in chronic psychotic patients, hitherto best managed with maintenance electroconvulsive therapy. Chlorpromazine can usually be relied on as a last resort when other measures have failed. The nursing personnel soon learned to appreciate its favourable effects, and the introduction of the drug has indeed changed the whole aspect of the acute treatment and observation wards through considerable reduction of noise and confusion, previously often associated with the management of acutely disturbed patients.

**Therapeutic Effect in Acute Psychotic Breakdowns**

The most promising application of chlorpromazine, however, seems to lie in the treatment of the manic phase of manic-depressive psychosis, in which the drug has been capable of bringing about a complete remission with-
in 40 days in 48% of our cases. In conditions of chronic manic excitement which have resisted a number of other therapeutic procedures, it often produces favourable results although the drug may have to be administered over a period of two or three months in these cases. Macchi, Manghi, and Saginario have failed to see any beneficial results in states of chronic mania but one may assume that they did not continue the treatment long enough.

We have found that a certain proportion of patients with acute psychotic breakdowns of different diagnostic categories which are associated with psychomotor excitement or pronounced emotional tension recover with chlorpromazine within an unusually short time without the help of insulin coma or electroconvulsive therapy. It is now our practice to administer chlorpromazine for two to four weeks to any patient suffering from an acute psychotic attack associated with excitement. Those patients who are not significantly improved during this time are then subjected to shock treatment if this is indicated. We have gained the distinct impression that the course of the illness is shortened even in those patients who require additional shock treatment following the use of chlorpromazine.

In a few cases we had good reason to believe that the prompt administration of chlorpromazine for a few days averted a psychotic attack in patients who had had previous psychotic episodes and were showing the typical prodromal symptoms.

Table I gives the diagnostic categories of our first 283 patients treated with chlorpromazine and the therapeutic results which were obtained. The number of patients with depressive, hysterical and anxiety symptoms is comparatively small in our material. The miscellaneous group comprises conditions of psychosis with mental deficiency, alcoholism, drug addiction, dementia paralytica, and ill-defined behaviour disorders of functional or organic etiology.

Table II is a breakdown of the 98 cases of schizophrenia treated with chlorpromazine with regard to the duration of their psychotic symptoms. It will be noted that complete recovery was obtained within 40 days of treatment in 28% of those patients whose symptoms had been present for one month or less. If the much im-

<table>
<thead>
<tr>
<th>TABLE I.</th>
<th>Recovered</th>
<th>Much improved</th>
<th>Improved</th>
<th>Controlled</th>
<th>Unimproved</th>
<th>Averted</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenic...</td>
<td>15 (15.3%)</td>
<td>7 (7.4%)</td>
<td>38 (38.6%)</td>
<td>26 (26.5%)</td>
<td>10 (10.2%)</td>
<td>2 (2.0%)</td>
<td>98</td>
</tr>
<tr>
<td>Manic. ..........</td>
<td>37 (48.0%)</td>
<td>9 (11.6%)</td>
<td>16 (20.6%)</td>
<td>11 (14.2%)</td>
<td>4 (5.6%)</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Depressed .......</td>
<td>1 (8.3%)</td>
<td>6 (50.0%)</td>
<td>7 (54.9%)</td>
<td>2 (15.0%)</td>
<td>1 (8.3%)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Hysterical ... ..</td>
<td>4 (31.0%)</td>
<td>3 (75.0%)</td>
<td>1 (25.0%)</td>
<td>3 (75.0%)</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety .........</td>
<td>1 (5.3%)</td>
<td>4 (40.0%)</td>
<td>3 (30.0%)</td>
<td>1 (10.0%)</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-ECT .......</td>
<td>2 (6.9%)</td>
<td>9 (31.1%)</td>
<td>16 (55.1%)</td>
<td>2 (6.9%)</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-lobotomy ...</td>
<td>2 (6.9%)</td>
<td>9 (31.1%)</td>
<td>16 (55.1%)</td>
<td>2 (6.9%)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epileptic .......</td>
<td>4 (16.0%)</td>
<td>3 (75.0%)</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senile ...........</td>
<td>1 (5.3%)</td>
<td>1 (5.3%)</td>
<td>11 (57.9%)</td>
<td>4 (21.0%)</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous ...</td>
<td>1 (5.3%)</td>
<td>1 (5.3%)</td>
<td>11 (57.9%)</td>
<td>4 (21.0%)</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recovered means cessation of all symptoms within 40 days.
Much improved means sustained reduction of symptoms within 40 days to the point where the patient may be discharged from the hospital.
Improved means sustained reduction of symptoms within 40 days but not to the point where the patient is able to leave the hospital.
Controlled means reduction of symptoms only for the duration of the treatment.
Averted means successful prevention of impending psychotic attack during the prodromal stage.

