

Progression of abnormalities in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy despite treatment with "Lorenzo's oil"

B M van Geel, J Assies, E B Haverkort, J H T M Koelman, B Verbeeten Jr, R J A Wanders, P G Barth, on behalf of the Dutch X-ALD/AMN Study Group

Abstract

Objectives—X-linked adrenoleukodystrophy (X-ALD) is an inherited disorder of peroxisomal fatty acid oxidation, biochemically characterised by the accumulation of saturated very long chain fatty acids (VLCFAs), particularly hexacosanoic acid (C26:0). Dietary treatment with a 4:1 mixture of glyceroltrioleate and glyceroltrierucate ("Lorenzo's oil") normalises plasma VLCFA concentrations, but neither ameliorates nor arrests the rapid progression of neurological symptoms in the cerebral variants of X-ALD. The efficacy of "Lorenzo's oil" in the milder phenotypes of X-ALD was assessed, as this has been much less investigated.

Methods—Twenty two patients who were treated with "Lorenzo's oil" for at least 12 months for a median period of 2.5 (range 1.0–6.0) years were studied. Two had asymptomatic ALD, four the "Addison only" variant, 13 adrenomyeloneuropathy (AMN), and three were symptomatic female carriers.

Results—The plasma C26:0 concentration normalised or near normalised in 19 patients (86%), in the three others it decreased significantly. Nevertheless, disability as measured with the extended disability status scale score increased mildly (0.5 (95% confidence interval (95% CI) 0.25–1.0)) in the 16 patients with neurological symptoms. Furthermore, one "Addison only" patient and one patient with AMN developed cerebral demyelination, and another "Addison only" patient developed AMN. Adrenocortical insufficiency evolved in one patient with AMN, and hypogonadism in one patient with asymptomatic ALD and two patients with AMN. Nerve conduction, evoked potential studies (SEP, BAEP, VEP), and abnormalities on cerebral MRI did not improve. On the other hand, side effects were often noted—namely, mild increases in liver enzymes (55%), thrombocytopenia (55%), gastrointestinal complaints (14%), and gingivitis (14%). We also found a mild decrease in haemoglobin concentration and leucocyte count.

Conclusions—The data suggest that treatment with "Lorenzo's oil" neither improved neurological or endocrine function nor arrested progression of the disease.

Furthermore, the oil often induced adverse effects. Therefore, it is advocated that "Lorenzo's oil" should not be prescribed routinely to patients with X-ALD who already have neurological deficits.

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Keywords: X-linked adrenoleukodystrophy; adrenomyeloneuropathy; Lorenzo's oil; peroxisome

X-Linked adrenoleukodystrophy (X-ALD) is an inherited disorder of peroxisomal metabolism, biochemically characterised by deficient β -oxidation of saturated very long chain fatty acids (VLCFAs), particularly hexacosanoic acid (C26:0).¹⁻³ The consequent accumulation of these fatty acids is associated with demyelination within the CNS, and with adrenocortical insufficiency and hypogonadism.^{4,5}

The phenotypic expression of X-ALD is highly variable, with adrenomyeloneuropathy (AMN) and childhood cerebral ALD (CCALD) accounting for 70% to 80% of all cases.⁵⁻⁸ In AMN, the spinal cord and peripheral nerves are mainly affected, resulting in spastic paraparesis, sensory abnormalities in the legs, and bladder or anal sphincter dysfunction. Neurological symptoms emerge in the second to fourth decade, and the progression is relatively slow. Childhood cerebral ALD is characterised by progressive cerebral demyelination in previously healthy boys, resulting in a persistent vegetative state or death within 3 years after the onset of symptoms. In 10% to 15% of patients with X-ALD only adrenocortical insufficiency is demonstrable (the "Addison only" phenotype), and in 5% to 10% an excess of plasma VLCFAs is the only manifestation (asymptomatic ALD). At least 15 to 30% of female carriers develop AMN-like symptoms.^{7,9}

As it was assumed that the excess of VLCFAs was toxic to myelin and the adrenal cortex and testis, several attempts were made to lower the plasma concentrations of VLCFAs. Restriction of VLCFA intake alone induced neither biochemical nor clinical improvement.¹⁰ The failure of this therapy seemed to be due to endogenous biosynthesis of VLCFAs via chain elongation of shorter chain fatty acids.¹¹ Rizzo *et al* discovered that oleic acid (C18:1) reduced the concentrations of VLCFAs in cultured fibroblasts of patients

Department of
Neurology
B M van Geel

Departments of
Internal Medicine and
Psychiatry
J Assies

Department of
Dietetics
E B Haverkort

Department of
Neurology, Division of
Clinical
Neurophysiology
J H T M Koelman

Department of
Radiology
B Verbeeten, Jr

Department of
Biochemistry
R J A Wanders

Departments of
Pediatrics and
Neurology, Academic
Medical Center,
University of
Amsterdam,
Amsterdam, the
Netherlands
P G Barth

Correspondence to:
Dr B M van Geel, Academic
Medical Center, University
of Amsterdam, Department
of Neurology, PO Box
22700, 1100 DE
Amsterdam, the Netherlands.
Telephone 0031 20 5663842;
fax 0031 20 6971438; email
b.m.vangeel@amc.uva.nl.

