was a marked increase in the absolute amount and percentage of nitrogen retained. The increase in food intake and in body weight is apparent. The changes in the percentage of nitrogen retained were due to changes in the proportion of ingested nitrogen excreted in the urine (Table II), whereas the percentage of the ingested nitrogen that was excreted in the faeces remained relatively constant. It is apparent (Chart) that nitrogen equilibrium was restored when the insulin injections were stopped. This latter change in nitrogen balance was accompanied by a fall in body weight. The loss of weight was due to the loss of fat or water or of both. No appreciable amount of protein was lost, since the animals did not exhibit a significantly negative nitrogen balance.

Discussion

The hypophysectomized insulin-treated rats were not maintained on a restricted diet, since this preparation is extremely sensitive to the hypoglycaemic action of insulin. The effect of the increased caloric intake has therefore not been defined. MacKay *et al.*[3] have shown that insulin enhances nitrogen retention in intact rats maintained on a restricted diet.

Our data suggest that a linear relationship may exist between insulin dosage and nitrogen retention. This relationship might have been more apparent if it had been possible to prevent compensatory decreases in pancreatic beta-cell activity which undoubtedly occurred. Chaikoff and Forker[4] have shown that in depancreatized dogs the amount of insulin administered is linearly related to the amount of nitrogen retained.

Since Banting, Campbell, and Fletcher[5] first showed that insulin decreases the nitrogen excreted by diabetic patients, abundant evidence has accumulated to indicate that insulin is intimately associated with protein synthesis. It has been shown *in vivo* and *in vitro* that the antidiabetic hormone stimulates the utilization of amino-acids and the synthesis of proteins and inhibits protein catabolism.[6-16] The results of our experiments are in accord with this evidence and they confirm and extend our previous reports.

Summary

The effect of insulin on nitrogen balance in the hypophysectomized rat has been studied. It has been found that under the conditions of this investigation hypophysectomized rats treated with insulin show a marked increase in the absolute amount and in the percentage of nitrogen retained. Over the range studied the percentage of ingested nitrogen retained bore an approximately linear relationship to the amount of insulin given.

The results of these experiments confirm and extend the earlier reports from this laboratory that insulin can function as a growth hormone in the absence of pituitary factors.

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THE USE AND ACTION OF CHLORPROMAZINE IN PSYCHONEUROSES

BY

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Of recent years a number of compounds with specific pharmacodynamic properties have been developed in France from derivatives of the aromatic base phenothiazine. These compounds include promethazine hydrochloride (" phenergan "), diethazine hydrochloride (" diparcol "), ethopropazine hydrochloride (" lysivane "), and promethazine 8-chlorotheophyllinate (" avomine "). Their usefulness lies in their specific antagonism towards naturally occurring histamine, adrenaline, and acetylcholine, and in the central depressant action which they show in varying degrees, the exact mechanism of which is not clearly understood.

A new derivative of phenothiazine—chlorpromazine hydrochloride (3 - chloro - 10-(3'-dimethylaminopropyl)-phenothiazine ; " largactil ")—is now available in this country. Like the others, it was developed in France, and clinical trials there indicated its possibilities in anaesthesia, as an anti-emetic agent, and in the treatment of psychiatric illness.

In the psychiatric field, Sigwald and Bouttier (1953a) claimed that the drug exerted a depressant action on the central and autonomic nervous systems, and that it displayed special properties which they have called " neuroplegic," producing results comparable to those of " frontal lobotomy." The drug has been employed in the treatment of both psychotic and psychoneurotic patients. Sigwald and Bouttier (1953b) published the results in a series of 48 patients, of whom 12 appear to have been cases of psychosis, while the remainder were psychoneurotic.

These investigators state that chlorpromazine nearly always improved the mood of their patients, and led to the disappearance of depression, with the frequent development of some degree of euphoria. Patients are said to have become indifferent to their worries. Anxiety was replaced by a feeling of calm and detachment, and morbid thoughts disappeared. They state furthermore that " the effect on obsessions is often significant, and sometimes remarkable," while there is " a rapid and complete alleviation of fears, scruples, doubts, and phobias." True obsessional states, on the other hand, are said to give poorer results, though the patient is able to overcome his obsessional thoughts more easily.

