PAPERS AND ORIGINALS

On the Risk of Multiple Sclerosis According to Age at Immigration to South Africa*

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Summary

In a national prevalence study of multiple sclerosis (M.S.) in the Republic of South Africa based on census day 1960 there were 118 individuals with M.S. who were born in Northern Europe (United Kingdom and other parts of North and Central Europe) and who had emigrated to the Republic by 1960. Their prevalence rate was 49 per 100,000 immigrants in comparison with a prevalence of 11 per 100,000 among native-born English-speaking white South Africans.

To study the possible effect of age at immigration it was necessary to relate the M.S. immigrants to the appropriate denominator—the population at risk according to age at immigration. The population at risk by age at immigration has been estimated by two methods in an indirect fashion with the assistance of the Bureau of Census (1960) and by surveys of the population at risk 1968-9. Both studies suggest that the risk of developing M.S. was reduced to less than a third of the expected risk among those who immigrated under the age of 15 or 16.

This study is further evidence that M.S. is an acquired exogenous disease, the precise nature of which is still not certain but, according to present knowledge, has as its leading contender the class of slow, latent, or temperate viruses.

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Introduction

In 1949 it was first reported that multiple sclerosis (M.S.) was very uncommon among the native-born white South Africans (Dean, 1949). About half the known cases were among immigrants from Europe though the immigrants were only 10% of the population at risk. Since 1956 an intensive study has been carried out in South Africa in order to discover all known cases of possible and probable multiple sclerosis (Dean, 1967a). To aid this study the South African Multiple Sclerosis Society was founded and full-time research staff was employed.

These South African studies showed that there was a high risk of M.S. among immigrants from Europe, of the same order of frequency as occurs in Europe. The risk of developing M.S. in the English-speaking white South African born was between a third and a quarter and in the Afrikaans-speaking white South African born only one-eleventh the risk in the immigrants from the United Kingdom and North and Central Europe. Immigrants from Northern Europe had a three times greater risk of M.S. than immigrants from the Mediterranean countries, and white immigrants from other African states had a low risk. The disease was extremely uncommon among the Cape Coloured and the Indian people of South Africa, and no single case of M.S. has yet been found among South Africa's 15 million Bantu (1960) (Table I, Figs. 1 and 2), though there are good Bantu hospitals with well-trained neurologists in the large cities.

With evidence of differential risk in migrants from a high-frequency M.S. region to a low-frequency region, it was considered necessary to seek an answer to the question of whether age at immigration was a deciding factor in this regard (Dean, 1967b; Kurtzke, 1967).

The patients were therefore subdivided by age at immigration according to place of origin and the relationship of immigration to the clinical onset of M.S. For those who entered South Africa below the age of 15 there is a pronounced scarcity of immigrants with M.S.

M.S. According to Age at Immigration

We needed to know what was the age at immigration for United Kingdom immigrants and for all North Europeans

TABLE I—*Prevalence of Probable M.S. in South Africans (1960)*

White South Africans	Population at Risk × 1,000			Probable M.S.			Rate/100,000	Age Corrected To Population of England and Wales
	Male	Female	Total	Male	Female	Total		
South African born	1,374	1,389	2,763	46	112	158	5·7	6·9
Afrikaans-speaking	927	910	1,837	20	37	57	3·1	3·6
English-speaking	446	479	925	26	75	101	10·9	12·7
Unspecified language group	0·4	0·4	0·8					
Immigrants	159	154	313	37	86	123	39·0	
Born U.K.	63	66	128	26	39	65	50·8	40·3
Born Central and Northern Europe	53	49	102	7	42	49	48·0	
Born South Europe	15	10	26	1	3	4	15·4	
Born Elsewhere	28	29	57	3	2	5	8·8	
Birthplace not known	0·9	0·9	1·9					
Total	1,534	1,544	3,078	83	198	281	9·1	11·0
Coloured	751	758	1,509	1	2	3		
Asian (Indian and Chinese)	242	235	477	3	3	6		
Bantu	5,512	5,416	10,928	—	—	—		
Total	8,039	7,953	15,992	87	203	290		