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with X-ALD, probably by competitive inhibition of the endogenous elongation system of saturated fatty acids.¹² Oral administration of oleic acid in triglyceride form, glyceroltrioleate (GTO), significantly lowered the plasma concentration of VLCFAs.^{13,14} In 1989 Rizzo *et al* reported that the combination of GTO and erucic acid (C22:1) in triglyceride form (glyceroltrierucate, or GTE) normalised the plasma concentration of C26:0 within 1 month in most patients with X-ALD.¹⁵ The combination of GTO and GTE in a 4:1 ratio became known as "Lorenzo's oil", a tribute to Lorenzo Odone, the first patient treated with the mixture.¹⁶

So far, several groups of investigators were unable to show any beneficial effect of "Lorenzo's oil" on the cerebral forms of X-ALD.¹⁷⁻²⁰ Although the efficacy of the oil has been studied much less in patients with milder variants of X-ALD, many are still using "Lorenzo's oil". Aubourg *et al* reported in 1993 that the oil failed to induce a clinically relevant benefit in AMN,²¹ but this finding is yet to be confirmed in a comparable group of patients. As in other countries, a non-randomised trial was conducted in The Netherlands to study the efficacy of GTO/GTE therapy in X-ALD.

Patients and methods

STUDY DESIGN

Male patients with X-ALD and symptomatic heterozygotes known to members of the Dutch X-linked Adrenoleukodystrophy/Adrenomyeloneuropathy Study Group were offered participation in a non-randomised trial with GTO/GTE dietary therapy between January 1990 and January 1995. They were scheduled to be seen every 3 months by a (paediatric) neurologist and endocrinologist, and a dietician. Blood samples were taken at 3 month intervals to study plasma VLCFAs, haematology, and the function of liver, kidneys, adrenal cortex, and testes. Furthermore, every 12 months electrophysiological studies (electronurography and evoked potential studies) and cerebral MRI were performed. End points were discontinuation of treatment or death after at least 1 year of treatment, or the end of our observation period.

PATIENTS

Twenty two patients were followed up according to the study protocol, and their test results were used for calculations. Two patients were asymptomatic (ages 23.6 and 27.9 years), four had the "Addison only" phenotype (median age 5.5 years; range 2.9-31.3), 13 had AMN (median age 43.9 years; range 30.3-55.2), and three were symptomatic heterozygous women (median age 52.0 years; range 50.3-55.6). At the initiation of the GTO/GTE therapy, the median duration of neurological symptoms in the AMN group was 8.0 (range 0.8-33.0) years, and in the female carriers this was 13.5 (range 13.1-18.0) years. The median duration of adrenocortical insufficiency in the four patients with the "Addison only" phenotype was 0.7 (range 0.2-0.9) years, and in the six of the 13 patients with AMN (46%) and adrenocortical insufficiency this was 6.4 (range

3.3-11.8) years. The median follow up period of the 22 patients was 2.5 (range 1.0-6.0) years; the median duration of observation was 1.6 (range 1.2-1.9) years in the asymptomatic patients, 2.1 (range 1.0-2.7) years in the "Addison only" group, 3.5 (range 1.9-6.0) years in the patients with AMN, and 3.7 (range 1.3-4.0) years in the symptomatic heterozygous women.

Only limited data were available on another five patients, all with the "Addison only" phenotype. Their median age at the start of the dietary therapy was 12.5 (range 3.7-12.7) years, and the median duration of adrenocortical insufficiency 5.8 (range 3.4-8.5) years. The median period of follow up was 4.9 (range 3.0-6.9) years.

Fifteen others started treatment, but they were not included in the study for the following reasons: death and short observation period (two patients with AMN); discontinuation of the diet due to rapid neurological deterioration (five patients with CCALD); and non-adherence to the diet or the follow up programme, or both (seven patients with AMN, one "Addison only" patient).

In all patients the diagnosis was confirmed by increased concentrations of C26:0 and C26:0/C22:0 ratios in plasma,²² cultured skin fibroblasts,²³ or both. The study protocol was approved by the local medical ethics committees of the participating centres, and all participants or their parents gave their informed consent.