The results of treatment with chlorpromazine are said to be characterized by a significant percentage of successes, and analysis of their results shows that these were " good " or " very good " in 50 to 60% of each of the psychoneurotic manifestations they investigated.

In view of the encouraging possibilities of chlorpromazine over such a wide field, it was decided to investigate its effect on a series of psychoneurotics comparable to that of Sigwald and Bouttier.

Administration

Our series of cases numbered 29 and all received chlorpromazine by the oral (as opposed to the intramuscular) route, so that we could standardize the results of in- and out-patient treatment.

The scheme of dosage followed was that suggested by the French investigators. Because of the side-effects reported, dosage was at first low, and the patients were kept in bed for three days at the beginning of treatment and thereafter advised to lie supine for half an hour after taking the drug, to counteract any postural hypotension. As our experience increased, however, we were able to dispense with these precautions, and patients are now only advised to rest for 15 minutes in a chair when starting treatment. After a week they are usually able to tolerate therapeutic doses with no special precautions.

We have found that it is better to start with a high dosage of chlorpromazine and increase quickly to the optimum. Patients are now given 25 mg. t.d.s., and this is raised by 25 mg. every other day to a maximum of 75 mg. t.d.s. In many cases the optimum effect is attained with 50 mg. t.d.s.; and no increased benefit was gained by raising the dose above 75 mg. t.d.s. in our series. Chlorpromazine in these amounts is well tolerated over a long period and out-patients are able to continue at work while undergoing treatment.

In the initial phases of our trial we started with smaller doses, and increased to an optimum over a longer period. We found, however, that many patients complained of an increase in tension and an exacerbation of symptoms, and this method of treatment was replaced by that outlined above. It seems that the maximum clinical improvement may be expected in four to six weeks of treatment. Thereafter a maintenance dose of 50–100 mg. daily is necessary. Cessation of treatment has usually led to a recurrence of symptoms, unless psychotherapy has been successfully employed in conjunction with chlorpromazine.

Complications

The side-effects of chlorpromazine are mainly attributable to its action on the autonomic nervous system, and in our series these have not caused much inconvenience. In two cases tachycardia and dryness of the mouth prevented continued treatment, and in one case there was complaint of weakness of the legs for one to two hours after dosage, but this proved to be only transient. Two further patients with hypertension developed tachycardia and a fall in blood pressure of over 40 mm. soon after taking chlorpromazine.

A far more disturbing complication has been the appearance of pyrexia—temperature 101–103° F. (38.3–39.4° C.)—after seven to ten days of treatment. This has occurred in 10% of all cases treated. At the onset of pyrexia these patients had received total amounts of chlorpromazine varying from 550 to 1,200 mg. Symptoms included profuse perspiration, nausea, and epigastric discomfort, while all displayed epigastric and right subcostal tenderness. On stopping chlorpromazine, the pyrexia subsided in 24 to 48 hours in all cases, with complete remission of symptoms. In two cases chlorpromazine was resumed and has been continued now for three months with no further ill effects. In three other cases the urine was found to contain bile salts, and liver-function tests showed abnormal bromsulphthalein retention, though flocculation tests and serum bilirubin were within normal limits. One of these latter cases was given chlorpromazine again on two separate occasions after the bromsulphthalein retention returned to normal, but each time a pyrexia developed within 24 hours, and treatment was discontinued in these three cases.

Nature of Cases

A brief clinical summary of each of the 29 cases follows. We have omitted any description of the personality setting, which did not appear to be correlated with the response to chlorpromazine to any degree further than already emerges from the diagnosis made.

Cases With Mainly Hysterical Features

Case 1.—Female, 63. Chronic hysteria. Main symptoms: paraesthesia of head. Three months' treatment. No improvement.

Case 2.—Male, 37. Reactive depression with hysterical features. Depression, headaches, abdominal discomfort. Eight weeks' treatment. No improvement.

Case 3.—Female, 57. Anxiety state with hysterical features. Abdominal pain, mild tension. Four weeks' treatment. Slight relief of tension. Relief of pain.

Case 4.—Female, 41. Chronic anxiety hysteria. Vomiting, moderate tension. Three months' treatment. Relief of vomiting, slight relief of tension.

Cases With Mainly Phobic Features

Case 5.—Male, 40. Phobic state. "Choking." Four weeks' treatment. Relief of tension; symptoms remain less obtrusive.