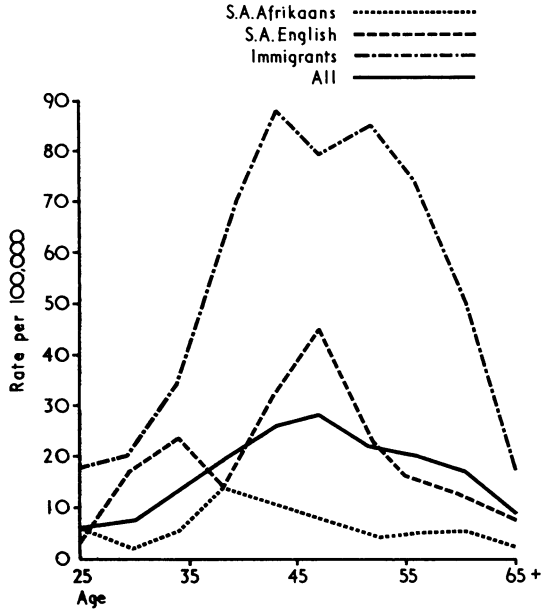

FIG. 1—Multiple sclerosis in white South Africans. Prevalence rates 1960.

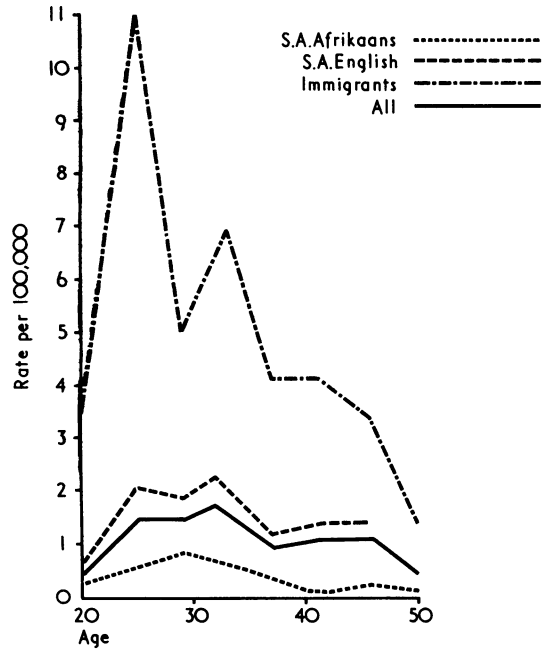

FIG. 2—Multiple sclerosis in white South Africans. Average annual incidence 1945-54.

who entered the Republic of South Africa between 1900 and 1959, who were living in the Republic in 1960, and who were then between the ages of about 25 to 69—as were the M.S. patients. By utilizing material available to the Bureau of Statistics of the Republic (courtesy of Mr. D. P. J. Botha, Director), we were able to reconstruct a matrix for age at immigration for U.K. immigrants for the years 1875-1959 according to expected survival to 1960, which is detailed elsewhere (Kurtzke *et al.*, 1970). That portion relating to 1900-59 immigrants aged 25-69 in 1960 was then abstracted and is used for our "population at risk" in this paper. The distribution of age in 1960 from this estimated population did in fact match well the known distribution (Dean, 1965) in that same year.

1968 M.S. and a Control Population

All survivors of the 1960 series who were still living in South Africa on 30 June 1968 were ascertained. To these were added all new M.S. cases discovered since 1960 who were living in South Africa on that date. These were 121 immigrants with M.S. compared with 118 at the earlier, prevalence day. Of these, 78 were survivors of the earlier series and 43 were later additions. The 1968 M.S. series is essentially the same as that of 1960.

Two surveys of the total white South African population at risk, chosen by random selection methods, have been undertaken by Market Research Africa (M.R.A.) in order to find out the age at immigration of the white South African immigrant population. The control population was divided into four age groups—16-24, 25-34, 35-49, and 50+. In the pilot survey there were 202 immigrants. In the second study 7,112 questionnaires were completed and there were 774 immigrants; 392 of these were immigrants from Britain. The number of M.S. patients in the age groups 16-24 (three) and 25-34 (10) are too small for comparison with the control population. We have compared the age at immigration of the M.S. patients and of the controls by their sex in the age groups 35-49 and 50+. From the surveys of the population at risk in the two age groups 35-49 and 50+ by sex and age at immigration the "expected" number of immigrants with M.S. has been calculated for each age at immigration. For all immigrants the actual number of M.S. patients who immigrated to South Africa below the age of 16 was six and the "expected" number was 25·8, so that the actual number is less than one-quarter of the "expected" number ($P < 0.01$) (Table II).