DIETARY TREATMENT

Aiming at the restriction of saturated VLCFA intake, only 10%-15% of the total caloric intake was provided as fat. Additionally, 4% of the energy intake consisted of GTE (Croda Universal, Ltd, Hull, UK), and 16% of GTO (Capital City Products Company, Columbus, OH, USA). To assess the adherence to the diet, patients or their parents were asked to keep a diary every 3 months for 7 days, and every 6 months they had to fill up a multiple choice questionnaire. This information was checked by the coordinating dietician (EBH). From January 1992 onwards, plasma concentrations of oleic and erucic acid were also measured every 3 months to further corroborate compliance to the dietary treatment.

CLINICAL STATUS

Disability was assessed with the extended disability status scale (EDSS)²⁴ and the Barthel index.²⁵ The EDSS score ranges from 0 (normal neurological examination) to 10 (dead), the Barthel index score ranges from 0 (totally dependent) to 20 (totally independent functioning). Handicap was rated according to the modified Rankin/Oxford handicap scale,²⁶ a score of 0 indicating no symptoms, and a score of 5 a severe handicap requiring constant attention. Detailed information about the scores is given in the table.

LABORATORY INVESTIGATIONS

Plasma fatty acid concentrations

The VLCFA assays were performed as described earlier.² Reference values in our laboratory are: C26:0, 0.45–1.57 $\mu\text{mol/l}$; C24:0/C22:0 ratio, 0.57–0.92; C26:0/C22:0 ratio <0.01–0.02. Plasma concentrations of oleic acid (C18:1) ranged from 1035 to 2025 $\mu\text{mol/l}$ in healthy controls, and plasma concentrations of erucic acid (C22:1) ranged from 0 to 8 $\mu\text{mol/l}$.

Haematology and liver and renal function

The reference values of our laboratory are as follows: haemoglobin (Hb) concentration 8.0–10.0 mmol/l for men and 7.5–9.8 mmol/l for women; leucocyte count $4.2\text{--}10.6 \times 10^9/\text{l}$; platelet count $150\text{--}350 \times 10^9/\text{l}$; plasma creatinine 75–110 $\mu\text{mol/l}$ for men and 65–95 $\mu\text{mol/l}$ for women; aspartate aminotransferase (ASAT, SGOT) <47 U/l; alanine aminotransferase (ALAT, SGPT) <37 U/l; γ -glutamyl transferase (γ -GT) <68 U/l for men and <48 U/l for women; and alkaline phosphatase (AP) 26–103 U/l for adults.

Endocrine function

The function of the adrenal cortex and testes was assessed as described previously.²⁷ We used

the following reference values: cortisol, 0.22–0.65 $\mu\text{mol/l}$ at 0900; dehydroepiandrosterone sulphate (DHEA-S) 2.0–10.0 $\mu\text{mol/l}$; adrenocorticotropic hormone (ACTH) 5–55 ng/l; testosterone 11.0–35.0 nmol/l; luteinising hormone (LH) 5–15 U/l; follicle stimulating hormone (FSH) 1–10 U/l.

ELECTRONEUROGRAPHY

Motor and sensory conduction of the median, peroneal, and sural nerves, compound muscle action potential (CMAP), sensory nerve action potential (SNAP), median nerve and peroneal nerve F wave latencies, and soleus H reflex response were studied. The procedures and reference values of our laboratory were described recently.²⁸ The test results of each investigation were additionally reviewed by an independent observer (JHTMK) and scored as (1) normal; (2) mildly abnormal; and, (3) markedly abnormal, based on the reference values of our laboratory.

EVOKED POTENTIALS

Somatosensory evoked potential (SEP)

Median nerve and posterior tibial nerve SEPs were elicited. Our procedures and reference values have been described previously.^{29,30} The median nerve N20 and the posterior tibial

