Exhibit P-39

TREATMENT OF THE CHRONIC PARANOID SCHIZOPHRENIC PATIENT*

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THE TREATMENT of chronic paranoid schizophrenia has long been considered one of the most difficult tasks for psychiatrists.

We are presenting a method of treatment which we have found to be more successful than any hitherto reported.

This method consists essentially in the use of prolonged sleep, lasting 30 to 60 days, combined with intensive electroshock therapy. This period of treatment is then followed by a stage of rehabilitation and follow-up therapy on an ambulant basis. This latter is carried on over a two-year period.

OBSERVATIONAL BASIS FOR TREATMENT

1. During the last 20 years we have found frequent occasion to verify Sakel's[1] original observation that a prolonged and severe so-called irreversible coma might have favourable effects in schizophrenic patients who had hitherto failed to respond to any other form of treatment. We have considered that the frequently severe although transient disturbance of brain function is an important factor in the favourable results. This disturbance is shown in terms of severe recent memory deficit, disorientation and impairment of judgment. Similar changes can readily be produced by a combination of sleep and electroshock treatment.

2. In recent years since we re-introduced the use of prolonged sleep with the assistance of chlorpromazine (Largactil)[2] we observed that schizophrenic patients responded well to this form of treatment. Our first attempts to use this treatment were with very excited schizophrenic patients who could not otherwise be managed in an open hospital.

3. Our third observation was that where coma insulin and electroshock were combined in the treatment of particularly difficult schizophrenic patients we got good results.

Thus it was decided to explore the possibility of using prolonged sleep combined with electroshock therapy; within a few months it became apparent that the best results were obtained where there was an extensive breakup of the behavioural patterns consequent upon a transient disturbance of brain function.

The observational basis for the two-year ambulant follow-up was derived from our observations of the use of a five-year follow-up period in patients suffering from recurrent manic depressive attacks as originally suggested by Geoghegan and Stevenson[3] and as carried out by ourselves for the last ten years. The second basis has been our observations of the disorganizing effects of emotional stress and the restoration of function once the disorganizing stress has been removed.[4]

CASE MATERIAL

The patient group in which the effects of this form of therapy was studied consisted of 26 paranoid schizophrenic patients. Of these, 16 had shown symptoms for more than two years. The remaining 10 had shown symptoms for less than two years and were diagnosed as suffering from acute paranoid schizophrenic breakdown. They were included for the purposes of comparison. Of the 26 patients, five were men and 21 were women. The age spread was from 17 to 54.

All patients were examined extensively before treatment. Clinical, biochemical, psychological and electrophysiological examinations were carried out. In addition the family structure and the general socio-economic background from which the patient came was investigated through the social service department. The diagnosis was made on the basis of the accumulated data and as established in joint discussions of the whole clinical team.

After the conclusion of treatment, routine examinations described above were repeated, the clinical team again assessed the degree of recovery which had been achieved, and at the same time plans were made for follow-up and rehabilitation work with each patient.

PROCEDURE

The sleep technique employed is that reported by Azima.[2] The objective of this technique is to produce a prolonged sleeping state resembling the normal as closely as possible. The patient sleeps an average of 20 to 22 hours a day and is wakened three times a day for meals and toilet. The drugs used are chlorpromazine (Largactil) and a combination of three barbiturates: secobarbital (Seconal) is chosen as a short-acting barbiturate, pentobarbital (Nembutal) as one of intermediate duration and phenobarbital or barbital (Veronal) as a long-acting drug. Solid food is given during the first week and from then on semi-solid foods, the minimum caloric intake is 1500 per day and the minimum amount of fluid 2000 c.c. The patients are given extra vitamin B and C parenterally. Posturing of the patients by the nurses is carried out every two hours and carbogen is administered if the respirations become shallow. Five units of globin-zinc insulin are given half an hour before each meal. The sleep is induced gradually and is also terminated gradually. At the end of 10 days, at which time sleep has been established, electroshock is commenced.

The objective of the electroshock therapy is to produce in combination with sleep a condition of confusion which we term complete depatterning. For purposes of identification we recognize three

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stages of depatterning. The first stage is when the patient begins to show serious memory deficits but still has no difficulty in orienting himself with respect to the fact that he is in hospital, that he is there because he is sick, and is still able to recognize at least some of the doctors and nurses and his own family when they visit him.