Case 6.—Female, 29. Anxiety state with phobic features, panic attacks. Eight weeks' treatment. Considerable relief of tension, panic attacks persist but more easily controlled.

Case 7.—Female, 29. Chronic anxiety state with phobic features. Panic attacks. Six weeks' treatment. Slight relief of tension, no effect on panic attacks.

Case 8.—Male, 31. Chronic anxiety state with phobic features. Pain in back, cancerophobia. Four weeks' treatment. Relief of tension with corresponding improvement in phobia. (Patient himself noted return of symptoms on voluntarily stopping chlorpromazine.)

Case 9.—Female, 34. Chronic obsessional state with marked phobic features. Tension, claustrophobia, agarophobia. Three months' treatment. No improvement.

Case 10.—Male, 42. Chronic anxiety state in an obsessional personality. Embarrassment. Eight weeks' treatment. Slight relief of tension only.

Cases With Mainly Depressive Features

Case 11.—Male, 51. Chronic anxiety depression. Depression, pain in head and abdomen. Four weeks' treatment. Slight relief of tension, symptoms unchanged. (This patient had a prefrontal leucotomy in 1949.)

Case 12.—Male, 63. Chronic depression. Guilt and depression. Six weeks' treatment. No improvement.

Case 13.—Female, 37. Reactive depression. Depression, malaise. Four weeks' treatment. No improvement.

Cases With Mainly Obsessional Features

Case 14.—Male, 51. Chronic anxiety state, with paranoid, obsessional, and hysterical features (a syndrome with poor prognosis). Tension, orbital pain, inability to read. Six weeks' treatment. Relief of tension, obsessions unchanged (fairly good clinical result, not much response to anything but chlorpromazine).

Case 15.—Female, 32. Endogenous depression with obsessional features. Macabre ruminations and severe tension. (Previous E.C.T. with only transient relief.) Eight weeks' treatment. Marked relief of tension, persistence of obsessional thinking, but decrease in associated features.

Case 16.—Female, 45. Chronic anxiety depression with obsessional features. Depression, phobias, panic attacks. (Previous E.C.T. with only transient relief.) Four months' treatment. Slight relief of tension, panic attacks more easily controlled. No improvement in depression or obsessional thinking.

Case 17.—Female, 41. Chronic obsessional state. Depression, phobias, panic attacks. Three months' treatment. Moderate relief of tension, with slight improvement of depression. Phobia and panic attacks unchanged. (E.C.T. combined with chlorpromazine.)

Case 18.—Male, 28. Chronic obsessional state. Smell from body, tension. Four weeks' treatment. Slight relief of tension, no change in obsessional thinking.

Cases With Pain as Main Feature

Case 19.—Female, 61. Chronic depression. Pain in perineum (central, non-psychogenic). Six weeks' treatment. No improvement.

Case 20.—Male, 64. Chronic involutional depression. Pain in perineum (central, non-psychogenic). No relief with E.C.T. Six weeks' treatment. No improvement.

Cases With Tension as Main Feature

Case 21.—Female, 54. Chronic reactive depression. Severe tension and depression. Ten weeks' treatment. Complete relief of tension, with disappearance of depression.

Case 22.—Female, 71. Chronic anxiety state. Severe tension, insomnia, pain in back, indigestion. Eight weeks' treatment. Relief of all symptoms.

Case 23.—Female, 36. Explosive diathesis—tension state. Severe tension, particularly premenstrually, with detonation. Six weeks' treatment (combined with phenytoin sodium). Marked improvement.

Case 24.—Female, 32. Reactive anxiety depression. Severe tension, tremor, irritability. Three weeks' treatment. Marked relief of all symptoms.

Case 25.—Female, 37. Chronic anxiety state with hysterical features. Moderate tension. Six weeks' treatment. Relief of tension.

Case 26.—Female, 28. Chronic anxiety state with phobic features. Moderate tension, indigestion and flatulence. Four weeks' treatment. Complete relief of all symptoms.

Cases of Dysmenorrhoea

Case 27.—Aged 23. Symptoms for six years. No relief with other treatment. Chlorpromazine gives "50% relief."

Case 28.—Aged 20. Symptoms for four years. No relief from analgesics. Chlorpromazine gives "considerable relief."

Case 29.—Aged 20. Premenstrual tension with dysmenorrhoea for two years. No relief with analgesics. Chlorpromazine gives "considerable relief."