The age at immigration of the British immigrants from the 1969 Market Research Africa survey has also been compared with the British immigrant M.S. patients by sex in the age groups 35-49 and 50+. The actual number of British

immigrants with M.S. who came to South Africa (five) is less than one-third the "expected" number, 16·7 ($P<0·01$) (Table II).

TABLE II—*Actual and "Expected" Number of Immigrants with M.S. Aged 35 and over by Age at Immigration. The "Expected" Number Calculated by Age (35-49 and 50+) and by Sex*

Age at Immigration	"Expected" No. of M.S. (M.R.A. Study)	Actual No. of M.S.
All Immigrants		
0-15* years	25·8	6
16-20 „	9·8	12
21-30 „	30·7	32
31-40 „	24·7	34
41+ „	17·0	24
Totals	108·0	108
British Immigrants Only		
0-15‡ years	16·7	5
16-20 „	5·4	7
21-30 „	19·2	18
31-40 „	15·7	21
41+ „	9·0	15
Totals	66·0	66

* The number of M.S. patients (6) who had immigrated before the age of 16 is less than a quarter of the "expected" number (25·8) ($P<0·01$).
‡ The number of M.S. patients (5) who had immigrated before the age of 16 is less than one-third of the "expected" number (16·7) ($P<0·01$).

Onset of M.S. after Arrival in South Africa

There are 53 among the immigrants from Britain and 38 among the immigrants from other parts of Europe with onset of M.S. after their immigration to South Africa. Despite the fact that about a quarter of all immigrants are less than 15 when they arrive, only 12 of these 91 people who later developed M.S. were under 15 on arrival. This suggests that early enough immigration to a low-risk area, such as South Africa, reduces the risk of M.S. This may readily be confirmed by more detailed analysis. Two main sources of data have been used. Kurtzke *et al.* (1970) used the size and the age structure of each new annual intake of British immigrants, and by inserting reasonable assumptions about subsequent mortality rates enabled the construction of separate tables of age by age at immigration for all British immigrants present in the Republic of South Africa in any one particular year; and Market Research Africa has carried out a randomly sampled survey of the age and age at immigration of all immigrants present in the Republic of South Africa in 1969.

With the use of the first of these sources the age at immigration was divided into subgroups, and we can then contrast, for our 53 British-born M.S. patients, the number of patients who actually fall into each age-at-immigration category with the number that would be expected to fall into that category, the "expected" numbers being calculated on the assumption that early immigration has no protective effect.* The observed and the expected numbers appear in Table III and the most striking discrepancy between them is in the 0-14 age-at-immigration group, where we find only six cases with the onset of M.S. after arrival in South Africa instead of the 18·1 expected. This difference is too big to be explained away as a chance finding ($P<0·01$ by the Kolmogorov-Smirnov test), and it must, therefore, be accepted that early immigration does provide some protection from M.S. onset.

* For each M.S. onset we calculated the probabilities, given the year in which it occurred and the age of the person to whom it occurred, that the age at immigration of that person lies in each of the various ages at immigration categories. Having calculated one set of probabilities for each of the 53 onsets, the "expected" numbers in Table III are obtained for each age at immigration category by summing the 53 different probabilities calculated for that category. For example, if one subject suffered M.S. onset at the age of 25 in 1950, then referring to Table IV of Kurtzke *et al.* (1970) we find that of the immigrants aged 25 in 1950 24% had been aged 0-14 years on arrival and 76% had been aged 15-24 years on arrival. If early immigration is assumed not to be protective, then the probability that the subject who suffered M.S. onset had been aged 0-14 on arrival is 0·24.