Assessment at baseline and at the end of the study

Patient	Phenotype	Age at t_0 (y)	Duration of therapy (y)	Disability		Handicap Rankin [‡] t_0/t_E	Endocrinology [§]		Electrophysiology [¶]					Remarks
				EDSS* t_0/t_E	Barthel [†] t_0/t_E		Adrenal cortex t_0/t_E	Testes t_0/t_E	ENG t_0/t_E	SEP t_0/t_E	BAEP t_0/t_E	VEP t_0/t_E	Cerebral MRI ^f t_0/t_E	
A	Asymp	23.6	1.9	0.0/0.0	20/20	0/0	n/n	n/n	1/1	1/1	2/2	1/1	1/1	Gingivitis
B	Asymp	27.9	1.2	1.5/0.0	20/20	0/0	n/n	n/n	1/1	1/1	2/2	1/1	1/1	Stopped diet
C	"Add-only"	2.9	2.7	0.0/0.0	20/20	0/0	i/i	–/–	1/1	2/2	2/1	2/1	1/3	CNS demyelination, BMT
D	"Add-only"	3.1	1.0	0.0/0.0	20/20	0/0	i/i	–/–	1/1	–/–	–/–	1/1	1/1	BMT (elective)
E	"Add-only"	8.0	2.1	0.0/0.0	20/20	0/0	i/i	–/–	1/1	–/1	1/1	1/1	1/1	
F	"Add-only"	31.3	2.1	1.0/1.5	20/19	0/1	i/i	n/i	1/1	1/2	2/2	1/1	2/2	AMN, hypogonadism, GTE intolerance, gingivitis
G	AMN	30.3	2.3	1.5/2.0	20/20	1/1	n/n	n/i	2/2	3/3	3/3	1/1	1/1	Hypogonadism, gingivitis
H	AMN	31.9	2.6	5.0/6.0	17/16	3/2	i/i	i/n	2/2	3/3	3/3	1/1	2/2+	
I	AMN	33.5	4.2	2.5/3.5	20/20	1/2	i/i	i/i	3/3	3/3	3/3	1/1	1/3	CNS demyelination
J	AMN	34.7	5.1	2.5/2.5	20/20	2/2	i/i	n/n	2/3	3/3	3/3	1/1	1/1	
K	AMN	35.5	6.0	5.5/6.5	19/18	2/3	i/i	i/i	2/2	3/3	3/3	1/1	2/2	
L	AMN	39.0	2.2	3.5/2.0	18/19	2/2	i/i	–/–	1/1	3/3	3/3	1/1	3/3	
M	AMN	43.9	2.2	6.0/6.0	20/18	2/2	n/n	i/i	3/3	3/3	3/3	1/1	2/2	
N	AMN	45.0	3.5	2.5/3.5	20/20	1/2	n/i	n/n	2/2	3/3	3/3	1/1	1/1	Adrenocortical insufficiency
O	AMN	45.2	4.3	5.0/6.0	–/18	3/2	i/i	–/i	2/2	3/3	1/3	1/1	–/–	
P	AMN	46.4	6.0	1.5/4.0	19/19	1/2	i/i	n/n	2/3	3/3	3/3	1/1	1/1	
Q	AMN	46.7	1.9	6.5/7.0	15/–	4/4	n/n	–/–	1/1	3/3	3/3	3/3	4/4	
R	AMN	52.7	1.9	5.5/5.0	20/19	3/3	n/n	–/i	2/2	3/3	3/3	1/1	1/1	
S	AMN	55.2	4.7	5.5/7.0	19/14	3/3	n/n	n/i	3/3	3/3	3/3	1/1	2/2	Hypogonadism
T	SHet	50.3	4.0	8.0/8.0	–/6	4/4	n/n	–/–	1/1	1/1	1/1	1/1	2/–	
U	SHet	52.0	3.7	5.5/6.0	20/18	2/3	n/n	–/–	2/2	–/3	1/1	–/1	3/3	
V	SHet	55.6	1.3	5.5/6.0	18/20	2/2	n/n	–/–	1/1	3/3	1/1	1/1	1/1	GTE intolerance

*Extended disability status scale (EDSS)²⁴ scores: 0=normal neurological examination; 1.0=no disability, minimal signs in one functional system (FS); 1.5=no disability, minimal signs in two FS; 2.0 = minimal disability in one FS; 2.5 = minimal disability in two FS; 3.0 = no more than mild disability, fully ambulatory; 3.5 = moderate disability though fully ambulatory; 4.0 = self-sufficient for up to 12 hours despite severe disability; 4.5 = requires minimal assistance, some limitations on activity, but able to work a full day; 5.0 = severe disability, unable to perform full daily activities, but ambulatory without aid; 5.5=severe disability precluding full daily activities, able to walk 100 m; 6.0=constant assistance required; 6.5=two canes or crutches required to walk; 7.0=unable to walk more than 5 m, essentially restricted to wheelchair; 7.5=restricted to wheelchair; 8.0=restricted to bed or chair.

†Barthel index²⁵ scores are the aggregate of bowel function (score, 0 to 2), bladder function (0 to 2), grooming (0 to 1), toilet use (0 to 2), feeding (0 to 2), transfer (0 to 3), mobility (0 to 3), dressing (0 to 2), stairs walking (0 to 2), and bathing (0 to 1); the maximum score is 20, indicating independent functioning.

