Metachromatic leucodystrophy: review of 38 cases

R MACFAUL, N CAVANAGH, B D LAKE, R STEPHENS, AND A E WHITFIELD

*Department of Neurology, Hospital for Sick Children, London and
Institute of Child Health, University of London*

SUMMARY Clinical and laboratory features of 38 children suffering from metachromatic leucodystrophy (MLD) are reported. Twenty-four children with the late infantile form of MLD presented between ages 6 and 25 (mean 17) months with a delay or deterioration in walking, followed by a general loss of abilities. There was severe handicap by age 3 years and death occurred between 5 months and 8 years after presentation. Neurological signs at the time of diagnosis were varied. Motor nerve conduction velocity was slowed in the 18 children tested. The disease became evident at a later age in 14 children. One boy presented at 13 years, while in the remainder there appeared to be two clinical patterns of the disease which could be termed (1) early juvenile or intermediate and (2) juvenile MLD. In 7 children with early juvenile or intermediate MLD a gait disorder developed between ages 4 and 6 (mean 5) years. This was accompanied in 4 children, and followed between 8 and 26 months later in the remaining 3, by loss of other abilities. Neurological signs were varied. Motor nerve conduction velocity was slowed in 2 of the 5 patients tested. Six children with juvenile MLD presented between ages 6 and 10 years with educational or behavioural difficulties. Motor disorders arose from 6 months to 4 years later. Neurological signs at the time of diagnosis, although mixed, were predominantly extrapyramidal and motor nerve conduction velocity was slowed in 2 of the 3 children tested. In the early juvenile and juvenile form of MLD, progression of the disease was slower than in the late infantile form and death occurred between 3½ and 18 years after presentation. Only one-third of patients had fits and these tended to be a late feature.

Metachromatic leucodystrophy (MLD) is a disorder with autosomal recessive inheritance, in which cerebroside sulphate (sulphatide) accumulates in the nervous system and other organs of the body. In the nervous system accumulation is mainly in the white matter of the brain and peripheral nerves, but it also occurs in other areas—for example the dentate nucleus and basal ganglia.¹ There is widespread symmetrical demyelination with neuronal and axonal loss in the cerebral and cerebellar hemispheres, basal ganglia, brain stem, and long tracts of the spinal cord.²

The metachromasia, from which the disorder is named, results from a shift of the absorption spectrum of certain blue cationic dyes towards red when reacted with anionic sulphatides. Although rare, MLD is one of the more common neurodegenerative disorders of childhood. The incidence in the UK is unknown, but in Sweden it is probably about 1 in 40 000 births.³

Although late infantile metachromatic leuco-

dystrophy is well described, cases of onset later in childhood have received less attention. This study was undertaken to identify the early clinical and laboratory features of the disease at all ages and to record the natural history.

Methods

Case records of 38 patients diagnosed at The Hospital for Sick Children, Great Ormond Street, between 1961 and mid-1978 were reviewed. Eleven of them have previously been reported.^{4–8}

Arylsulphatase A activity in leucocytes was measured in a mixture (final volume 175 µl) containing 0.34 mol/l acetate buffer pH 5.0; 80 mmol/l NaCl; 8 mmol/l 4-nitrocatechol sulphate, and supernatant (containing 70–200 µg protein) from a water homogenate of leucocytes. After incubation at 37°C for 1 hour the reaction was stopped by adding 400 µmol/l NaOH, and then after 5 minutes the mixture was centrifuged. In the blank assay,

enzyme protein was added after adding the NaOH. Absorbance of the clear supernatant was measured at 500 nm.

For the measurement of urinary arylsulphatase A activity fresh unpreserved urine was centrifuged and dialysed overnight in water at room temperature. The assay mixture (final volume 500 μ l) contained 0.4 mol/l acetate buffer pH 5.0; 5 mmol/l 4-nitro-catechol sulphate, and 200 μ l dialysed urine. After incubation at 37° for 1 hour the reaction was stopped by the addition of 750 μ mol/l NaOH and the absorbance measured at 500 nm after 10 minutes. Examination of urinary deposits for metachromatic material was performed as described in the Appendix.

Results

The patients (19 boys and 19 girls) were grouped according to their age at onset of symptoms as recalled by parents, and findings are summarised in Table 1.