<table>
<thead>
<tr>
<th>TABLE II.</th>
<th>Recovered</th>
<th>Much improved</th>
<th>Improved</th>
<th>Controlled</th>
<th>Unimproved</th>
<th>Averted</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute schizophrenia...</td>
<td>15 (27.9%)</td>
<td>6 (11.1%)</td>
<td>24 (44.5%)</td>
<td>5 (9.1%)</td>
<td>2 (3.7%)</td>
<td>2 (3.7%)</td>
<td>54</td>
</tr>
<tr>
<td>Subacute and chronic schizophrenia</td>
<td>1 (2.3%)</td>
<td>14 (31.8%)</td>
<td>21 (47.7%)</td>
<td>8 (18.2%)</td>
<td>44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acute schizophrenia: psychotic symptoms present for less than one month.
Subacute and chronic schizophrenia: psychotic symptoms present for more than one month.
proved patients are added to this number, we find that 39% of our 54 acute schizophrenic patients who had been treated with chlorpromazine improved in less than two months to the point where they could be discharged from the hospital. In two cases of this group of acute schizophrenics, an imminent breakdown was successfully averted. No recoveries and only one case of considerable improvement appear among the 44 subacute and chronic schizophrenic patients whom we treated with chlorpromazine but symptomatic improvement and control could be obtained in a large proportion of cases.

We had occasion to treat 22 patients who had previously been admitted to a mental hospital two or more times for psychotic attacks associated with psychomotor excitement and who had a diagnosis of manic depressive, manic or schizo-affective psychosis. It has often been observed that there is a tendency for recurrent psychotic attacks to increase in length as the patient grows older. In order to test this clinical observation and to determine whether chlorpromazine really was effective in shortening psychotic attacks, the following procedure was adopted: the number of psychotic attacks a patient had suffered prior to the last one was divided by two and the average duration of the first half of the psychotic attacks in a patient’s life, as well as the average duration of the second half of attacks, was determined and compared with the duration of the last attack, which was treated with chlorpromazine. A total of 124 psychotic attacks were analyzed for this study. It should be noted that some patients were treated with chlorpromazine alone while in others chlorpromazine therapy was either combined with, preceded or followed by electroconvulsive or insulin coma treatment. Almost all of the patients had received electrical or insulin shock treatments during their previous attacks.

The mean duration for the early attacks when averaged in the 22 patients was found to be 6.7 months. The mean duration for the later attacks in the same patients was 8.5 months. The mean duration for the last attacks when chlorpromazine was used in the treatment of these patients was 3.2 months. The difference in these values is statistically significant; this confirms the observation that recurrent psychotic attacks tend to increase in length as patients grow older and also that chlorpromazine is a most effective factor in shortening a psychotic attack. A 50% reduction in the probable duration of a psychotic attack may be expected with chlorpromazine therapy in psychotic breakdowns characterized by psychomotor excitement or emotional tension.

**Other Neuropsychiatric Applications**

A clinical investigation of the effects of chlorpromazine in neurological conditions seems to be warranted. We have seen one dramatic therapeutic result with the drug in a case of very severe Sydenham’s chorea which had resisted other forms of therapy. It can be shown that chlorpromazine is capable of temporarily reducing the involuntary movements in chronic cases of choreo-athetosis. It is also capable of diminishing or abolishing temporarily the tremor in patients with Parkinsonism. We were able to demonstrate these effects by slow-motion movies. Italian workers’ report good symptomatic effects in chorea and Parkinsonism although they have found that prolonged administration of the drug in Parkinsonism may lead to undesirable motor inhibition and autonomic disturbances.

It has been reported from various sources that chlorpromazine is of value in the treatment of pain associated with terminal carcinoma. The effect in these cases is probably similar to that observed following a frontal lobotomy, when the patient will still experience pain but without the emotional distress that usually accompanies it.

**Side-Effects and Complications**

We have not encountered any tendency to habit formation with chlorpromazine, probably because the drug does not produce euphoria as so many other sedatives frequently do. Patients receiving chlorpromazine usually complain of a dry mouth and a stuffy nose. Intramuscular injections are somewhat painful and may produce swelling and induration which may remain present for several days at the site of injection. Many patients dislike the “empty feeling” resulting from the reduction of drive and spontaneity which is apparently one of the most characteristic effects of this substance. The lassitude and hypotension which result from its administration are responsible for a feeling of weakness which most patients describe.