The second stage is when the patient has lost his spatial and temporal image but is very conscious of the fact and makes repeated attempts to find re-orienting points. He asks, "Where am I?", "how did I get here?" and "what is this place?" In the third stage the feeling that he ought to have a spatial-temporal image is also lost and the patient is now quite smiling and unconcerned. He answers simple questions but does not recognize anyone, has no idea where he is and is not troubled by that fact. He usually shows urinary incontinence and has difficulty in performing quite simple motor skills. During the first stage of depatterning his original delusional ideas are usually still present. During the second stage they are becoming broken up and in the third stage are completely absent, as are all other evidences of his schizophrenic behaviour. To achieve this, electroshock therapy frequently has to be carried out once daily and sometimes in the form of a Page-Russell[5] treatment, namely, the giving of four or five shocks within a period of two or three minutes. The rate of administration of electroshock therapy is set so that complete depatterning is achieved somewhere between the 30th and the 60th day of sleep and after about 30 electroshock treatments.

Once complete depatterning is obtained, it is maintained for five to seven days. The amount of sleep medication is gradually reduced (too rapid reduction of barbiturates may produce convulsions) and the rate of administration of electroshock is reduced to three a week, the Offner apparatus being used.

After about four or five days the patient is able to get up and the phase of rehabilitation is then initiated. Care is taken as far as possible to assign one person to looking after the patient so that he can the more rapidly begin to orient himself, at least with respect to one person. He joins the other patients at meals and as soon as his memory will permit he is referred to the occupational therapy department.

During the period of recovery continuous observations are carried out with respect to any evidence of a recurrence of his schizophrenic behaviour. Should any sign of his previous delusional thinking appear, electroshock is again intensified, the patient being given daily treatments for a few days until the delusional thinking is once more broken up. Ordinarily such relapses do not occur, but in some patients they may recur repeatedly during the period of rehabilitation and on each occasion further electroshock is given until they are broken up again.

Care should be taken to distinguish actual schizophrenic relapses from forms of behavioural disturbance which we have noted in about 25% of our cases at the point of transition from the second to the first stage of depatterning. At this phase in the recovery of the patient—namely, when his attempts to re-establish his space-time image are becoming satisfactory but while there are still severe memory deficits—there may appear states of excitement or depression and states of actual delusional formation, this being in contrast with the placidity and the freedom from any delusional thinking which one finds in the third stage of depatterning. Our experience has shown that this transition period of disturbance of behaviour is best treated conservatively. The patient is usually put on chlorpromazine or reserpine (Serpasil) in moderate doses and is given a great deal of support and reassurance from the start. Such periods of disturbance ordinarily last less than a week and gradually subside as the patient emerges into the first stage of depatterning.

The period of rehabilitation in hospital ordinarily lasts about a month, at the end of which time the patient can be discharged and put on an ambulant follow-up basis. During this period, moreover, through our social service department we plan the patient's rehabilitation on the outside. Preparations are made for the last phase of stabilization and prevention. This generally lasts two years and requires the patient to come to the hospital for one electroshock treatment a week for the first month after discharge and one treatment a month for the next two years. We have repeatedly found that the patients do much better if they remain in the Montreal area and attend the Institute than if they return after discharge to their home city and place themselves under the care of one of our colleagues, being treated in a manner precisely the same as they would be if they had been in Montreal. This interesting observation demonstrates the great significance to the patient of the therapeutic milieu in which he recovered and the need for him to remain in this milieu during the period of stabilization.

The form of psychotherapy which we carry out with these schizophrenic patients during the period of rehabilitation in the hospital and during the two-year follow-up period when they are ambulant is limited to meeting the needs of the patients for support and acceptance and for guidance in their attempts to re-establish themselves in the community and in a job. We do not, save in the rare instances where there are marked neurotic tendencies, undertake any form of depth psychotherapy. Specifically we do not attempt to uncover unconscious motivations. Our efforts are directed rather to building a strong personal relationship between the patient and the therapist. The therapist takes every opportunity to strengthen this relationship, particularly during the period immediately after prolonged sleep when the patient is

attempting to re-orient himself and is gradually recovering from the period of helplessness engendered by his prolonged sleep and electroshock therapy. This relationship constitutes a fixed point of strength and support for a patient and is continued throughout the whole two years, care being exercised to see that, as far as possible, the same therapist is available to the patient. It is important to underscore the fact that the therapist brings to his work not only knowledge and skill but also attitudes. We are increasingly impressed with the fact that the attitudes of the therapist are crucial for the outcome. In dealing with the long-term schizophrenic patient the therapist must have great persistence. He cannot afford to give up easily. He must continually focus his attention and that of his staff and the patient on the gains which have been made, even though for a time they should be small.

