St Moritz Jan 1974.

DISCUSSION of the paper by

Prof. P. Pichot: The treatment of depression.

Prof. Pichot has given us a concise and comprehensive overview of the various treatments of depression currently applied by clinical psychiatrists and explored by researchers. I fully agree with him when he states that in this rapidly changing field only two things seem to be firmly established: 1. that in the treatment of endogenous depressions the biological methods are most effective - I would even add that depriving a patient suffering from an endogenous depression of antidepressant pharmacotherapy or electroconvulsive treatment is bad medicine and endangers the patient's life - and 2. that electroconvulsive treatment is still more effective than antidepressant pharmacotherapy. He has pointed out that, in spite of a great deal of research activity in this field, we still have no reliable means of determining which particular antidepressant drug or biogenic amine precursor is indicated in any particular case of depression. It would certainly be desirable for every clinician to possess the means of determining this before he starts treating any depressed patient, and many existing methods have been suggested - from therapeutic trials with amphetamines (Maas, 1972) to 5-hydroxyindoleacetic acid levels in the spinal fluid (van Praag, 1972) and MHPG levels in the urine (Schildkraut, 1972), in addition to the differential clinical classification of depressive states - but a recent paper by Fakhr El Islam (1973) throws some doubt, at least on the possibility of finding such differential therapeutic criteria on the basis of previous therapeutic responses. Fakhr El Islam has, over a period of 4½ years, treated 158 depressed patients, for a total of 417 depressive episodes, and

analyzing the therapeutic responses of these patients in relation to their responses to previously given treatments, he finds that it made no difference whether a patient had previously responded well to an MAO inhibitor or a tricyclic antidepressant, as far as his response to the next treatment was concerned. Patients who had responded well to an MAO inhibitor during a former depressive attack, often responded just as well to a tricyclic the next time and vice versa. The author concludes that a patient might, during a lifetime of recurrent attacks, run the gamut of any conceivable type of depression.

~~Prof. Pichot has referred to the~~ controversial findings regarding plasma levels of tricyclic antidepressant drugs and their correlation with clinical findings. This correlation appears to be of a nonlinear type, and, in view of the great interindividual differences in plasma levels after identical doses of tricyclics, the problem remains how to determine the optimal level. It seems that we still have to rely on the empirical method of clinical trial and error, using the appearance of side effects as a guide even before a therapeutic response is observable. One might add that in elderly patients and those who have a history of symptoms of circulatory disease, an electrocardiogram would be indicated prior to starting treatment with tricyclic drugs, and electrocardiographic monitoring should be continued throughout the treatment period, since it is known that these drugs might have cardiotoxic effect.

~~Prof. Pichot mentioned that~~ many clinicians now lower the dose of prophylactically given lithium when a depressive attack supervenes. This is certainly a wise procedure, not only because lithium clearance seems to be

impaired during a depressive state, but also because lithium blood levels might suddenly rise considerably when tricyclic drugs are prescribed simultaneously, an interaction we have recently observed in a patient on lithium who became depressed and was then put on imipramine.

I was intrigued by the findings of the enquiry among French general practitioners on which Prof. Pichot reported. It is certainly encouraging to realize that 7 out of 10 general practitioners in France now undertake to treat depressions, even if only 3 out of 10 are also ready to give psychotherapy when it is indicated. Most heartening, however, was the finding that there seems to be a well established parallelism between the therapeutic principles for the management of depressions adopted by general practitioners and specialists.

The pharmacological difference between anxiolytic sedatives and antidepressants has apparently been grasped by the non-specialist physician, and that means that he has been alerted to the important psychopathological difference between anxiety and depression. It would be interesting to establish, by means of another enquiry, how many non-specialist physicians who prescribe antidepressants are also informed about the underlying neurophysiological and psychoparmacological rationale of this treatment. I would guess, not many; yet, it should not be difficult to teach the current theoretical framework of the biology of depression - either in continued education and postgraduate courses, or through dissemination of educational literature of the pharmaceutical industry.

I noted that one of the two most widely prescribed antidepressants in France - clomipramine - is not yet marketed in North America. What I cannot understand - and apparently

Prof. Pichot is at a loss about this phenomenon himself - is that 64 per cent of physicians prescribe levomepromazine and 48 per cent haloperidol for depressed patients. Both drugs are clearly classified as neuroleptics, and not as thymoleptics, in Canada and the United States. Even if it is recognized that levomepromazine often has some secondary antidepressant effect, that is certainly not true for haloperidol which, in fact, may not infrequently precipitate a depression in a manic patient who receives the drug for the control of his manic symptoms.