TABLE III—*Numbers of Cases of M.S. Onset (1960+1968 series pooled) Occurring among Immigrants Who Arrived from Britain before 1960*

Age at Immigration	Actual No. of Subsequent M.S. Onsets	"Expected" No. of Subsequent M.S. Onsets, Assuming that early Immigration has no Protective Effect
0-4 years ..	2 } 6	8·58 } 18·08
5-9 „ ..	3	5·68
10-14 „ ..	1	3·82
15-19 „ ..	7	4·16
20-24 „ ..	9	7·61
25-29 „ ..	14	8·59
30-34 „ ..	7	8·15
35-39 „ ..	6	4·34
40+ „ ..	4	2·07
All ages ..	53	53·00

This conclusion is reinforced when we examine the 38 M.S. patients with onset of M.S. in South Africa among immigrants from parts of Europe other than Britain. Among this group M.S. onset is mainly in the age-range 25-49 (the mean age of onset being 37). In 1969 the Market Research Africa survey found that among immigrants then aged 25-49 from other parts of Europe, 31% (63/201) had been aged less than 15 at immigration, whereas only 16% (6/38) of the 38 patients who later developed M.S. after arrival were less than 15 on arrival in South Africa.

Exclusion of Possible Sources of Bias

We have compared the distribution of age at immigration among people who suffer M.S. onset in South Africa with the distribution of age at immigration in the population as a whole, and we have found a pronounced discrepancy between the proportions who arrived in childhood (up to 15 years of age). From this we have inferred that immigration in childhood confers some protection against M.S. There is no reason to suspect disproportionate underdetection of cases of M.S. among people who arrived as children, so the only possible source of bias is unreliability of our control data involving considerable overestimation of the proportions, present at any one time, of people who immigrated as children. However, when we use our control data to predict the distribution of age and age at immigration found in the 1969 Market Research Africa random sample of immigrants, the conformity is excellent with, if anything, a slight underestimation of the proportion who immigrated as children. There is, therefore, no evidence of bias in the control data.

Discussion

We have presented evidence that there is less than one-third the risk of M.S. among those immigrants who come to South Africa from Europe before the age of 15 or 16.

There are two major possibilities to explain these findings: (1) subclinical "infection" in early childhood protects against later clinical manifestations (G.D.); and (2) the disease is "caught" about age 15 with long latency before clinical expression (J.F.K.).

It is proposed that M.S. is normally a mild infection of infancy, perhaps a viral gastrointestinal disorder spread in areas with poor sanitation. If, however, childhood infection does not occur there is susceptibility to an adult attack which may in certain people result in a precarious balance between

the infection and immunity which causes the syndrome we call multiple sclerosis. Poskanzer *et al.* (1963) made this same analogy for M.S. with paralytic *v.* non-paralytic poliomyelitis, with support by Eadie *et al.* (1965) though Kurtzke (1965a) disagreed. In South Africa poliomyelitis in adults was formerly twice as common among immigrants from Northern Europe as in the white South African born and much more common among the white South African born than among the non-white. For instance, only three adult Bantu had been admitted to the Johannesburg fever hospital with paralysis caused by poliomyelitis in a 20-year period (Dean, 1967c).

In M.S. the prevalence is high among immigrants from Northern Europe unless they immigrate before the age of 15, only one-quarter as common among the English-speaking white South African born, and only one-eleventh as common among the Afrikaans-speaking white South African born who, as a whole, have closer contact with the non-white population than the English-speaking. M.S. is extremely rare among the Coloured, or half-caste, people of the Cape and the people of Asian stock, and no single case has yet been found among South Africa's 15 million Bantu.

WHITE NATIVE-BORN SOUTH AFRICANS VISITING EUROPE

Few Afrikaans-speaking white South African born M.S. patients or controls have visited Europe. Among the English-speaking South African born male M.S. patients, 11 out of 29 had visited Europe by prevalence day 1968, 2 of the 11 after the onset of M.S. and one of these two for treatment of M.S. From the Market Research Africa survey the calculated "expected" number of male M.S. patients to have visited Europe is 12 (Table IV). Among the English-speaking South African born females 38 had visited Europe out of 92,

TABLE IV—*Actual and "Expected" English-speaking South African Born "Probable M.S." Visiting Europe (1968-9)*

Age	Before Onset	After Onset	Total M.S.	"Expected" No. M.R.A. Survey 1969
Male				
25-34 years	–	–	4	1·1 (204)
35-49 „	4	1	11	4·2 (277)
50+ „	5	1	14	6·7 (302)
Total	9	2	29	12·0 (783)
Females				
25-34 years	3	2	13	2·7 (235)
35-49 „	6	5	35	7·6 (323)
50+ „	17	5	44	13·7 (353)
Total	26	12	92	24·0 (911)

Half the visits to Europe after onset of M.S. were for medical consultation because of M.S. Numbers in parentheses are sample size.

but 12 of these had visited Europe after the onset of M.S., six of them so that the diagnosis of M.S. could be confirmed or for treatment of M.S. The "expected" number in these age groups is 24. There is thus no significant difference between the number of M.S. patients who visited Europe for reasons other than M.S. diagnosis or treatment (40) and the number expected from the Market Research Africa survey (36). It therefore seems to be very unlikely that visiting Europe from South Africa increases the risk of developing multiple sclerosis.