During this period of stabilization and prevention outside the hospital, the patient ordinarily works. Some of our patients have married and have had children. Some have shown relapses. Where evidence of relapse is reported to us, the patient is treated again within a few hours or at the most within two days by intensive electroshock therapy on an ambulant basis. We have an arrangement with a nursing organization in the city by which all our ambulant schizophrenic patients are visited once a week, and their relatives or landladies are instructed to get in immediate touch with this nursing organization if there is any evidence of a relapse. This may take the form of moodiness, of sleeplessness, of lack of interest, of impairment of appetite, or of the appearance of thinking difficulties or beginning delusional ideas. We have found that where this happens we are always able to terminate the relapse within two or three days and often within 24 hours by intensive electroshock therapy. In the last two years we have only rarely had to readmit a patient.

RESULTS

It is proposed to report the results of the two groups of paranoid schizophrenic patients separately, namely, those patients having symptoms of more than two years' duration and those patients having symptoms of less than two years' duration. With regard to the first group, which is comprised of 16 patients, the initial results were favourable in that all patients could be discharged home save for one patient who left against advice and has been readmitted for further treatment.

The follow-up results of those discharged were good except in five patients, two of whom refused follow-up care, developing paranoid reactions of such fixity that we could not persuade them to continue. They were nonetheless able to remain outside the hospital. Two others had to be readmitted for further treatment and were later discharged again and have done well. One other had to be readmitted and as indicated above is still under treatment. A number of others have had minor relapses but could be managed on an ambulant basis. Out of all the patients now discharged, paranoid trends were apparent only in the two patients mentioned above as having refused further treatment and in the one patient who had treatment in hospital subsequent to readmission. It should, however, be pointed out at the same time that although most of them are able to lead active lives as housewives and also in other occupations on the outside, some evidence of schizophrenic damage can be seen in the majority of these chronic patients. This takes the form of some blunting of affect, some loss of drive relative to that shown in earlier years.

TABLE I.—RESULTS IN THE TREATMENT OF PARANOID SCHIZOPHRENIC PATIENTS WITH SYMPTOMS OF OVER TWO YEARS' DURATION

Number of patients	16
Number discharged	16
Number readmitted	3
Number re-discharged	2
Number still in hospital	1
Number refusing follow-up treatment but still ambulant	2

Those in the group with symptoms of less than two years' duration have all been discharged and the results are also good, indeed more favourable than in those with symptoms of over two years' duration. None of them have had to be readmitted. Occasional relapses have been seen but these have been managed quite successfully on an ambulant basis. The evidence of lasting schizophrenic damage in the form of blunting of affect, or reduction in drive and initiative, is rarely apparent in this group of short-term paranoid cases.

TABLE II.—RESULTS IN THE TREATMENT OF PARANOID SCHIZOPHRENIC PATIENTS WITH SYMPTOMS OF LESS THAN TWO YEARS' DURATION

Number of patients	10
Number discharged	10
Number readmitted	0

DISCUSSION

Earlier in this paper we presented the observational basis for the development of this technique. We now wish to present the theoretic basis. Our working theories or premises are three in number:

1. That schizophrenia represents a biological process which can be arrested but which tends, particularly when of any intensity or duration, to leave behind permanent damage.

2. That recovery consists primarily in: (a) halting the process, and (b) a reorganization of the individual which results in a short-circuiting or inactivation of the damaged area but which does not result in an abolition of the established damage.

3. That a considerable proportion of schizophrenic relapses, though certainly not all, constitute not a reactivation of the process but a breakdown

of the reorganization of the individual, usually under emotional stress.

Turning now to deal with the premises in more detail we may say that we have found chemical and physical therapies to be the only satisfactory means of halting the schizophrenic process. The objective of our initial intensive physical and chemical therapy is two-fold, first to bring the process to an end and second to break up completely, through the procedure of depatterning already described, the ongoing structure of the behavioural patterns of the individual. This results in breaking up at the same time the pathological schizophrenic thinking and general symptomatology.

