Psychopharmacologia (Berl.) 44, 105–110 (1975) – © by Springer-Verlag 1975

The Effect of L-Dopa on Young Patients with Simple Schizophrenia, Treated with Neuroleptic Drugs

A Double-Blind Cross-Over Trial with Madopar and Placebo

JES GERLACH and KURT LÜHDORF

Sct. Hans Hospital, Depts. E and H, Roskilde, Denmark

Received May 29, 1975

Abstract. Thirteen out of 18 young out-patients with simple schizophrenia under neuroleptic treatment completed a double-blind cross-over trial with Madopar® [L-Dopa + benserazid (a peripheral decarboxylase inhibitor)] and placebo. Nine patients were given 900 mg L-Dopa + 225 mg benserazid daily, 1 patient received 600 mg L-Dopa + 150 mg benserazid, and 3 patients, 300 mg L-Dopa + 75 mg benserazid. In these doses, L-Dopa was effective against emotional withdrawal, blunted affect, tendency to isolation and apathy, without inducing or aggravating productive, accessory symptoms. The activity score, according to the specific activity-withdrawal scale, was significantly increased ($P < 0.05$), whereas the total BPRS score (Brief Psychiatric Rating Scale) was slightly, but significantly reduced ($P < 0.05$). In cases where L-Dopa had to be limited to 600 and 300 mg daily, a tendency to anxiety, distortion of thinking, and a sense of unreality were observed, depending on the dose of L-Dopa. In no case were gastrointestinal, cardiovascular or neurological side-effects observed.

Key words: Schizophrenia simplex – L-Dopa – Madopar.

Simple schizophrenia is characterized by reduction of interest in human relationships and the outside world, impoverishment of the personality, apathy, and indifference (Glasner, 1969). The patients become affectively and intellectually weaker; the will seems to lose its power; the capacity for work, for caring for themselves diminishes (Bleuler, 1950). As distinct from the hebephrenic, catatonic and paranoid types of schizophrenia, productive accessory symptoms are rare and fleeting.

L-Dopa has a good therapeutic effect in Parkinsonian patients, on neurological symptoms as well as on mental functions such as cognition-perception, emotinal function and the level of activation and arousal. The patients become more interested in the outside world, wish to take part in conversation and in other people's activities (Barbeau, 1972; Duvoisin and Yahr, 1972; Riklan, 1973). Increasing the dose of L-Dopa involves a risk of mental side-effects such as agitation, aggression, depression, paranoid ideas, hallucinations and confusion (Celesia and Barr, 1970; Ginath *et al.*, 1971; Goodwin, 1971). Just as the effect on the akinesia, with increasing doses of L-Dopa, tends to be transformed into involuntary hyperkinesia (Barbeau, 1969), the above-mentioned mentally activating effect may give rise to productive psychotic phenomena.

The effect of L-Dopa in schizophrenia seems also to depend on the dosage. Bruno and Bruno (1966) found that 2 mg/kg of L-Dopa, given intravenously to schizophrenic patients treated with neuroleptics, produced transient improvement, as evidenced by a smaller degree of bradyphrenia, greater emotinal participation and a feeling of well-being. In a double-blind trial, Inanaga *et al.* (1972) found that 400–600 mg L-Dopa had a good effect in hebephrenic patients treated with neuroleptic drugs and with a duration of illness of less than 5 years. In particular, the capability of communication and the apathy improved. Higher L-Dopa doses accentuate psychotic symptoms already present both in untreated schizophrenic patients (Angrist *et al.*, 1973a), and in patients treated with neuroleptic drugs (Yaryura-Tobias *et al.*, 1970, 1972).

In normal, non-psychotic individuals, L-Dopa in relatively high doses (3–11 g daily) has a psychomotor arousal or activating effect (Murphy *et al.*, 1972, with further references).

L-Dopa has never been tried in the treatment of simple schizophrenia. The aim of the present study was to assess the effect and side-effects of L-Dopa in young patients with simple schizophrenia treated with neuroleptic drugs.

Methods

Patients. Eighteen out-patients from departments A, D, E and H at Sct. Hans Hospital consented to participate in the trial. They all met the following criteria: ages between 25 and 35 years, diagnosis of simple schizophrenia, no paranoid delusions or hallucinations during the previous 6 months, duration of illness ranging from 1–15 years, unchanged treatment with neuroleptic drugs for at least 3 months and no neurological or serious somatic disorders.