‡Rankin/Oxford handicap scale²⁶: 0=no symptoms; 1=minor symptoms that do not interfere with lifestyle; 2=minor handicap; 3=moderate handicap; 4=moderately severe handicap; 5=severe handicap, totally dependent requiring constant attention.

§Endocrine function: n=normal; i=insufficient; –=not tested.

¶Electrophysiological studies: 1=normal; 2=mildly abnormal; 3=clearly abnormal; –=not tested; ↓=worsening of markedly abnormal test results.

f Cerebral MRI: 1= normal; 2=mild focal abnormalities in basal ganglia, internal capsule or mesencephalic or pontine cortico spinal tracts; 3=moderate focal white matter abnormalities in basal ganglia, internal capsule, corticospinal tracts in mesencephalon and pons, or periventricular white matter; 4=extensive periventricular white matter abnormalities; –=not performed; and, +=lesions more pronounced without signs of progressive demyelination.

ENG=electroneurography; SEP=somatosensory evoked potential; BAEP=brainstem auditory evoked potential; VEP=visual evoked potential; Asymp=asymptomatic ALD; "Add-only"="Addison only" phenotype; AMN=adrenomyeloneuropathy; SHet=symptomatic heterozygote; BMT=bone marrow transplantation; t_0 =baseline assessment; t_E =assessment at the end of follow up.

nerve P37 latencies were particularly studied. The mean median nerve N20 latency (SD) was 19.5 (1.7) ms, the mean posterior tibial nerve P37 latency (SD) was 40 (2.5) ms.

Brainstem auditory evoked potential (BAEP)

Alternating clicks with an intensity of 75 dB above the hearing threshold with a maximum of 95 dB were delivered. The frequency of stimulation was 11 Hz. Stimuli were presented monaurally with contralateral masking using a noise 40 dB above threshold. Two series of 2000 potentials were recorded, averaged, and superimposed with a Nicolet Pathfinder I (Nicolet Instruments Corporation, Madison, WI, USA). BAEPs were recorded with surface electrodes over the mastoids and referenced to C₂. Electrode impedances were less than 5 kΩ, the bandpass was 0.16–3.2 kHz, and the time of analysis was 10 ms. We measured the I–V intervals. The upper limit of normal I–V latency in adults in our laboratory is 4.43 ms.

Visual evoked potential (VEP)

A full field pattern reversal paradigm was used. A high contrast chequerboard (square size 3.2×3.2 cm) was presented monocularly at a distance of 1.45 m with a stimulation rate of 1.3 Hz. Two series of 100 stimuli presented to each eye were recorded, superimposed with a Nicolet Pathfinder I unit, and checked for reproducibility. Recording electrodes were placed over the midocciput and 5 cm laterally on both sides, and referenced to C_z. Electrode impedances were less than 5 kΩ. The bandpass was 0.16–80 Hz, and the time of analysis was 250 ms. The P100 latencies were determined. The upper limit of normal P100 latency for adults in our laboratory is 118 ms.

The BAEP, VEP, and SEP studies were reviewed by an independent observer (JHTMK) and scored as: (1) normal; (2) mildly abnormal; and (3) markedly abnormal, based on our reference values.

NEURORADIOLOGY

Most of the cerebral MRI was performed with a Siemens 1.5T unit (Siemens AG, Erlangen, Germany). Axial T2 weighted, proton density, and T1 weighted images without and with gadolinium enhancement were performed, and from January 1994 onwards sagittal T2 weighted imaging was carried out as well. The MR images were reviewed by two observers (BV and BMvG) and scored as: (1) normal; (2) mild focal white matter abnormalities in basal ganglia, internal capsule, or corticospinal tracts in mesencephalon and pons; (3) moderate focal white matter abnormalities in basal ganglia, internal capsule, or mesencephalic and pontine corticospinal tracts; and (4) extensive periventricular white matter abnormalities.

STATISTICAL ANALYSIS

To detect significant changes in EDSS and Barthel and Rankin scores, the results were paired and the difference of the median and the 95% confidence interval (95% CI) were calculated using a Wilcoxon based non-parametric test. For the other variables the values at base-

line were paired with those at 1 year of treatment and those at the end of treatment; to determine the significance of changes the mean of the differences and the 95% CI were calculated (Confidence Interval Analysis, British Medical Journal, London, UK).