Turning to the second premise, namely, that recovery requires reorganization, we wish again to emphasize the need to break up old pathological patterns before the new ones can be re-established. We may also indicate the value of psychotherapy at this point. The psychotherapy is, as indicated, supportive and also directive in so far as the pressures of the social setting are brought to bear on the patient in an attempt to get him to establish acceptable patterns of behaviour.

Numerous reports in the literature indicate that where a patient has made a good clinical recovery psychological tests may well show the same amount of schizophrenic damage as before. We see this as supporting the premise which we have put forward, namely, that recovery consists not in repair of damaged aspects of the individual's personality but in a rearrangement. The damaged parts are, as it were, bypassed or omitted from the key areas of the patient's new organization. We are further of the opinion that every individual possesses reserve capacities—alternative ways of managing reality and latent assets—which can be called upon and woven into the new organization of the self. This means, of course, that the damaged areas which have suffered schizophrenic damage are still present within the individual and that there always remains the possibility of a breakdown in the new organization and a return to the old but still existing patterns of schizophrenic behaviour.

This takes us to the third premise, namely, that under the impact particularly of emotional stress the new organization may break down, disorganization[4] may occur and the previous schizophrenic patterning may reappear. It is to protect the patient against the possibility that the earliest evidences of damage due to stress might not be noticed and hence that the patient would begin to pass into disorganization that our plan of treatment requires weekly visits by the nursing organization and monthly interviews with the therapist, together with a monthly electroshock treatment over the two-year period. When relapses do, nonetheless, occur they are treated on an ambulant basis; the patient is seen if necessary daily for three or four days and receives an electroshock treatment daily on an ambulant basis. Under these circumstances we have almost invariably succeeded in bringing the relapse to an end within a few days.

SUMMARY

The results of combined prolonged sleep and intensive electroshock treatment with subsequent rehabilitation and follow-up ambulant therapy in chronic paranoid schizophrenic patients have been presented.

The group of patients consists of 16 chronic paranoid patients having had symptoms of two or more years' duration contrasted with a group of 10 paranoid schizophrenic patients with symptoms of less than two years' duration.

Three of the long-term cases have been readmitted and two of these have been subsequently discharged. One is still in hospital undergoing re-treatment. The longest period of follow-up subsequent to discharge is two years.

Two of the long-term patients have broken treatment and have again showed paranoid symptomatology but remain outside the hospital.

Minor relapses have occurred in several of the patients, in both the long-term and short-term cases, but these have been managed successfully on an ambulant basis. None of the short-term cases has had to be readmitted.

In the long-term cases some residual evidence of schizophrenia can be seen. This takes the form of reduction in drive and blunting of affect. In only three of the long-term cases (two who have broken therapy and the one who has been readmitted) and in none of the short-term cases is there any evidence of paranoid thinking.

Our primary purpose in this presentation is to show that our therapeutic procedures have advanced to the point where it is now possible for schizophrenic patients, even when suffering from the most severe forms of the illness, to be passed through a phase of intensive treatment followed by long-term rehabilitation measures and thereby be enabled to live, and in many instances work, outside the hospital.

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RÉSUMÉ

Les auteurs de cet article ont récemment fait l'essai d'un traitement combiné de sommeil prolongé et de sismothérapie intense chez des schizophrènes paranoïdes chroniques, réhabilités par la suite, et suivis à la clinique externe. La présente série comprenait un groupe de 16 malades dont les symptômes remontaient à au moins deux ans et que l'on a comparé à un autre groupe de dix malades dont les symptômes étaient d'origine plus récente. Trois malades du premier groupe durent être hospitalisés de nouveau, mais deux d'entre eux ont depuis reçu leur congé. Le troisième est encore sous traitement. Ces malades furent vus pendant deux ans à différents intervalles après leur sortie de l'hôpital. Deux autres malades du premier groupe abandonnèrent le traitement et retombèrent sous l'effet de leur symptomatologie paranoïde, mais sans toutefois revenir à l'hôpital. Certaines recrudescences de peu d'importance furent notées chez plusieurs malades des deux groupes et toutes répondirent au traitement à la clinique externe. Aucun malade du deuxième groupe n'eut à être hospitalisé de nouveau. On peut encore déceler