The lowering of blood pressure calls for continued medical supervision and nursing care of the patient as long as he is receiving large doses of the drug. We record blood pressure, temperature, and pulse every 12 hours. Because of the
ganglion-blocking effect of the drug, syncope due to orthostatic hypotension may become a complication in ambulant patients, particularly during the first few days of the treatment. The nursing personnel must be instructed to be on guard against such accidents, for instance, in a patient who has gone to the bathroom unassisted. Patients who have fainted because of orthostatic hypotension recover usually within a few minutes if placed in a horizontal position with the legs elevated. The usual analeptics are of little avail although caffeine sodium benzoate or aminophyllin may be given. We have had the impression that nikethamide (Coramine) and Metrazol may occasionally complicate the patient's condition further if given after the administration of chlorpromazine. Chlorpromazine must never be given to patients who are in coma due to intoxication with cerebral depressants such as alcohol or barbiturates.

French authors\(^7\) have reported venous thrombosis as a complication. We have not encountered it in our material, possibly because most of our patients are ambulatory after the first week.

Five per cent of patients receiving the drug for more than one week developed allergic manifestations such as urticaria or angioneurotic edema. Three per cent of our patients have shown gastro-intestinal symptoms such as nausea, vomiting, diarrhea, or abdominal cramps. A tendency to constipation develops in many patients while receiving the drug. It is interesting to note that allergic symptoms sometimes develop, although chlorpromazine has a slight antihistaminic action, and that nausea and vomiting are occasionally produced by the drug which is known to have a very pronounced antiemetic effect in human subjects and animals. We have usually discontinued the drug when allergic symptoms appeared but have not always stopped its administration because of gastro-intestinal complaints. Laxatives or enemas may be required when constipation develops during the treatment.

In 4 to 6% of patients an extrapyramidal syndrome resembling Parkinsonism is observed when chlorpromazine in large doses is given over a long period of time. The patients have a "mask-like" face, shuffling gait with loss of associated movements, and sometimes even muscular rigidity and tremor. These symptoms disappear within a few days after the drug has been discontinued. It is rather intriguing to speculate on the pharmacological and neurological mechanisms which are responsible for the fact that chlorpromazine in smaller doses can relieve the symptoms of paralysis agitans, while under other conditions the same drug may actually produce a neurological picture resembling Parkinsonism.

Several of our patients who had a history of epileptiform seizures developed convulsions while receiving chlorpromazine. While it has been claimed that the drug has an anticonvulsant action, we have seen no evidence of such an effect. In three cases without previous epileptic manifestations, we observed tonic and clonic phenomena almost amounting to a grand mal seizure during a syncopal attack due to orthostatic hypotension when the patient was ambulatory on the first day of treatment. We feel that cerebral hypoxia because of insufficient blood flow to the brain was responsible for this phenomenon.

Eight of our patients developed jaundice during treatment or within a few days after it had been discontinued. All of these cases responded well to discontinuation of the drug and supportive treatment. The clinical signs of jaundice disappeared within three to ten days, and liver function tests such as cephalin cholesterol flocculation and serum bilirubin were normal within two weeks, with the exception of one case of a young schizophrenic man who remained jaundiced for six weeks. Laboratory tests in patients receiving chlorpromazine may reveal a tendency to impaired liver function in about one-third of all cases, although this tendency is usually slight, always reversible, and may not lead to values outside the normal limits. Since only 7 to 8% of chlorpromazine is excreted in the urine, one must assume that most of it is metabolized in the body and that the task of the liver is probably greater than that of any other organ in dealing with the drug. Jaundice as a complication was first reported by Lehmann and Hanrahan and later confirmed by Winkelman, who reported three cases of jaundice in 143 neuropsychiatric patients treated with chlorpromazine. One fatality has been reported from another hospital in a patient who had developed jaundice following treatment with chlorpromazine and on whom a liver biopsy had been performed. The patient succumbed to a hemorrhage and other surgical complications. The nature of the jaundice following chlorpromazine
therapy is not yet clear. Certain evidence points to a condition of biliary stasis. Some of the cases of jaundice observed with chlorpromazine may have been due to infectious hepatitis and their appearance during the course of therapy with chlorpromazine merely a coincidence. However, until more is known about this particular manifestation, definite caution is indicated when administering chlorpromazine to patients with impaired or questionable liver function. For this reason we feel that one should be careful with the use of this drug in alcoholics, at least if it is administered for more than two or three days, and we question the wisdom of using chlorpromazine in combination with Antabuse (disulfiram) for the treatment of alcoholic intoxication as advocated by Friend and Cummins. Nor does it appear justified to use the drug routinely as an antiemetic as long as other methods will inhibit vomiting with equal effectiveness. Jaundice may develop in about 3% of patients treated with chlorpromazine over extended periods of time, and conservative treatment of this complication is recommended at present.