Results

DIETARY TREATMENT

The table shows demographic data and results. According to the diaries, questionnaires, and the amount of dietary products used, all patients adhered strictly to the diet and GTO/GTE supplementation. We found raised plasma concentrations of oleic and erucic acid in all but one patient (T), further corroborating the adherence to the dietary therapy. Two of the 22 patients developed severe gastrointestinal complaints (E and V), two others acute necrotising ulcerative gingivitis (F, G), and one patient (A) had both. This led to early discontinuation of dietary therapy in two (A and V).

CLINICAL STATUS

Disability as measured by an increase in the EDSS score progressed in 11 patients (50%), and improved marginally in two of the 22 patients (9%). The mean EDSS score of the 16 neurologically symptomatic patients at baseline was 4.5 and this increased mildly but significantly (0.5; 95% CI 0.25–1). We did not see significant changes in the subscales of the EDSS (in particular the pyramidal, sensory, and bowel and bladder functions), Barthel index, or Rankin/Oxford handicap scale.

LABORATORY INVESTIGATIONS

Plasma VLCFA concentrations

We found a significant decrease in the plasma C26:0 concentration in all 22 patients, and normalisation or near normalisation in 19 (86%). The mean plasma C26:0 concentration before the start of treatment was 2.76 μmol/l and decreased 1.02 μmol/l (95% CI 0.54–1.50) after 3 months of treatment, 1.28 μmol/l (95% CI 0.81–1.75) after 1 year, and 0.86 μmol/l (95% CI 0.36–1.36) at the end of the observation period (fig 1). In three patients (G, H, and S), the plasma C26:0 concentrations in general were above 2.00 μmol/l. The mean C24:0/C22:0 ratio was 1.41 before "Lorenzo's oil" was started, and remained raised in all patients; the mean C24:0/C22:0 ratio decreased significantly to 0.40 (95% CI 0.26–0.53) at 1 year of treatment, and to 0.34 (95% CI 0.23–0.45) at the end of follow up. We found no changes in the mean C26:0/C22:0 ratio, which was 0.06 at baseline.

Haematology

One patient (R) developed unexplained anaemia; his Hb concentration recovered spontaneously. We found a significant decrease in mean Hb concentration, which was 9.3 mmol/l at baseline: 0.45 mmol/l (95% CI 0.15–0.75) mmol/l after 1 year of treatment, and 0.47 (95% CI 0.16–0.78) mmol/l at the end of the observation period. The mean leucocyte count before the start of the dietary treatment was

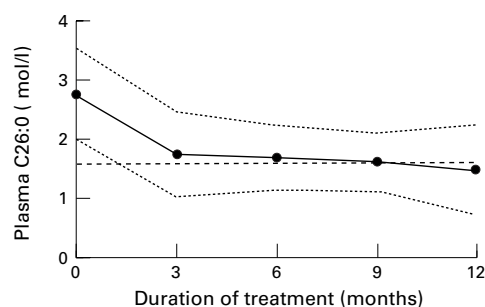


Figure 1 Mean plasma hexacosanoic acid (C26:0) concentration (solid line) \pm SD (dotted lines) in the first year of treatment with "Lorenzo's oil". The horizontal dashed line indicates the upper limit of normal plasma C26:0 concentration (1.57 μ mol/l). In all but three of the 22 patients the plasma C26:0 concentration became normal or near normal ($< 2.0 \mu$ mol/l) during follow up.

7.1 $\times 10^9$ /l, and at the end of follow up it was 1.2 $\times 10^9$ /l lower (95% CI 0.1–2.2). In two patients (I and M) we regularly found counts between 3.0 and 3.5 $\times 10^9$ /l.

In 12 patients (55%) the number of platelets fell to abnormally low concentrations, and in 10 of these patients the count was regularly between 50 and 100 $\times 10^9$ /l. The lowest count was 51 $\times 10^9$ /l (patient D). None of the patients developed haemorrhagic diathesis. The mean platelet count before the use of the GTO/GTE dietary therapy was 232 $\times 10^9$ /l, and decreased, with 63 $\times 10^9$ /l (95% CI 29–96) at 1 year of treatment, and with 76 $\times 10^9$ /l (95% CI 46–105) at the end of follow up.

Liver and renal function

Mild increases in liver enzymes were seen during treatment in 12 of the 22 patients (55%). Nine had a mild transient increase in plasma ALAT concentration (F, G, I–K, M, O, P, and R), and one (N) a mild transient increase in both plasma ASAT and ALAT. Two patients had a mild transient increase in plasma γ -GT concentration (J and U). The plasma AP concentration became mildly increased in four patients (B, G, M, and V). The mean plasma concentrations of ALAT, ASAT, γ -GT, and AP did not change significantly. The plasma creatinine concentration remained normal in all patients, and the mean concentration did not change.