Among the English-speaking South African born who had visited Europe there is no suggestion that visiting Europe before the age of 15 increases the risk of M.S. Only 18 out of 65 had visited Europe before the age of 15 and there is no clumping of patients who had visited Europe about the age of 15 (Table V).

One of us (J.F.K.) advances an alternative theory. This is that M.S. is acquired in "endemic" areas (such as Northern Europe) at about the age of 15. Whether the disease remains truly latent for many years or whether it takes this period of years for a sufficiency of lesions to develop so that symptoms are not manifest over this silent period is conjectural, but he suggests that the disease is "caught" at about the age of 15 in high-risk areas and manifests itself years afterwards regardless of later geography. In this fashion we would expect the migrants who move at older ages to show the prevalence rate of their original homeland, the site of acquisition. If one moves before the susceptible age, then the chances of getting M.S. are once again dependent on the prevalence of M.S. locally when the person concerned is near the age of 15. It is also possible that some 15 years of exposure to the agent are required before the disease can be acquired, a less likely explanation. Previously Kurtzke (1965b) had tentatively concluded that the onset of M.S. seems to take place between the ages of 10 and 15 years. Against this theory is the absence of any apparent increased risk among the English-speaking South African born who visit Europe up to the age of 15 (Table V).

TABLE V—*Age at First Visit to Europe. English-speaking South African Born with Probable M.S.*

Age	At 1960 Census			Added Since 1960			Total		
	M.	F.	Total	M.	F.	Total	M.	F.	Total
0-4 years ..	2	3	5	1	3	4	3	6	9
5-9 „ ..	1	3	4	—	1	1	1	4	5
10-14 „ ..	—	2	2	—	2	2	—	4	4
15-19 „ ..	2	5	7	1	1	2	3	6	9
20-24 „ ..	4	6	10	—	1	1	4	7	11
25-29 „ ..	1	8	9	1	3	4	2	11	13
30-34 „ ..	3	3	6	—	1	1	3	4	7
35-39 „ ..	—	1	1	—	1	1	—	2	2
40-44 „ ..	—	—	—	—	2	2	—	2	2
45-49 „ ..	—	2	2	—	1	1	—	3	3
Total ..	13	33	46	3	16	19	16	49	65

Some of these patients have since died.

Further clarification might be achieved if we had more information on the opposite migration—from low-risk M.S. areas to high—to confirm the information we have about the white South African born who visit Europe.

Whichever explanation is viewed as the more probable, we are agreed that the most likely class of candidate for the aetiological agent in M.S. seems to be that it is a "slow, latent, or temperate virus" disorder. And we are agreed, too, that more definitive epidemiological studies may well direct further the laboratory worker in his specific search for the origin of this fascinating, enigmatic disease.

This epidemiological study was made possible by the co-operation of hundreds of people who cannot be named individually and whose satisfaction is the contribution they have made to the solution of the problem of M.S. Our special thanks are due to the medical profession in South Africa for their co-operation over many years and also the hard-working members of the South African National Multiple Sclerosis Society, now under the chairmanship of Mrs. Scottie Cullis, who helped us trace patients with possible or probable M.S. We are most grateful to Mr. Wally Langschmidt, the Managing Director of Market Research Africa, and his staff for carrying out the study of the control population, and to the South African Broadcasting Company who allowed additional questions to be added to their large-scale survey of listeners and so made it possible for us to obtain the age at immigration of the population at risk at a nominal cost. We would like to thank the National Multiple Sclerosis Society, New York, for its continued support and for the help given by their advisers, especially Dr. Leonard Kurland, of the Mayo Clinic, and Dr. Donald Acheson, Dean of Medicine, the University, Highfield, Southampton. Statistical information about the immigrants to South Africa since 1900 was provided by Mr. D. P. J. Botha, the South African Secretary for Statistics. Mr. Richard Peto, of the department of the regius professor of medicine, Oxford, provided invaluable advice about statistical methods.