We feel that every patient receiving this drug should be seen at least once a week by his physician. He should be closely observed for the appearance of any icteric tinge of the sclera. We recommend that the patient's urine be examined for bile at least once a week. Smith's iodine test for bile in the urine or the commercial Ictotest, both of which are easily applied and might even be done by the patient himself, are fairly sensitive indicators of disturbed bile metabolism. If the test becomes positive during the period of treatment, the administration of the drug should be stopped for some time and only be resumed with caution. No cases of disturbed bile metabolism have been observed in patients receiving chlorpromazine for less than four days and so far all cases of toxic jaundice following chlorpromazine administration have occurred during the first four weeks of treatment, so that one may assume that only the first month is critical with respect to possible impairment of liver function.

No untoward effects on bone marrow or kidney function have been observed even with prolonged administration.

Administration and Dosage

In psychiatric patients, the drug is usually administered by the intramuscular or oral route. Only occasionally has one to resort to intravenous administration. Intramuscular administration is more reliable and more effective than oral, and about three to four times the intramuscular dose must be given by mouth to obtain the same effect. Recently we have obtained satisfactory results with suppositories.

Tolerance develops within a few days. The patient's drowsiness diminishes, blood pressure and temperature become stabilized, and the dosage may have to be increased.

In states of acute excitement, we begin treatment with intramuscular injections of 25 mgm. of chlorpromazine three times a day, and if necessary at night, and increase the dosage the following day to 50 mgm. intramuscularly three times a day, and again during the night if necessary. If this is not sufficient, individual intramuscular doses may be increased to 75 mgm., or 50 to 100 mgm. given by mouth may be added two or three times during the day. We insist that our patients who receive a daily dose exceeding 75 mgm. of chlorpromazine by mouth remain confined to bed for at least two or three days and we encourage bed rest for five to eight days. After the first week we usually discontinue the injections and change to oral medication, in most cases in amounts of from 100 to 300 mgm. per day divided into three or four doses. Occasionally daily doses up to 800 mgm. have been well tolerated over a period of two weeks. We have gained the impression that it is important to produce a state of distinct drowsiness in the patient during the first few days. Rapid control of the psychomotor excitement seems to offer better chances for effective shortening of the psychotic attack. In cases of very severe psychomotor excitement, individual doses up to 100 mgm. given intramuscularly may be required, and it may be necessary to repeat them within four or five hours. It is advisable, however, not to exceed 50 mgm. given parenterally the first time. Once the patient's reactions to the drug are known with regard to blood pressure changes and central nervous system response, the dose may be increased as required.

In less disturbed patients, when chlorpromazine is given over an extended period of time for the control of anxiety and tension states, much smaller doses are indicated. In such cases, 25 mgm. given by mouth two to four times a day is usually sufficient.
COMMENTS

This drug with its interesting pharmacological properties has a broad therapeutic spectrum. It will probably establish itself in anaesthesia because of its potentiating action in combination with other anaesthetics, for "hibernation treatment" and possibly as a protective agent in the prevention of shock following trauma. Laborit conceives of its action as suspending the various defensive processes resulting in the general adaptation syndrome. He is of the opinion that the very forces which are brought into play to maintain or re-establish homeostasis often overshoot their mark and can be more disturbing to the maintenance of equilibrium in the body than the original trauma.

In the management of pain in terminal cancer cases, chlorpromazine may prove to be a pharmacological substitute for lobotomy.

For research in neurophysiology, chlorpromazine seems to offer interesting possibilities, as it is capable of producing an extrapyramidal syndrome resembling Parkinsonism, and under other conditions can counteract the symptoms of this disease. The drug may find clinical application in the treatment of chorea.