Medication. No changes were made in the current neuroleptic treatment (see Table 1).

L-Dopa was administered as Madopar® capsules containing 100 mg L-Dopa and 25 mg benserazid (a peripheral decarboxylase inhibitor, by which the central effect of L-Dopa is increased about 5 times). During the control period, placebo capsules of a similar appearance were given. The capsules were given to the patients every 2 weeks in prepacked dosage containers. No vitamins were given during the trial period.

Design. The trial was carried out as a double-blind cross-over study, each patient being treated with L-Dopa and placebo in randomized order. Each treatment period was 12 weeks, with no drug-free interval.

The initial dose was 1 capsule 3 times daily. After 2 weeks the dose was increased gradually by 1 capsule weekly or forthnightly to a total dose of 3 capsules 3 times daily, the dosage remaining unchanged for the last 4 weeks. In case of side-effects or subjective complaints the dose was gradually reduced.

Evaluation. The therapeutic effect was assessed applying the *Brief Psychiatric Rating Scale* (BPRS) (Overall and Gorham, 1962), an *Activity-Withdrawal Scale* [slightly modified from the scale of Venables (1957)], and a specially designed scale for *global evaluation.* Side-effects of neuroleptic drugs and L-Dopa were recorded by means of a special *side-effect scale.*

Table 1. Patient data

No., initials	Age in years	Duration of Sch. in years	Previous and possible actual productive schizophrenic symptoms	Medication (minus L-Dopa) during investigation				
				Neuroleptic drug	Dose[a]	Duration in years	Anti-Parkinson drugs	Dose/ 24 hrs
2. B.D.	34	10	–	Clozapine	75 mg	1	–	
3. T.H.	25	5	–	Flupenthixol	6 mg	1	Biperiden	6 mg
4. M.H.	27	3	Aggression, del. and hall. 3 years ago	Perphenazine	48 mg	1	Orphenadrine	150 mg
5. T.S.	30	10	Del., hall. 8 years ago. Still slight hypoch. ideas	Clozapine	200 mg	1	–	
8. F.H.	25	6	–	Flupenthixol decanoate	100 mg/ 14. day	2	Orphenadrine	150 mg
9. J.P.	29	3	Del., 2–4 years ago. Still slight hypoch. ideas	Penfluridol	80 mg/ 7. day	1	–	
10. G.J.	25	2	–	Flupenthixol decanoate	100 mg/ 14. day	2	Biperiden	12 mg
11. L.A.	25	3	Depers., hall., self mutilation 3 years ago	Flupenthixol decanoate	60 mg/ 14. day	1/4	–	
12. C.P.	31	15	Del., hall. 10 years ago	Penfluridol, Levomepromazine	60 mg/ 7. day 100 mg	1/4	Orphenadrine	100 mg
13. R.K.	26	4	Depers., hall. 5 years ago. Still feeling of snakes around the legs	Flupenthixol decanoate	80 mg/ 14. day	1	Procyclidine	15 mg
16. J.D.	27	1	Depers. during hash smoking 1 year ago	Penfluridol	40 mg/ 7. day	1/4	–	
17. E.L.	27	2	–	Penfluridol	60 mg/ 7. day	1/2	–	
18. H.H.	35	14	Persecutory del. 14 years ago	Penfluridol	60 mg/ 7. day	1	–	

Abbreviations: *Sch.* schizophrenia; *del.* delusions; *hall.* hallucinations; *depers.* depersonalization; *hypoch.* hypochondriac
[a] Where nothing else is stated, the dose is per 24 hrs.

Table 2. Dosage, total BPRS score, activity-withdrawal score, global evaluation and side-effect for each patient