Group 1. Late infantile metachromatic leucodystrophy (24 patients).

Age at presentation

They were aged between 6 and 25 (mean 17) months (Figure).

Symptoms at presentation

In 23 patients, gait disorder had been the first problem to cause their parents to suspect an abnormality. Eight children never walked alone. In 7 children immature gait persisted and in 12 children deterioration occurred in walking ability (poor balance, toe walking, or foot turning in or out). In the remaining child, the first abnormality was a squint. The motor

Figure Age at which symptoms started in 37 patients with metachromatic leucodystrophy.

development of 4 children appeared to have been slightly delayed in the first year of life.

Subsequent symptoms

Progressive loss of social and linguistic abilities occurred in the course of the illness. However, the onset of speech difficulties was often delayed for some time after the onset of the gait disorder, while in some patients speech abilities progressed, and in others the rate of progress of speech acquisition slowed as motor abilities were lost.

Other prominent symptoms were misery, lack of interest in toys, and irritability and apparent frustration.

Fits occurred in 6 patients between ages 2 and 3 years.

The rate of physical and mental deterioration was greatest in the first year or two after the onset of the

Table 1 Summary of the clinical features of the different forms of metachromatic leucodystrophy

Group	Age at which symptoms started	Symptoms	Age at diagnosis	Motor signs at diagnosis	Fits	Death
1. Late infantile (n=24)	6*–25 months (mean 17)	Gait disorder, followed within months by a general loss of abilities	15–60 months (mean 34)	Mainly pyramidal and cerebellar. Ankle reflexes absent in 11 in presence of extensor plantars in 7 of the 11	Later in 5	5 months to 8 years after onset
2. Intermediate or early juvenile (n=7)	4–6 years (mean 5)	Gait disorder with simultaneous educational and behavioural problems in 4	5½–12 years (mean 8½)	Mainly extrapyramidal but also cerebellar and pyramidal. Ankle reflexes absent in one	Early in 1, later in 5	3½ to over 17 years from onset
3. Juvenile (n=6)	6–10 years (mean 8)	Educational and behavioural problems, followed 6 months to 4 years later by gait disorder	8½–14 years (mean 11)	Predominantly extrapyramidal and some pyramidal. Ankle reflexes absent in one	Later in 4	5 to over 11 years from onset
4. Atypical (n=1)	13 years	Mild gait disorder followed 3 years later by intellectual deterioration	16 years	Extrapyramidal	—	Alive 6 years after onset

* Only one patient younger than 12 months.

illness. The ability to sit without support was lost between 22 months and 3 years (mean $2\frac{1}{2}$ years) in the 17 children in whom this feature was recorded.

Fourteen patients died aged between $2\frac{1}{4}$ and 8 (mean $4\frac{3}{4}$) years.

Five patients were still alive, one at $5\frac{1}{4}$ years (onset 15 months), one at $6\frac{1}{2}$ years (onset 16 months), one at $6\frac{3}{4}$ years (onset 15 months), one at $7\frac{1}{2}$ years (onset 15 months), and the fifth at $8\frac{1}{4}$ years (onset 25 months). Information was not available on the remainder.

Signs at confirmation of diagnosis, aged 15–60 (mean 34) months

Pyramidal signs (spastic hypertonus or hyper-reflexia, or both of these) were present alone in 4 patients, and were combined with cerebellar signs (ataxia/nystagmus/dysarthria/intention tremor) in a further 5 children. Cerebellar signs alone occurred in 3 patients. Extrapyramidal signs (rigid hypertonus/bradykinesia/positive glabellar tap) occurred alone in 4 patients and were combined with cerebellar signs in 1 patient. An opisthotonic posture (extended neck, back, and legs) with flexion of the arms and equinovarus posture of the legs was present in 7 patients who were diagnosed at a fairly late stage of their illness.

All tendon reflexes were absent in 4 patients and tendon reflexes were pathologically brisk in a further 4 in whom toe jerks (flexion of the toes when the skin of the lower leg or dorsum of the foot is tapped) were also present. Between these two extremes, there were varying combinations of brisk and depressed reflexes in individual patients. Ankle jerks were absent in 11 patients, other tendon jerks being present or absent (combined with extensor plantar responses in 7, flexor in 2, and unknown in 2) and were present in 12 patients (combined with extensor plantars in 7).