In psychiatry, the drug provides us with a new therapeutic approach, namely, that of selective inhibition of motor drive and affect in states of severe psychomotor excitement. Its action is still unique, as no other short-acting and powerful sedative in clinical use at the present time has the qualities of producing sedation without significant clouding of consciousness or disinhibition of affect. There is much evidence that chlorpromazine in contrast to other sedatives produces comparatively little depression of cortical functions and acts more selectively than other inhibitory agents on the mesencephalic-diencephalic system. The drug has shown its capacity to shorten the duration of acute psychotic episodes and also to prevent psychotic breakdowns if given in the prodromal stage. In that respect, its action is equalled only by electroconvulsive treatment. The time required for full recovery, however, is sometimes shorter than with electroconvulsive treatment and, furthermore, the patient's insight is often better because amnesia and confusion do not develop under treatment. We have had the impression that patients who first received chlorpromazine for the control of acute symptoms and later were given electroconvulsive therapy required fewer shocks and therefore developed less amnesia.

A considerable number of clinical observations on chlorpromazine in psychiatry have now been reported in the literature and it would seem appropriate to attempt a comparison of the results obtained by various workers. Our own findings, at least as far as the therapeutic results are concerned, are substantially in agreement with those of the French authors who have had the longest and most extensive experience with chlorpromazine. We cannot explain the fact that apparently no cases of jaundice have been reported by French, Italian or German authors while 3% of our chlorpromazine-treated cases, 5% of those observed by Azima and Ogle, and three cases among 143 reported by Winkelman developed this complication. Although Azima and Ogle state that the dosage of the drug did not appear to have any particular influence on the incidence of jaundice, we feel that there may be a positive correlation between dosage, length of administration, and incidence of jaundice. While some patients developed the complication while receiving 100 mgm. or less daily, the majority received between 200 and 400 mgm. a day. In small and moderate doses, chlorpromazine seems to be a drug of low toxicity. Even when very large doses are given in severe psychotic conditions, the drug causes few complications within the first week or two. Our findings with regard to the incidence of allergic reactions and the appearance of an extrapyramidal syndrome after large doses of the drug have been administered for more than two weeks, are in close agreement with those reported by Azima and Ogle. It should be noted, however, that the latter complication disappeared in all of our patients within a few days after the drug was discontinued, while two of their patients required two months for the syndrome to subside. In contrast to their procedure and in accordance with the French workers, we have found it better to insist on bed rest at least for the first few days of chlorpromazine therapy; all our patients with the exception of three were hospitalized. Constant and careful medical and nursing supervision are, in our opinion, essential requirements whenever chlorpromazine is administered in daily doses exceeding 150 mgm.

Our comparatively high rate of remissions with chlorpromazine therapy in early schizophrenia requires some comment. We did not expect these
results when we began to give the drug to patients with acute schizophrenia. German authors have reported good results in the treatment of paranoid conditions. In our own material we found that delusions, hallucinations and other schizophrenic manifestations were influenced by chlorpromazine only if they were of very recent origin, that is, had existed for less than one month, and had not yet established a stabilized psychotic pattern. French and Italian authors state that the drug is not particularly effective in schizophrenic psychoses but they report excellent therapeutic results in acute confusional psychoses, and traumatic and reactive psychotic states, most of which would be diagnosed as acute schizophrenic reactions or schizo-affective breakdowns on this continent. We have seen dramatic recoveries within a week or two of chlorpromazine therapy in patients with acute catatonic stupor or acute catatonic excitement. The American authors report some favourable results with schizophrenic patients. Azima and Ogle observed only a moderate reduction of symptoms associated with better ward behaviour and socialization in their schizophrenic patients on chlorpromazine. They also mention that in their experience any definite favourable effects occurred within the first few days of treatment. In our material, however, we have found that two or three weeks' treatment will sometimes produce remarkable therapeutic results even if little change in the basic symptomatology is observed during the first few days. Possibly some of their acute schizophrenic patients would have responded more favourably if chlorpromazine had been continued for a longer period before shock treatment was administered.

All those who have worked with this drug in psychiatry agree that it is most effective in states associated with psychomotor excitement and emotional tension, and that its effect is questionable in depressed conditions, which still seem to respond best to electroconvulsive treatment. Of psychoneurotic disturbances, anxiety and acute hysterical symptoms show the most favourable response. This has been confirmed in the recent study of Azima and Ogle.

In view of the greatly increased therapeutic activity and optimism that have of late prevailed in psychiatry, it seems to us that time factors should be considered more critically in reporting on therapeutic results. Such terms as "acute" or "recent" should be strictly defined in terms of days, weeks or months. The quality of "improvement" and "recovery" should be determined in terms of presence or absence of symptoms and length of treatment required. This is particularly important in those psychiatric conditions which have a tendency to spontaneous recovery, as in the affective psychoses and in some psychoneurotic reactions.