I cannot judge the great popularity of sulpiridine among French physicians because we have had no experience with this drug which is not marketed on the North American continent and has not yet been studied extensively there. But Prof. Bichot suggests that French physicians do not seem very well informed about the use of this drug either - a situation which seems to indicate somewhat premature and overzealous promotional efforts on the part of the industry.

Let me now take the remaining minutes of my allotted time to review some of the general issues concerned with the home treatment of depressed patients.

There is first of all the problem of diagnosis. This question has been dealt with extensively at the last meeting of this group in 1973. Depression does not always manifest itself in its classical textbook form. The physicians' task may be divided into the following four steps:

1. recognition of the existence of a depressive state;

2. decision whether the depression is pathological or not; that is, a decision whether the depression requires medical treatment;

3. differential diagnosis of the pathological depression;

4. decision what treatment should be given.

There are, of course, depressive states that do not call for treatment according to the medical model, for instance, grief reactions and certain existential depressions. In that connection I should like to draw your attention to a recent investigation by Zung (1972) - reported in a paper entitled: How normal is depression? - who found that in a sample of 1,108 normal subjects 48 per cent of those under 19 years and 44 per cent of those over 65 years of age could be considered as having depressive symptoms of clinical significance, when their score on a self-rating scale was taken as the criterion. Nevertheless, it does not follow that these people - younger and older than the average - all need medical treatment for the depressive symptoms.

Once the decision has been made to treat the depressed person medically, the next question to be faced is whether to treat the patient at home in ambulatory fashion or to hospitalize him. Table I lists the advantages and disadvantages of home and hospital treatment respectively. Advantages of hospital treatment are better supervision and, therefore, better safeguards against suicide. The hospital also provides facilities for special treatments that may be required, e.g. intravenous infusions, intensive ECT, etc. Finally, the hospital often can remove the depressed p atient from a stressful environment, if his family or other features of his home environment are some of the stress-producing factors; and, by the same token, the family may be relieved from stress if the patient leaves the home.

On the other side of the ledger, we have to consider the potentially traumatizing effect on a person of having to be hospitalized, the various inconveniences imposed by a break in the patient's habits and social environment, the burden of the greater financial cost, the difficulty of finding a hospital bed immediately when it is needed and, in some cases, the risk of creating "hospitalism", that is, a pathological dependence on the hospital.

As for the home, the advantages are: possibly a better therapeutic environment, particularly when there is a very supportive family attitude, and chances for a more rapid rehabilitation once the acute symptoms have subsided.

Table II summarizes the clinical grounds for the decision where the patient should be treated. Presuming generally that home treatment of depression is to be preferred to hospital treatments, the balance would be tipped in favour of hospital treatment only if the patient is extremely agitated, presents very severe suicidal danger, is unfavourably influenced by his home environment, requires treatments that can only be given in a hospital setting - particularly when the patient has proved to be refractory to the usual treatments given at home - and, finally, if the patient's family is in urgent need of relief from the presence of the depressed patient.

Table III show the treatments that are available for the depressed patient in his domicile or in the hospital. Home treatment consists mainly of antidepressant pharmacotherapy and, if necessary, ambulatory ECT as an outpatient. The hospital can offer, in addition, intravenous drug therapy, certain combined treatments, e.g. MAO inhibitors with tricyclics - a therapy connected with some risks that should be absorbed, at least in the early phases, in an hospital environment - prolonged narcosis, and its converse, sleep deprivation.

Some thoughts bearing on the question home vs hospital treatment have been discussed in recent papers by Prusoff et al (1972) and Scott (1973). The first group of investigators compared depressed patients' self-reports on their condition with the clinician's observations and found that a depressed patient's selfreports are valuable in the later stages of his illness, but not during the acute phase, when selfreports on the severity of the patients' condition are not reliable. Scott has drawn attention to the fact that psychiatric patients, including depressives, are really not entirely helpless victims of a pathological process, social conditions or family milieu, but rather are often "unrecognized agents" who are much more knowledgeable about their relationship with their family and treatment personnel than the latter expect, and thus can play an unsuspected important role in the therapeutic process, a role to which Scott refers as a potential "treatment barrier".