Family history

In two families there was one other sibling with proved late infantile MLD, with no parental consanguinity.

In one other family 2 older siblings, and in another family one older sibling, had died from an undiagnosed but similar degenerative disease.

The parents of 2 other patients were 1st cousins but in neither family was another sibling affected.

Group 2. Intermediate or early juvenile MLD (7 patients).

Age at presentation

They were aged between 4 and 6 (mean 5) years.

Symptoms at presentation

In 3 patients (aged 4, 4, and 6 years) tripping or falling was the only concern at first and one child had always been thought to be clumsy. In the remaining 4 children (aged between 3 and 4, 5, $5\frac{1}{2}$, 6 years) deterioration in gait was accompanied at the same time by evidence of intellectual deterioration which took the form of school difficulties (poor concentration, poor memory) and regression to a more immature pattern of behaviour (soiling, enuresis, social withdrawal, aggression). There was one child in whom concern was expressed about development and mood at 3 years.

Subsequent symptoms

In the 3 children who presented with gait disturbance alone, evidence of intellectual deterioration followed after an interval of between 8 and 26 months.

Three patients lost the ability to walk within 1 to 3 years of onset of the deterioration, at the ages $7\frac{1}{4}$, 5, and 7 years, and lost sitting ability soon afterwards. Speech was lost within 3 months to $2\frac{1}{4}$ years of onset of the deterioration at ages 5, $5\frac{1}{2}$, and $7\frac{1}{2}$ years.

Fits occurred in 3 patients between 5 and 11 years, and in one child a fit occurred with a fever 3 months before loss of abilities became apparent.

Two patients died within 3 and 6 years of the onset of their illness at ages $8\frac{3}{8}$ and 10 years. Three children were alive at 14, 18, and 21 years (9, 14, and 17 years after the onset of their illness).

Signs at confirmation of diagnosis, aged $5\frac{1}{2}$ –12 (mean $8\frac{1}{4}$) years

Extrapyramidal signs were present alone in 3 patients, cerebellar signs alone in another patient, and the remaining 3 patients showed both pyramidal and cerebellar signs. Ankle reflexes were absent in only one of the 6 patients in this group.

Family history

The parents of one patient were 1st cousins and the patient's sister had died at 18 months having been retarded since birth with developing optic atrophy. Another patient had a sibling who had MLD showing signs at a similar age.

Group 3. Juvenile MLD (6 patients).

Age at presentation

They were aged between 6 and 10 (mean 8) years.

Symptoms at presentation

In 4 of these patients school difficulties and behavioural disturbance were the presenting features. In the remaining 2, unsteadiness occurred at the same time as intellectual deterioration.

Subsequent symptoms

From within a few months to 4 years after the onset of their educational and social difficulties, the 4 patients had started to deteriorate physically. Loss of sitting ability was recorded in 3 patients and occurred between 2½ and 5 years of the onset of their physical deterioration which started at ages 9½, 10, and 13 years. Emotional lability was often present. One exceptional patient was still able to walk at age 17 years, 9 years after his illness had begun.

Fits occurred in 4 patients aged between 8 and 14 years.

Two patients died, one at age 11 the other at age 15 years, 5 years after the onset of their illness. Three patients aged between 12½ and 19 years were still alive (8 years, 6½ years, and 11 years) after the onset of their illness.

Signs at confirmation of diagnosis, aged 8½–14 (mean 11) years

Extrapyramidal signs predominated in all 6 patients in this group, although in 3 of them there were associated pyramidal signs and in 2 cerebellar features (as shown by a mild intention tremor) present early. Cogwheel rigidity was noted in 1

patient and a pill-rolling tremor in another. Ankle reflexes were absent in one of these 6 patients.

Family history

The apparently normal mother of 2 of the patients in this group had leucocyte arylsulphatase A levels in the homozygous range and intracellular metachromatic material in her urine. There was another sibling of these 2 patients, not reported here, whose illness started at 6½ years with behavioural disorder, anxiety, deterioration in school work, and slowing of speech. Motor problems started one year later and MLD was diagnosed by biopsy at age 7½ years.¹ His parents were not consanguineous.

Group 4. Atypical MLD (1 patient).