Endocrine function

One patient with AMN (N) developed adrenocortical insufficiency. In one of the "Addison only" patients (F) and in four of the six patients with steroid hormone substitution therapy (H, I, K, and P) we saw greatly increased concentrations of plasma ACTH, regularly exceeding 2000 ng/l in two (H and I) despite adequate substitution. There were no significant changes in the mean ACTH and cortisol concentrations. Plasma DHEA-S concentrations were not determined routinely in the adult male patients, but we measured extremely low values in 13 of 14 (93%) men tested.

In a subset of 12 male patients in whom gonadal function was evaluated before the start of the diet, two had abnormally increased

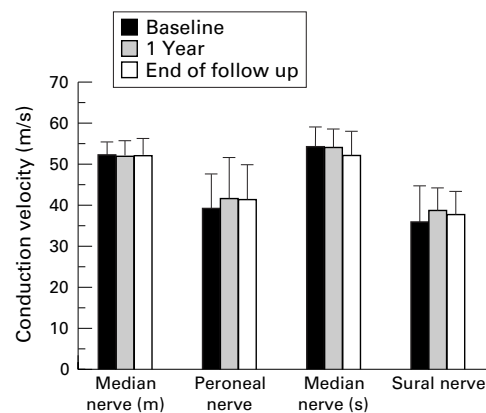


Figure 2 Mean values (SD) of motor nerve (median nerve (m), peroneal nerve), and sensory nerve (median nerve (s), sural nerve) conduction at baseline, after 1 year of treatment, and at the end of the observation period in 13 patients with AMN and three symptomatic female carriers. Despite treatment with "Lorenzo's oil" the conduction velocities did not improve.

plasma concentrations of LH and FSH (H, M). Gonadal function improved in one of these patients (H). During dietary treatment another three (25%) developed gonadal insufficiency: in one patient (F) the LH concentration became abnormally increased, in another (S) the FSH concentration increased above the upper limit of normal whereas the testosterone became abnormally low, and in one (G) the plasma testosterone concentration became abnormally low. The mean plasma LH concentration (9.0 U/l at baseline) rose marginally but significantly (3.1 U/l (95% CI 0.3–6.0)) at 1 year of dietary treatment; the increase at the end of the follow up period was not significant. The FA index was within the normal range in all patients at baseline, at 1 year of treatment, and at the end of the observation period, but the mean value had decreased significantly at the end of follow up (6.3 (95% CI 0.7–11.9)). The mean concentrations of FSH, testosterone, and SHBG did not change.

ELECTRONEUROGRAPHY

In the six neurologically asymptomatic patients nerve conduction was normal at baseline and remained normal.

In the 16 neurologically symptomatic patients we found normal nerve conduction in four (L, Q, T, and V), mild abnormalities in nine (G, H, J, K, N–P, R, and U), and marked abnormalities in three (I, M, and S). Most often, the results were compatible with a predominantly axonal sensorimotor polyneuropathy.²⁸ During the follow up period the individual test results worsened in two patients (J and P), but the motor and sensory nerve conduction velocities (fig 2) and other variables that were studied did not change significantly.

EVOKED POTENTIALS

SEP

The median nerve SEP remained normal in three of four neurologically asymptomatic patients tested (A, B, and F); it normalised in the fourth patient (C). In six of the 13 AMN