certains signes de schizophrénie chez les malades du premier groupe dont la symptomatologie remontait à plus de deux ans. Ces signes se manifestent par un dynamisme réduit et un émoussement de l'affectivité. Dans seulement trois des cas du premier groupe (ceux qui abandonnèrent le traitement et celui qui dut revenir à l'hôpital), trouve-t-on encore des signes d'interprétation paranoïde; tous les malades du deuxième groupe en sont exempts. Le but que se proposaient les auteurs de cette présentation est de montrer que grâce aux procédés thérapeutiques actuels, il est possible que des schizophrènes, même s'ils sont affectés de la forme la plus grave de cette maladie, peuvent subir une phase de traitement intensif suivie de mesures de réhabilitation à longue échéance pour en arriver enfin à vivre et même souvent à travailler ailleurs que dans un milieu hospitalier.

THE CLINICAL AND METABOLIC EFFECTS OF GLUCAGON*

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SHORTLY AFTER the discovery of insulin it was noted that the intravenous administration of crude preparations of this hormone produced a transient hyperglycæmia before the characteristic hypoglycæmic action of insulin occurred. On the basis of these observations Murlin[1] suggested that pancreatic extracts contained, in addition to insulin, a hyperglycæmic substance which he named glucagon.‡ Burger and Brandt[2] were among the first to study the physiological effects of glucagon. They worked with crude preparations of this material. Partial purification of glucagon was achieved by Sutherland *et al.*[3] and the material was finally isolated in crystalline form by Staub and co-workers[4] in 1953. Glucagon has been chemically characterized as a single polypeptide chain of low molecular weight.[5]

Most studies dealing with the metabolic effects of glucagon in humans have been carried out over a short period of time. The only consistent effect obtained has been the rapid breakdown of liver glycogen which raises the blood sugar level quickly but temporarily.

Recently Salter, Davidson and Best[6] have shown that if glucagon is administered to experimental animals by multiple daily injections, or in a medium that delays absorption, sustained hyperglycæmia and increased excretion of urea nitrogen results. The net effect on protein metabolism is similar to that induced by the glucocorticoid hormones.

It was this similarity to cortisone that led Salter to suggest the cautious administration of glucagon to patients with rheumatoid arthritis and allied disorders to determine whether long-acting glucagon would lead to protein depletion in humans and whether this action would be accompanied by an anti-inflammatory effect.

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‡Also known as the hyperglycæmic-glycogenolytic factor.

METHODS AND PROCEDURES

We have given crystalline glucagon by slow intravenous drip to eight patients with rheumatoid arthritis and allied disorders. The dose ranged from 2.5 mg. to 25 mg. a day. It was usually dissolved in 500 c.c. of normal saline. The infusion was begun one hour before breakfast and allowed to run in over a period of 10 hours. The longest uninterrupted course was four days. Some patients were given intramuscular and hypodermic injections so that the effectiveness of these different methods of administration might be compared. This report deals chiefly with the effects of intravenous administration of glucagon.

RESULTS AND COMMENT

Clinical Effects:

(a) Nausea was common to all of these patients. In three of them metabolic balance studies had to be discontinued because of vomiting. Although nausea was sometimes noted when the blood sugar was rising rapidly, it also occurred when blood sugar was normal or low. There have been other reports that glucagon has an inhibitory effect on gastric and intestinal smooth muscle.[7, 8]

(b) Anti-inflammatory action. Our patients could be divided into two groups: Five of them had active synovial inflammation in several joints; three had long-standing disease with gross destruction of articular surfaces and irreversible deformity.

In all of the patients of the first group there was considerable reduction in pain and stiffness in the joints, apparent two or three days after glucagon was started. Two patients with fluid in knee joints showed a measurable decrease in the size of the effusions. The erythrocyte sedimentation rate did not change significantly although there was a reduction of over 100 mg. in the plasma fibrinogen level in one patient. Relapse occurred in all of these patients a few days to a few weeks after glucagon was discontinued.

None of the patients with chronic destructive arthritis had more than slight symptomatic benefit from the administration of glucagon even though the metabolic effects obtained were equivalent to those observed in patients of the first group.

Metabolic Effects:

(a) *Carbohydrate Metabolism*

(i) Hyperglycæmia: In all of the patients the blood sugar rose before breakfast at 9:00 a.m. under the influence of glucagon given at 8:00 a.m.