This patient presented with a disturbance of gait at age 13 years. At diagnosis aged 16 years he showed pyramidal, extrapyramidal, and cerebellar features. All his reflexes were present and brisk. Within 3 years of the onset of his illness he had shown increasing physical and intellectual deterioration. He was still alive 6 years later.

Since most of these children were not seen at this hospital at the beginning of their illness, there was

Table 2 Results of urine and leucocyte arylsulphatase A in some patients and their families

Group	Urine ASA (μmol/g creatinine per hour)				Leucocyte ASA (nmol/mg protein per hour)			
	Patient	Father	Mother	Siblings	Patient	Father	Mother	Siblings
Late infantile								
1	0							
2	<3				11			
3	0	19						
4	0	43	53		0, 8	27	30	
5	<3				5			
6	5, 3				4	24	36	
7	0, 5, 0.5							
8					6	27	35	
9					14		39	13, 6
10					8			
11					5	18	10	
12	0				9			
13	6, 5, 4, 2	31	17					
14	8, 0				7, 13	40, 44	36, 33	
Intermediate or early juvenile								
25	4		8					
26	2, 5, 0		16	66	3			
27	6		19	9		12	7	
28					9			
29		34	11					
Juvenile								
32	0				10			
33	5	29	17	26	5	19	32	
34	3, 3, 4	7	20, 4		4, 3	0, 10	5*	
35	9			2	2	28	24	25
Atypical				165				
38	2, 3	22	8					
Control range		31–323				25–146		

* Intracellular metachromatic material in urine.
ASA = arylsulphatase A

often no adequate record in their notes of the earliest physical signs. The mean interval which elapsed between the onset of the first symptoms and confirmation of the diagnosis of MLD was 17 months in group 1, $3\frac{3}{4}$ years in group 2, $2\frac{3}{4}$ years in group 3, and 3 years in the patient in group 4.

Results of diagnostic investigations

Table 2 records the results of the measurement of urine or blood leucocyte arylsulphatase A, or both of these, in 24 patients. The diagnosis in other patients was made by finding metachromatic material either in renal tubular cells voided in fresh urine or in biopsies of skin, sural nerve, rectum, or brain.

The examination of urine for intracellular metachromatic material was performed as described in the Appendix. Two separate freshly voided specimens from 30 patients were each examined. Intracellular metachromatic material was found in at least one of the specimens of all the patients in whom urine renal tubule epithelial cells were present.

Table 3 summarises the motor nerve conduction velocities in three groups (the patient in group 4 was not tested). Using surface electrodes, nerve conduction velocity was measured in 26 patients. In 24, the velocity was measured in the lateral popliteal nerve, stimulating at the head of the fibula and at the ankle, and recording over extensor digitorum brevis: in the remaining 2, velocity was measured in the ulnar nerve, stimulating at the elbow, and wrist, and recording over abductor digiti minimi. There was poor correlation between the briskness of tendon reflexes and nerve conduction. In 5 patients tendon reflexes were abnormally brisk when motor nerve conduction was reduced (Table 4).

Cerebrospinal fluid was examined in 16 patients and the protein was raised in 14 of them to between 440 and 2250 (mean of 1120) mg/l. The Lange test was mildly abnormal with a midzone rise in 2 patients. Air encephalography was performed in 8 patients and showed the presence of generalised atrophy in 7.

Table 3 Summary of nerve conduction velocities in patients with metachromatic leucodystrophy

Group	Number tested	Normal when tested	Abnormal velocity (metres per second)		Age when tested (years)	
			Mean	Range	Mean	Range
1 (n=24)	18	0	15	0-30	3	$2\frac{1}{4}$ - $6\frac{1}{2}$
2 (n=7)	5	2	12	0-20	9	7-12
3 (n=6)	3	1	18	10-28	12	9-14

Normal range for nerve conduction velocities in the lateral popliteal nerve in children aged 7 years is 57 m/second (45-74) and in the ulnar nerve 68 m/second (51-78) (Gamstorp⁴⁴).

Table 4 Nerve conduction when tested in children with brisk tendon jerks

Group	Age at onset of symptoms	Age tested	Motor nerve conduction (m/s)
1	15 months	2 years 10 months	17
	15 months	2 years 10 months	23
	15 months	5 years	10
2	4 years	10 years	17
	5 years	7 years	20

Computerised axial tomography was performed in 3 patients. In 2 patients (aged $2\frac{1}{2}$ and $2\frac{3}{4}$ years) the results were normal 7 and 19 months after the onset of the illness, but in the third, a $6\frac{1}{2}$ -year-old girl, a scan 9 months after the onset of illness showed a dilated 3rd ventricle and the white matter showed low attenuation of a kind often seen in disorders with demyelination of the central white matter.