Finally, it is hoped that other workers will test our method of assessing the value of a therapeutic agent by comparing the duration of the psychotic attack treated by it with the duration of previous attacks in the same patient treated by other methods, thus using the patient as his own control. Such an analysis seems to us more reliable than the simple accumulation of group data which may compare under the common heading of "improvement" such diverse conditions as Huntington's chorea and anxiety neurosis. Future research with the drug will have to establish its effect on cerebral metabolism, and particularly the acetylcholine turnover in the central nervous system, since it may well be that chlorpromazine, like its close chemical relative Phenergan, possesses an anti-acetylcholine action on the neuraxis.

**Summary**

Chlorpromazine is a new chemical agent with remarkable inhibitory action on the central nervous system. It also affects the autonomic nervous system, both the parasympathetic and the sympathetic. It differs from other short-acting sedatives because of its more selective effect on mesencephalic-diencephalic structures and thus provides a new therapeutic approach to certain troublesome psychiatric conditions. In acute psychotic breakdowns associated with affective disturbances, more specifically psychomotor excitement and emotional tension, it may shorten or prevent full development of an attack and may be preferable to electroshock therapy. Possible side-effects and complications make it necessary to administer the drug under medical supervision and nursing care, particularly if large doses are given. Further research with chlorpromazine may reveal new clinical applications for this pharmacological agent which possesses already an unusually broad therapeutic spectrum with intriguing neurophysiological aspects.

Thanks are extended to Dr. George E. Reed, Medical Superintendent of the Verdun Protestant Hospital, for his co-operation and kind permission to publish this paper.
A CHARACTERIZATION OF LISTERIOSIS IN MAN AND OTHER ANIMALS*


The world-wide distribution of listeriosis and the features of epizootics in domestic animals, with the almost total lack of knowledge of its transmission and maintenance, give this disease a measure of importance. Human listeriosis has, up to now, been considered sporadic, but recent evidence from Germany gives it a much more momentous incidence and character. The variety of susceptible hosts, with the clinical and pathological variations they exhibit, brings into prominence problems in comparative pathology of its causative organism, Listeria monocytogenes, presents unusual characters, not alone because it lives up to its name in certain hosts, but because of its tolerances, its liability to be overlooked or confused with other kinds, and, not the least, because of its insidious behaviour. Thus, this disease and its causative organism present an unusual variety of possibilities for research, which might well not only clarify the significance of listeriosis but also develop new approaches to problems in pathology, bacteriology, immunology and biochemistry. These would sequentially enlighten clinical and epidemiological concepts and practices.

Listeria monocytogenes has been isolated and identified in a minimal list of 27 species of animal (rabbit, hare, guinea-pig, gerbille, lemming, mouse, rat, hamster, chinchilla, vole, sheep, goat, cattle, swine, horse, fox, dog, ferret, raccoon, chicken, canary, duck, goose, eagle, capercaillie, unspecified birds and man) and the variety indicates that yet more will be revealed in time. Most instances are in domestic or captive animals, but that certain hosts are abundant wild species, of which some are predatory and others migratory, indicates that the disease should be more widely sought in mortalities of wild fauna. That certain of these may contribute to its introduction to herds is a real possibility, especially since some studies conclude that in domestic animals it is most commonly a disease of winter and spring, when the animals are confined. Evidently the incidence and distribution of Listeria monocytogenes in wild life deserves more attention than it has received.

Migratory and predatory habits, especially the devouring of carcases, seems worth some attention. These, each in their own way, may contribute to the seemingly universal distribution of listeriosis which has been reported from 26 countries in five continents, ranging from the Arctic to the tropics. The list comprises: Argentina, Australia, Austria, Brazil, Canada, Cuba, Denmark, England, Finland, France, Germany, Holland, India, Italy, Japan, New Zealand, Norway, Palestine, Poland, Russia, Scotland, South Africa, Sweden, the United States and Uruguay. In contiguous countries from which it has not yet been reported adequate investigation will no doubt reveal its presence.

A disease with so widespread a distribution, implicating such unrelated and varied hosts, involving widely differing food and living requirements, and, apparently, every kind of climate, must present features and conditions of singular interest. The clinical, pathological and bacteriological characters of listeriosis vary individually and collectively in different hosts and there is no indication whatever that this is due to differences...