No.	First drug	Daily L-Dopa dosis (mg)	Total BPRS score			Activity score			Global evaluation						Neuroleptic-induced Parkinsonism	
			Pl	Ma	Diff	Pl	Ma	Diff	Emotional withdrawal		Anxiety		Therapeut. effect			
									Pl	Ma	Pl	Ma	Pl	Ma	Pl	Ma
2.	Ma	300	23	21	− 2	26	31	− 5	−	0	0	0	0	0	0	0
3.	Pl	900	22	19	− 3	26	26	0	0	0	0	0	0	0	0	0
4.	Ma	900	16	16	− 0	27	29	− 2	0	+	0	0	0	+	0	0
5.	Pl	900	17	17	− 0	44	50	− 6	0	0	0	0	0	0	0	0
8.	Ma	900	17	17	− 0	23	23	− 0	0	0	0	0	0	0	0	0
9.	Ma	900	33	30	− 3	29	39	10	0	+	0	0	0	+	2[a]	0
10.	Pl	900	21	20	− 1	26	30	4	0	+	0	0	0	+	3	2
11.	Ma	600	17	10	− 7	29	34	5	0	+	+	+	−	+	0	0
12.	Pl	300	19	11	− 8	27	33	6	0	+	0	+	0	+	2	1
13.	Pl	300	16	20	4	39	33	− 6	0	0	+	+	−	−	0	0
16.	Ma	900	19	13	− 6	30	30	0	0	0	+	0	0	+	1	1
17.	Pl	900	15	14	− 1	34	37	3	+	0	+	0	+	0	0	0
18.	Pl	900	15	11	− 4	30	37	7	+	+	0	0	+	+	0	0

Abbreviations: *Ma.* Madopar; *Pl.* placebo; *Diff.* difference.
In the global evaluation: + means improvement; 0 unchanged; − deterioration.
The decrease in total BPRS score and the increase in activity score during Madopar compared to placebo is significant ($P < 0.05$, Wilcoxon test for pair diff.). The changes in global evaluation is not significant ($P > 0.05$, the sign test).
[a] Indicates acute dystonia.

Statistics. The results from the BPRS and the Activity-Withdrawal Scale were evaluated statistically by applying Wilcoxon's test for paired data, and the sign test for the global scales.

Results

Patients. Drop-outs: Five of the 18 patients had to be excluded during the initial stage of the trial: No. 1 refused to continue after 2 months because of lack of effect (placebo); No. 6 stopped taking the neuroleptic drug and 2 months later also the trial drug (placebo); Nos. 7 and 15 refused to co-operate without any further explanation or apparent change in their condition (both Madopar), and No. 14 stopped taking the trial drug (Madopar) after 4 days of treatment because of anxiety and restlessness (this case is mentioned later under the global evaluation of the anxiety-producing effect of L-Dopa).

The characteristics of the remaining group of 13 patients with regard to age, symptoms, duration of illness and medication are shown in Table 1. All the patients had a characteristic BPRS-profile showing a high score in emotional withdrawal, motor retardation and blunted affect; in some cases an awkward attitude and behaviour, slight fear and anxiety were observed. None of the patients had hallucinations, but a few presented vague hypochondriac complaints. However, several of the patients had previously been through one or more episodes with productive symptoms (see Table 1).

Dosage. As appears from Table 2, the maximum dose of 900 mg L-Dopa + 225 mg benserazid was given in 9 out of 13 cases, whereas, in 1 case, the dose had to be reduced to 600 mg and in 3 cases to 300 mg daily. In these 4 cases the limitation of dosage was determined by the patients' own description of their mental state: in 3 cases (Nos. 11, 12 and 13) it was incipient anxiety and restlessness and in one case (No. 1) a vague feeling of not being able to control thoughts and behaviour if the dose was further increased.

Previous medication with neuroleptic and anticholinergic anti-Parkinsonian drugs was maintained unchanged throughout the trial period (see Table 1).

The Effect of L-Dopa on the Psychotic Condition. No psychotic exacerbations were observed, neither accentuation of existing symptoms nor development of others. Two patients complained of incipient "troubled thoughts" and a feeling of unreality. No. 11 had a feeling of being slightly influenced by "speed" (central stimulant drugs). Productive symptoms did not appear.

As will be seen from Table 2, regarding the material as a whole, L-Dopa produced a slight but significant reduction in the total BPRS score ($P < 0.05$),

i.e., L-Dopa improved the psychotic condition as compared with placebo.

The Effect of L-Dopa on Emotional Withdrawal and Apathy. The above-mentioned beneficial therapeutic effect on the psychotic condition was mainly evident against blunted affect, emotional withdrawal, autism and apathy. The patients became more active, slept less, were more alert during the day, became more interested in contacts.

As appears from Table 2 (withdrawal activity score), the arousal-activating effect of L-Dopa was significant ($P < 0.05$).