Discussion

An analysis of these 38 children with MLD suggests that among cases starting after the late infantile period, two separate forms can be recognised. An intermediate, or early juvenile form may be distinguished with an onset with motor difficulties at a younger age than the juvenile form which presents with behavioural or scholastic difficulties before motor difficulties are apparent.

Late infantile MLD is the most common form and 63% of our patients (group 1) came into this category. The clinical features of our cases did not differ from those described previously,^{9 10} and the occasional combination of hypotonia and areflexia should not lead to difficulties described by some¹¹⁻¹⁴ in distinguishing this condition from spinal muscular atrophy. The onset was at about age 17 months with a persisting immature gait or deterioration in walking ability, sometimes preceded by delay in starting to walk. In some, language and social development up to this time and for a short while afterwards were normal and then they tended to slow down before there was actual loss of abilities. Physical examinations showed mainly a combination of progressive pyramidal and cerebellar signs. The state of reflexes was variable, reflecting both the central nervous system and peripheral nerve involvement, but at the time of presentation the combination of absent ankle jerks with extensor plantar responses and brisk tendon jerks elsewhere provided a clinical clue in up to 30% of patients. During the next few months, and generally by age 3 years, the children had lost the ability to sit, feed themselves, or speak, and they became miserable and withdrawn. A decorticate

posture was soon evident after which death either occurred quickly or was delayed for several years.

Although cases of MLD with onset later than the late infantile form have been described, there is considerable confusion over nomenclature and age at onset. Scholz in 1925¹⁵ was the first to recognise MLD in childhood after the initial description of it in adults¹⁶ but since then cases starting between 6 and 20 years of age,¹⁷ 5 and 15 years,¹⁸ 13 and 20 years,¹⁹ 4 and 10 years,⁴ and even in patients as young as 18 months,²⁰ have all been called juvenile. In one review of childhood MLD²¹ there was no mention of juvenile MLD, although in another,²² up to 30% of all cases had onset after late infancy.

Despite this confusion, there are several reports of cases similar to our intermediate early juvenile group,^{4 23-26} although they have not been called this, and a number of cases similar to our juvenile group.^{2 27-32} Presumably, the reason why all these cases have hitherto been regarded as belonging to one category with no distinction made between early juvenile and juvenile onset, is that the number of patients in each reported series has been small. This is the largest series of childhood MLD yet reported.³³

The early juvenile or intermediate form of MLD presents in a previously normal child between 4 and 6 years of age either with a gait disorder alone shown by tripping and falling, or in association with intellectual deterioration. Extrapyrarnidal or cerebellar signs are the most common physical findings, and ankle reflexes are usually present. The rate of progression of this form of MLD is generally slower than in the late infantile form, but eventually the same severely handicapped state is reached leading to death usually within months although sometimes not for several years.

The juvenile form of MLD presents between 6 and 10 years of age in a previously normal child. Educational and behavioural difficulties are the early features and may be present for up to 4 years before the slow development of gait disorder. Examination shows a demented child with predominantly extrapyramidal signs and preserved ankle jerks, although often there are associated pyramidal signs. Progression of this form of the disease is generally slower than the earlier onset variants with complete crippling by between 3 and 6 years from onset.

The later onset forms of MLD appear to be genetically distinct from the late infantile form. We have been able to find reports of only two instances in which a late infantile and later-onset case occurred in the same kinship,^{20 34} and no ready explanation for such variation in the clinical expression of a biochemical derangement present from

early life. An example of very early involvement is shown in a report in which examination of a 20-week aborted fetus with reduced arylsulphatase activity showed the presence of morphologically normal myelin but the sulphatide content was increased 6-fold.³⁵

The apparently normal mother who had a leucocyte arylsulphatase A level in the homozygous range and intracellular metachromatic material in the urine had a third sibling affected by the disease in a similar way to her 2 children in group 3. She could be a preclinical case of late adult MLD as described by Pilz and Hopf.³⁶