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Idiopathic Parkinsonism Treated with an Extracerebral Decarboxylase Inhibitor in Combination with Levodopa

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Summary

The clinical actions of levodopa in Parkinsonism, given with and without an extracerebral decarboxylase inhibitor, L-alpha-methyldopahydrazine, were compared. Twenty-one patients were investigated in a "double-blind cross-over" study, administering levodopa in maximum tolerated dosage. L-Alpha-methyldopahydrazine failed to augment the overall therapeutic actions of levodopa but it consistently alleviated nausea. It is concluded that L-alpha-methyldopahydrazine will prove useful in the management of some Parkinsonian patients who have difficulty in taking levodopa alone.

Introduction

Accumulating evidence indicates that dopamine is a synaptic transmitter in the brain and that the striatum is severely depleted of dopamine in Parkinsonism. The clinical improvement induced by levodopa is thought to stem from replenishment of dopamine in the central nervous system. Orally administered dopamine is therapeutically inactive because it does not easily cross the blood-brain barrier. Its immediate precursor, levodopa, can, however, enter the brain where decarboxylation to dopamine occurs. Levodopa itself is pharmacologically inert, all its actions being dependent on the production of metabolites.

The therapeutic action of levodopa in Parkinsonism is now well established. Dose-dependent side effects are common, and these may limit its value and sometimes preclude administration. Much of the levodopa given to patients is decarboxylated to catecholamines (dopamine, noradrenaline, and adrenaline) which are in turn converted to phenolic carboxylic acids.

Some of the adverse effects of treatment with levodopa are likely to result from the formation of catecholamines outside the brain. Bartholini *et al.* (1967) pointed out that drugs are available which block decarboxylation of levodopa to catecholamines but do not themselves readily cross the blood-brain barrier. Such drugs can be expected to potentiate the therapeutic action of levodopa in several ways. They should reduce those unwanted actions which arise as a result of catecholamine formation at the periphery. By blocking extracerebral metabolism, raised and more sustained plasma levels should be achieved. Initial clinical reports have been encouraging (Barbeau, 1969; Bartholini *et al.*, 1969; Cotzias *et al.*, 1969; Siegfried *et al.*, 1969; Tissot, 1970; Barbeau *et al.*, 1971).

In the following investigation the effects of levodopa were compared with a combination of levodopa plus an extracerebral decarboxylase inhibitor, L-alpha-methyldopahydrazine (Porter *et al.*, 1962). Both regimens were administered in maximum tolerated dosage in a double-blind cross-over study.

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Patients and Methods

Patients.—Twenty-one patients (9 men and 12 women) with idiopathic Parkinsonism were studied. Their ages ranged from 35 to 72 (mean 59·8) years. The criteria for admission to the study were: (1) no evidence of cardiac, hepatic, renal, or haematological disease; (2) availability for outpatient attendance at fortnightly intervals; (3) patient's acceptance of the "blind" protocol for investigation of a new drug. Before treatment 16 of the patients could walk unaided, four could walk only with assistance, and one was unable to walk even with help. They represented a typical group of Parkinsonian patients attending the outpatient department of a general hospital.

Routine Therapy.—Nineteen of the patients had been receiving conventional anti-Parkinsonian drugs (benzhexol, benztropine, orphenadrine) before entering the study. Such treatment was maintained, unaltered, throughout the investigation. None of the patients was taking amantadine, pyridoxine, or monoamine oxidase inhibitors.

Levodopa.—All patients had been receiving tablets of levodopa before admission to the trial. On entering the study they were told that two drug regimens would be tested, but they were not informed that each involved further administration of levodopa. In order to maintain a "blind" setting, the levodopa given during the trial was presented in white capsules of 25, 50, 100, or 250 mg, quite dissimilar in appearance from the 500-mg tablets of levodopa which they had previously received.

L-alpha-methyldopahydrazine.—This extracerebral decarboxylase inhibitor was administered in a dose of 300 mg/day, as capsules of 50 mg which were easily distinguishable from the capsules of levodopa.