Global Evaluation (see Table 2) of 1. emotional withdrawal, 2. anxiety, 3. productive schizophrenic symptoms and 4. mood during L-Dopa treatment showed: 1. a tendency to increased activity (not significant); 2. anxiety in a few patients, the incidence, however, being the same as that found during placebo medication; one patient (No. 14) was excluded for this reason, 3. no productive schizophrenic symptoms and 4. a much more cheerful mood in patient No. 1 during Madopar treatment and slight depression in patients Nos. 1, 11 and 16 during the placebo period as compared with Madopar.

Table 2 shows that 6 out of 13 patients on the whole derived therapeutic benefit from L-Dopa as compared with placebo, while the opposite was seen in one case.

Effect of L-Dopa on Neuroleptic-Induced Parkinson Syndrome. Prior to the trial the patients had been treated for any neuroleptic-induced neurological side-effects present, by the administration of anticholinergic anti-Parkinsonian drugs. Nevertheless, during the placebo period, 4 patients (see Table 2) presented slight akathisia and Parkinsonism. Both symptoms were slightly alleviated during Madopar treatment. In one case (No. 9), acute dystonia developed when changing from Madopar to placebo.

Side Effects of Madopar. None of the patients presented gastrointestinal or cardiovascular side-effects during Madopar treatment. During the entire trial period only 2 patients (Nos. 16 and 17) had nausea and vomiting, both of them during placebo periods. No involuntary hyperkinetic movements were observed at any time during the trial. The mental side-effects have already been described.

Discussion

In spite of the limited group of patients, the present study allows some statistically conclusive data concerning the effect of L-Dopa on the schizophrenic patients concerned. This is especially owing to the homogeneity of the patient material as regards diagnosis, symptom profile, age and duration of illness and also to the cross-over design applied.

The most important result of this trial is that L-Dopa is able to activate young schizophrenic patients marked by emotional withdrawal, blunted affect, tendency to isolation and apathy, without inducing productive schizophrenic symptoms. This is in agreement with the findings reported by Bruno and Bruno (1966) and Inanaga *et al.* (1972) (see Introduction). Signs of approaching anxiety, restlessness and feelings of unreality could be alleviated by a slight reduction in dosage. Consequently, the effect of L-Dopa—similar to the effect in Parkinson's disease—depends both qualitatively and quantitatively on the dose level.

The mechanism controlling this activating effect is presumably the L-Dopa-induced stimulation of dopaminergic and noradrenergic receptors, both of which influence motor activity (Svensson and Waldeck, 1970; Andén *et al.*, 1973; Marsden *et al.*, 1974) and mental arousal phenomena, including learning and memory (Murphy *et al.*, 1972).

Considering repeated observations of development or aggravation of psychotic symptoms during L-Dopa treatment of schizophrenic patients (Goodwin *et al.*, 1971; Yaryura-Tobias *et al.*, 1970, 1972; Angrist *et al.*, 1973a, b), it is remarkable that a similar tendency was not revealed in our study in spite of the rather high doses (900 mg L-Dopa + 225 mg benserazid which have the same effects as 4—5 g L-Dopa). The most likely explanation is that our young patients still possess their biological "buffer capacity" against influences on the catecholaminergic systems.

The potential risk of aggravating psychotic symptoms should of course always be taken into consideration when using L-Dopa for psychomotor stimulation. There is also a risk of inducing increased sensitivity to L-Dopa during long-term treatment, as has been observed in animal experiments (Langelier *et al.*, 1973) and in L-Dopa treatment of Parkinsonian patients, who may develop hyperkinesias in spite of a gradually reduced dosage (Cotzias, 1971; Barbeau, 1974).

There is much evidence indicating that productive accessory schizophrenic symptoms are related to dopaminergic hyperactivity (Randrup and Munkvad, 1972; Klawans *et al.*, 1972; Stevens, 1973). Results of Angrist *et al.* (1973b) indicate that the psychosis-activating effect of L-Dopa in schizophrenic patients is due to a specific pharmacological stimulation of the pathogenetic processes of the disease and not to a non-specific activation of predisposed reaction patterns. However, it remains to be clarified whether the "negative" symptoms, the apathy, the emotional shallowness, the enervation and the lack of concen-

tration power are caused by the same factors. The data reported here suggest that various biochemical mechanisms control the various schizophrenic symptoms.