Quantitative or qualitative differences in storage material in the different groups of MLD are disputed¹⁸ and there seem to be no quantitative differences in leucocyte arylsulphatase A activities between groups in this study and in others.^{37 38} However, in pulse labelling experiments in which degradation of S-sulphatide was studied in intact fibroblasts, it was shown that the late infantile and adult forms of the disease could be differentiated. Also, those parents for whom the level of arylsulphatase A was biochemically homozygous in fibroblast homogenates could be classified as heterozygotes when intact cells were used.³⁹ Qualitative differences in the physical properties of enzymes have been suggested by differing electrophoretic patterns.⁴⁰

Some of the methods by which the diagnosis of MLD was made in some patients in this study are no longer justifiable in view of the less invasive tests now available. The most reliable investigation is measurement of arylsulphatase A in blood leucocytes or skin fibroblasts, and it is probably advisable to confirm the storage of metachromatic material in tissue—for example renal tubular cells shed in the urine. Other tissues which have been examined include dental pulp.⁴¹ We have had no experience with this technique but would point out that dental pulp contains mucopolysaccharides which would falsely show metachromasia. A number of other findings—such as slow motor nerve conduction velocities and raised cerebrospinal fluid protein concentration—may reinforce a clinical suspicion but they are not in themselves diagnostic, and may be abnormal in other diseases affecting both central nervous system white matter and peripheral nerves.

Prenatal diagnosis of MLD is reliable when a clear differentiation can be made between the level of residual arylsulphatase A activity in an index case and the heterozygous level of the parents. This distinction was not possible in 3 of the 9 families in the present series in which the enzyme was measured in both parents. Either one or both parents were found to have low enzyme activities in leucocytes

which could not be reliably distinguished from affected homozygous levels. It is important therefore that the enzyme levels of the parents of MLD patients should be measured in other tissues—such as cultured fibroblasts—before prenatal diagnosis is considered.

Nerve conduction velocities were reduced in 23 out of the 26 patients tested, a finding that had been noted by several others.^{1 42 43} Two of the patients with normal velocities were in group 2; one was in group 3. There were no significant differences between the mean velocity in each group. In group 1 there was no correlation between the degree of slowing and the age when tested, although in 2 out of 3 patients who had repeated tests, there was a reduction in velocity with increasing age. There were too few patients to comment on this in the other groups. It is worth emphasising that nerve conduction velocity can be reduced in the presence of exaggerated limb reflexes.

At present there is no treatment or cure for MLD. Moosa and Dubowitz⁴³ reported initial improvement over 6 weeks in a patient with the late infantile form on a low vitamin A diet, but this benefit was not confirmed in the only one of our patients (group 3) who was treated similarly for 5 months.⁶

Appendix

Urine test for intracellular metachromatic granules

The urine must be fresh to minimise precipitation of urinary phosphates and urates. Early morning specimens should be avoided since these tend to be stale and too concentrated with consequent lysis of cells.

Method

- (1) Centrifuge urine. Discard supernatant and make 3 smears, each about 2 cm in diameter on glass slides.
- (2) Air dry and fix in formaldehyde vapour at 60°C for 1 hour.
- (3) Wash briefly in tap water.
- (4) Stain overnight in 0.01% toluidine blue in McIlvaine buffer pH 5.0.
- (5) Rinse briefly in tap water.
- (6) Dehydrate in acetone (*not* alcohol), clear in xylene, and mount in DPX.

A positive result is shown by brown metachromasia in renal tubule cells (mainly collecting tubular cells). Bladder epithelial cells and other cells have a darkish blue nucleus with pale blue cytoplasm. Numbers of positive cells vary and sometimes there may be only one per slide.

The colour is a golden sandy brown and the

material is intracellular and often granular. In polarised light the material shows greenish birefringence. Extracellular material may be occasionally seen but is not pathognomonic. If found, repeat urine specimens should be obtained and a high index of suspicion maintained.

We thank Elisabeth Young for advice and help with biochemistry, Dr E M Brett and Dr J Wilson for permission to report their patients and for constructive criticism, and Professor A D Patrick for help with writing this paper.

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Correspondence to Dr R MacFaul, Department of Paediatrics, Pinderfields General Hospital, Aberford Road, Wakefield, West Yorkshire WF1 4DG.

Received 21 May 1981