The greatest immediate danger in every depressive state is always suicide. Regarding the problem of judging this risk, the physicians must keep in mind that the only times a depressed patient is relatively secure as far as suicide is concerned, are when he is asleep, when he is occupied - for instance, working if he is still capable of it - and when he is engaged in social interaction. Any time a depressed patient is left to his own resources, that is idle, thinking, fantasying or lying in bed sleeplessly, he is likely to start ruminating - always a dangerous state for a depressed individual. The practical conclusion to be drawn from this, is that depressed patients living alone are greater suicidal risks than those living with their family. The need for hospital treatment should, therefore, always seriously be considered in depressed persons living alone, even more so if they are elderly and/or alcoholic; and the need for tranquilizers or hypnotics, in addition to

antidepressants, for such patients is particularly great.

May I now conclude this presentation - which, in the nature of many discussion remarks, has been somewhat of a potpourri - with a few desiderata, some facts and informational items I had hoped to receive as Christmas presents from whoever is the Santa Claus equivalent of Aesculapius. I did not find them under the Christmas tree this year - perhaps next year, perhaps in 10 years? Anyway, here they are, the procedures and the information we need badly to facilitate the home as well as the hospital treatment of depressed patients:

1. a simple, practical procedure that can be carried out in any clinical laboratory, or, preferably, by the patient himself at home, to determine the level of antidepressant drugs in the plasma, or preferably in saliva. This hope is not so farfetched as it may appear at first glance, for some successful work has already been reported by Russian investigators on the determination of lithium levels in saliva (apparently 10 times higher than in blood) (Mikhalenko and Leontyev, 1973), and on the determination of labelled catecholamine metabolites as well as MAO inhibitors in saliva by Rosenblatt et al (1973) in a New York laboratory.

2. a simple procedure to determine which particular treatment would be indicated in any individual depressed patient. I am thinking here of a simplification and confirmation of one or several of the methods that have been proposed by several investigators and to which I have already referred.

3. a simple, easily repeatable procedure that would give a valid and reliable measure of the changes that have occurred, toward improvement or deterioration, in the clinical condition of a depressed patient. I am thinking here of such relatively objective procedures as the perceptual rate of change of a Necker cube, the measurement of disinhibition in conditional reflexes, the degree of facial asymmetry in a photograph, etc. - any practical experimental procedure that would make us more independent from the present methodological tyranny of rating scales.

I think it will be only a question of time until these measures will be available. In the meantime, we should remain thankful for the progress in our treatment of depressions, and in our knowledge about their pathophysiology, we have made in the last 15 years.

REFERENCES

FAKHR EL ISLAM , M. "Is response to antidepressants an aid to the differentiation of response - specific types of depression?". Brit. J. Psychiat. 123: (1973) 509.

MAAS, J.W., FAWCETT, J.A. and DEKIRMENJIAN, H. "Catecholamine metabolism, depressive illness and drug response". Arch. Gen. Psychiat. 26: (1972) 252-262.

MIKHALENKO, I.N. and LEONTYEV, V.G. "Study of lithium concentration in the blood during treatment of patients with manic depressive psychosis". Zr. Nevropat. Psilhiat. Korsakov. 73/2: (1973) 279-284.

PRUSOFF, B.A. KLERMAN, G.I. and PAYKEL, E.S. "Concordance between clinical assessments and patients' self report in depression". Arch. Gen. Psychiat. 26/6: (1972), 546-552.

ROSENBLATT, S., LEICHTON, W.P. and CHANLEY, J.D. "Dopamine-B-Hydroxylase: Evidence for increased activity in sympathetic neurons during psychotic state". Sc. Vol.182: (Nov. 30, 1973) 923-924.

SCHILDKRAUT, J.J., DRASKOCZY, P.R., GERSHON, E.S. et al. "Catecholamine metabolism in affective disorders: IV. Preliminary studies of norepinephrine metabolism in depressed patients treated with amitriptyline". J. Psychiat. Res. 9/3, (1972) 173-185.

SCOTT, R.D. "The treatment barrier: Part 2. The patient as an unrecognized agent". Brit. J. Med. Psychol. 46/1: (1973), 57-67.

VAN PRAAG, H.M., KORF, J., DOLS, L.C.W. and SCHUT, T. "A pilot study of the predictive value of the probenecid test in application of 5 hydroxytryptophan as antidepressant". Psychopharmacologia (Berl.) 25/1, (1972), 14-21.

ZUNG, W.W.K. "How normal is depression?". Psychosomatics 13/3: (1972), 174-178.