This assumption is supported by Møller Nielsen (1974) and Møller Nielsen and Christensen (1974) who in animal experiments have studied the interaction between the cataleptic effect and the receptor hypersensitivity following a single dose and following repeated doses of a neuroleptic (teflutixol). They found that the hypersensitivity takes the lead in the course of time, in other words that a facilitation of the dopaminergic transmission is achieved. The antipsychotic effect of neuroleptics may thus in part be explained by this facilitation of dopaminergic functions.

The hypothesis may be advanced that the "negative" symptoms could be due to a hypofunctional condition in certain transmitter systems, *e.g.* the catecholaminergic, whereas the productive schizophrenic symptoms could represent a hyperfunctional condition, perhaps as a secondary hypersensitivity within the same transmitter system. The insidious course of certain types of schizophrenia, initially with "negative", subsequently with more productive symptoms, supports this assumption.

The activating effect of L-Dopa observed may be caused by an antagonistic effect on the reduced mobility, the apathy, inertia and mental indifference, which accompany any neuroleptic treatment (Delay *et al.*, 1959), and which cannot be sufficiently counteracted by anticholinergic drugs. It might be that neuroleptic drugs, to a varying extent, inhibit the function in the various dopaminergic neuron systems (*e.g.*, the striatal, the limbic and the cortical) and noradrenergic neuron systems in the brain. Some of these inhibitory functions may be decisive for the antipsychotic effect, others not. L-Dopa in low doses might reverse some of these inhibitory functions, without influencing the antipsychotic effect of neuroleptic drugs.

Irrespective of its mechanism of action, L-Dopa may, as described above, exert a favourable effect in some types of schizophrenic patients treated with neuroleptic drugs. Similar results are obtained with amphetamine-like drugs (Cesarec *et al.*, 1974, with further references). However, additional studies with other catecholamine agonists are required on this subject. Such clinical studies with the aim of clarifying the antipsychotic mechanism of action are not only justifiable, but imperative as long as the present neuroleptic drugs are insufficient in therapeutic efficacy against schizophrenic symptomatology, especially the "negative" symptoms described in this study, and furthermore tend to induce neurological, autonomic and mental side-effects.

References

Andén, N.-E., Strömbom, U., Svensson, T.: Dopamine and noradrenaline receptor stimulation: reversal of reserpine-induced suppression. Psychopharmacologia (Berl.) **29**, 289–298 (1973)

Angrist, B., Sathananthan, G., Gershon, S.: Behavioural effect of L-Dopa in schizophrenic patients. Psychopharmacologia (Berl.) **31**, 1–12 (1973a)

Angrist, B., Sathananthan, G., Wilk, S., Gershon, S.: Behavioural and biochemical effects of L-Dopa in psychiatric patients. In: Frontiers in catecholamine research. 3rd Intern. Catecholamine Symp. Strasbourg-Fr. E. Usdin and S. Snyder, eds., pp. 991–994. Oxford: Pergamon 1973b

Barbeau, A.: L-Dopa therapy in Parkinson's disease: a critial review of nine years' experience. Canad. med. Ass. J. **101**, 791–800 (1969)

Barbeau, A.: Dopamine and mental function. In: L-Dopa and behavior, S. Malitz, ed., pp. 9–33. New York: Raven Press 1972

Barbeau, A.: The clinical physiology of side effects in longterm L-Dopa therapy. In: Advances in neurology, vol. 5. Fl. H. McDowell and A. Barbeau, eds., pp. 347–365. New York: Raven Press 1974

Bleuler, E.: Dementia praecox or the group of schizophrenia, pp. 235–239. New York: International Universities Press 1950

Bruno, A., Bruno, S.: Effects of L-Dopa on pharmacological parkinsonism. Acta psychiat. scand. **42**, 264–271 (1966)

Celesia, G., Barr, A.: Psychosis and other psychiatric manifestations of levodopa therapy. Arch. Neurol. (Chic.) **23**, 1993–2000 (1970)

Cesarec, Z., Eberhard, G., Nordgren, L.: A controlled study of the antipsychotic and sedative effects of neuroleptic drugs and amphetamine in chronic schizophrenics. Acta psychiat. scand. Suppl. **249**, 65–77 (1974)

Cotzias, G.: Levodopa in the treatment of Parkinsonism. J. Amer. med. Ass. **218**, 1903–1908 (1971)