Results

The response to the drug has been considered from two points of view. In the first place we have noted the response of the patient as a whole unit to therapy, and these results are set out in Table I. "Much improved" includes cure or relief so substantial that no further treatment is required other than the continued administration of chlorpromazine at periodic brief interviews. "Somewhat improved" means relief of symptoms to a material degree appreciated by both patients and doctor, but leaving therapeutic work to be done. "No relief" includes slight relief.

TABLE I.—*Clinical Assessment of Results*

	Case Nos.	Total No. of Cases
Much improved ..	15, 21, 22, 23, 24, 25, 26, 27, 28, 29	10
Somewhat improved	4, 6, 8, 14, 17	5
No relief	1, 2, 3, 5, 7, 9, 10, 11, 12, 13, 16, 18, 19, 20	14

Our second approach to the results was to determine the effect of chlorpromazine upon *individual* features of each patient's symptom-complex so that we might determine whether any particular symptom responded irrespective of the diagnostic setting in which it occurred. These results are set out in Table II, and some duplication can be observed. Thus primary tension, secondary tension, and phobias could be distinguished in Case 5, which therefore appears in three columns.

TABLE II

Symptoms	Phobias	Depression	Obsessional Thinking	Psychogenic Pain	Non-psychogenic Pain	Diffuse Tension	Tension Following Obsessional Thinking
Much improved		21		3, 22, 27, 28		6, 15, 21, 22, 23, 24, 25, 26, 27, 28, 29	
Somewhat improved	6, 8, 16	17		29		3, 4, 5, 7, 8, 14, 17	5, 6, 8, 14, 15, 16, 17, 18
No relief	5, 7, 9, 17	11, 12, 13, 16	14, 15, 16, 17, 18	1, 2	19, 20	9, 1, 2, 10, 11, 12, 13, 16, 18	9

Discussion

We have tried to give adequate data to permit the drawing of some reasonably firm inferences, where homogeneity of results justifies this even in a small series. It is notable that *all* the cases in which tension was predominant were much improved. We should note, however, that no cases of *agitation* as opposed to tension occur in the series, and we have no observations to offer on the effect of chlorpromazine on such cases. Our three cases of dysmenorrhoea, which we regarded as basically tension states, were also "much improved." Of our 29 patients, 18 showed a significant degree of relief of tension.

Those patients with notable hysterical features, those with mainly phobic features, and the depressed did badly. Results in patients with predominant obsessional symptomatology were poor, except for one (Case 15) in whom the symptom was secondary to a depression.

With regard to pain, our series is too small for anything save the diffident suggestion that psychogenic pain appears to have been relieved, whereas in two cases which we have called "central" pain—probably due to arteriopathic changes in the brain—no relief occurred.

We have not, therefore, been able to confirm the findings of Sigwald and Bouttier concerning the relief given by chlorpromazine to patients with obsessional, depressive, or phobic symptoms. Nevertheless we are convinced of the value of the drug in alleviating tension both in its affective and in its muscular sense. In this respect our findings are similar to those of the French workers, but we cannot go further than that. We believe that all our good results, in whatever type of patient, are explicable on the grounds of relief of tension alone. This feature has been of great value in bringing some patients within the scope of psychotherapy who might otherwise have been outside it. A combination of chlorpromazine, psychotherapy, and relaxation treatment (Garmany, 1952) appears to give the best results at present obtainable in the treatment of the tension state.

Summary

A clinical investigation of the effects of chlorpromazine upon 29 psychoneurotics has not confirmed the value claimed for the drug in the treatment of "psychasthenic" illness.

Its value in the treatment of tension states appears to have been adequately established.

Toxic effects upon the liver have been noted in a few cases; and in two cases of hypertension an alarming tachycardia was observed despite treatment in bed.

We wish to thank Messrs. May and Baker, through whose courtesy supplies of "largactil" were made available.

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The number of permanent houses completed in Great Britain during June, 1954, was 30,973, compared with 26,598 in June, 1953. In the first six months of 1954, 167,695 permanent houses were completed, which was an increase of over 22,000 compared with the figures of the previous year. So far this year about 40,000 houses and flats have been built for sale. The number of houses and flats under construction on June 30, 1954, was 316,305, and the total number of permanent houses and flats completed in Great Britain since the war now amounts to 1,742,745.