Delay, J., Deniker, P., Robert, R., Beek, H., Barande, R., Eurieult, M.: Syndromes neurologiques expérimentaux et thérapeutique psychiatrique. I. Éffects neurologiques d'un nouveau neuroleptique majeur, le 7843 RP. Press med. **67**, 123 (1959)

Duvoisin, R., Yahr, M.: Behavioural abnormalities occurring in Parkinsonism during treatment with L-Dopa. In: L-Dopa and behavior, S. Malitz, ed., pp. 57–72. New York: Raven Press 1972

Ginath, Y., Lavy, S., Abramsky, O., Carmon, A.: Mental complications of L-Dopa therapy in Parkinson's patients. Israel Ann. Psychiat. Related Disciplines **9**, 252–264 (1974)

Glasner, S.: The schizophrenias. In: Handbook of psychiatry. P. Solomon and V. Patch, eds., pp. 310–324. Los Altos: Lange Medical Publications 1969

Goodwin, F.: Psychiatric side effects of levodopa in man. J. Amer. med. Ass. **218**, 1915–1920 (1971)

Inanaga, K., Tanaka, M.: Effects of L-Dopa on schizophrenia. In: Psychopharmacology, sexual disorders and drug, T. A. Ban, J. R. Boissier, G. J. Gessa, H. Heimann, L. Hollister, H. E. Lehmann, I. Munkvad, H. Steiberg, F. Sulser, A. Sundwall, and O. Vinar, eds., pp. 229–233. Amsterdam-London: North-Holland and Prague: Avicenum, Czechoslovak Medical Press 1973

Klawans, H., Goetz, C., Westheimer, R.: Pathophysiology of schizophrenia and the striatum. Dis. nerv. Syst. **33**, 711–719 (1972)

Langelier, P., Roberge, A., Boucher, R., Poirier, L.: Effects of chronically administered L-Dopa in normal and lesioned cats. J. Pharmacol. exp. Ther. **187**, 15–26 (1973)
Marsden, C., Dolphin, A., Duvoisin, R., Jenner, P., Tarsy, D.: Role of noradrenaline in levodopa reversal of reserpine akinesia. Brain Res. **77**, 521–525 (1974)
Murphy, D., Henry, G., Weingartner, H.: Catecholamines and memory: Enhanced verbal learning during L-Dopa administration. Psychopharmacologia (Berl.) **27**, 319–326 (1972)
Møller Nielsen, I.: Pharmacological vs. clinical physiognomy of neuroleptics, with special reference to their sedative and antipsychotic effects. In: Clinical physiognomy of thioxanthenes. Acta psychiat. belg. **74**, 473–484 (1974)
Møller Nielsen, I., Christensen, A. V.: Long term effects of neuroleptics drugs. J. Pharmacol. **5**, Suppl. 2, 68 (1974)
Overall, J., Gorham, D.: The brief psychiatric rating scale. Psychol. Rep. **10**, 799–812 (1962)
Randrup, A., Munkvad, I.: Evidence indicating an association between schizophrenia and dopaminergic hyperactivity in the brain. Orthomolecular Psychiat. **1**, 2–7 (1972)
Riklan, M.: L-Dopa and Parkinsonism. A psychological assessment. Springfield, Ill.: Thomas 1973
Stevens, J.: An anatomy of schizophrenia? Arch. gen. Psychiat. **29**, 177–189 (1973)
Svensson, R., Waldeck, B.: On the role of catecholamines in motor activity: Experiments with inhibitors of synthesis and of monoamine oxidase. Psychopharmacologia (Berl.) **18**, 357–365 (1970)
Venables, P.: A short scale for rating "activity-withdrawal" in schizophrenics. J. ment. Sci. **103**, 197–199 (1957)
Yaryura-Tobias, J., Diamon, B., Merlis, S.: The action of L-Dopa on schizophrenic patients (a preliminary report). Curr. ther. Res. **12**, 528–531 (1970)
Yaryura-Tobias, J., Diamond, B., Merlis, S.: L-Dopa: A psychiatric tool. In: L-Dopa and behavior, S. Malitz, ed., pp. 121–130. New York: Raven Press 1972

J. Gerlach, M.D., Sct. Hans Hospital, Dept. E, DK-4000 Roskilde, Denmark

Announcement