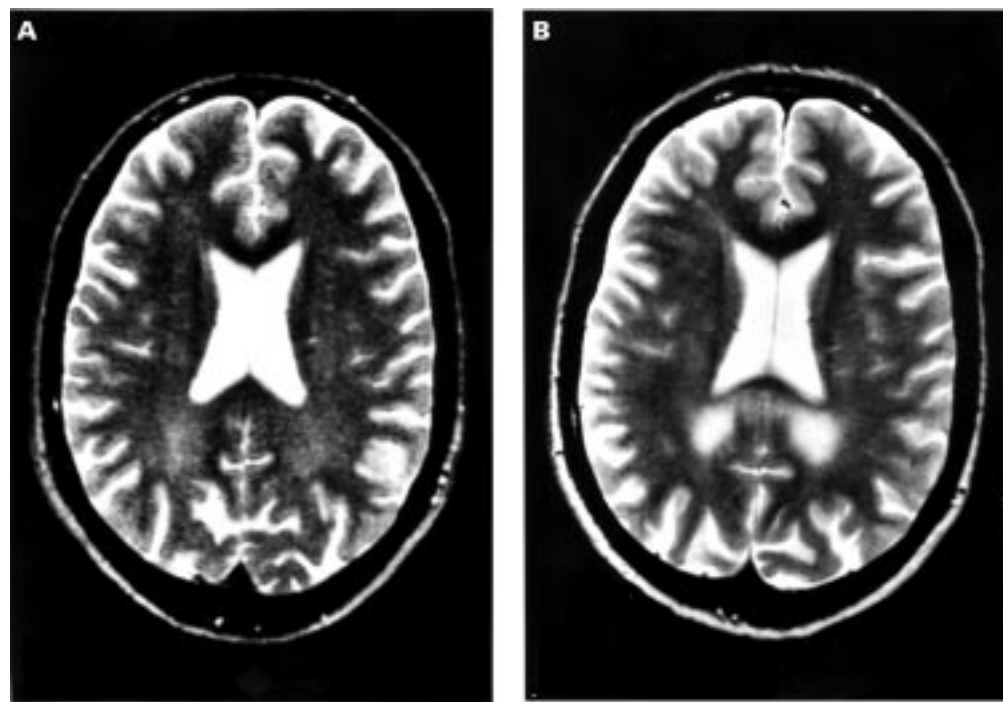


Figure 3 Development of occipital periventricular white matter abnormalities in patient I with AMN who used GTO and GTE compliantly for more than 4 years. The MRI of the brain before the start of treatment was unrevealing. At the left (A), the cerebral T2 weighted MRI show mild hyperintensity after 1 year of treatment. At the right (B), the occipital demyelination is clearly visible 3 years later.

patients and the three heterozygotes the median nerve SEP was normal at baseline; it remained normal in five men (H-J, N, and Q) and the three female carriers (T-V), and became mildly abnormal in one patient with AMN (G). In seven patients with AMN the median nerve SEP was mildly delayed before the start of dietary treatment; it remained mildly abnormal in six (K, M, O, P, R, and S), and normalised in one (L). The mean value of the N20 latency (20 ms at baseline) did not change significantly.

The posterior tibial nerve SEP remained normal in two of three neurologically asymptomatic patients tested at baseline; one "Addison only" patient (F) developed a mildly abnormal posterior tibial nerve SEP. All but one (T) of the 16 symptomatic patients had markedly abnormal test results at baseline: in eight (G, H, J, N, P, R, S, and U) the P37 wave was absent. During follow up P37 responses eventually could be elicited in five of these patients (G, N, P, R, and S), but in two others (I and M) with a previously recognisable potential the SEP could not be detected any more. The mean of the P37 latency before the start of the dietary treatment (52 ms) did not change significantly.

BAEP

In the neurologically asymptomatic patients the BAEP remained normal in one patient (E), mildly abnormal in three (A, B, and J), and it normalised in one patient (C). The 13 patients with AMN had prolonged I-V intervals at baseline: in 12 the latencies remained markedly prolonged, and in one patient (O) the I-V interval changed from mildly to markedly abnormal. In the three female carriers (T-V)

the intervals remained normal. We found no significant changes in the mean I-V latency during follow up.

VEP

The abnormal P100 latencies found at baseline in a boy with the "Addison only" phenotype (C) improved at the end of the observation period; in the patient with AMN and severe occipital demyelination (Q) the prolonged P100 latency became even more markedly abnormal. There were no significant changes in mean P100 latency.

NEURORADIOLOGY

The MR images in the two asymptomatic patients were normal at baseline and at the end of the observation period. The oldest of the four "Addison only" patients (F) manifested mild focal abnormalities of the pontine corticospinal tracts, which did increase; another "Addison only" patient (C) developed demyelinating lesions in the splenium of the corpus callosum, and underwent bone marrow transplantation.^{31 32} In the other two patients with this variant of X-ALD we found no signs of demyelination.

At baseline, cerebral MRI was performed in 12 patients with AMN, and was abnormal in six (50%): four (H, K, M, and S) had mild abnormalities in the internal capsule, mesencephalon, pons, the basal ganglia or the periventricular white matter, one patient (L) had moderate focal white matter abnormalities, and one patient (Q) manifested extensive lesions in the periventricular occipital white matter. During follow up, one patient (I) developed progressive demyelination in the occipital periventricular white matter (fig 3), and in

another (H) the lesions in the corticospinal tracts became more pronounced. We found no other significant changes. In a patient with AMN with a pacemaker (O) cerebral CT was carried out, and showed no abnormalities at baseline and during follow up. One of the heterozygotes (U) showed moderate periventricular white matter abnormalities, and in another (V) we found no white matter lesions, both at baseline and at the end of follow up. In a claustrophobic female carrier (T) MRI was only performed before the start of treatment, and showed mild abnormalities in the mesencephalon.

OTHER PATIENTS

Limited data were available on five patients with the "Addison only" phenotype. In four the cerebral MRI remained normal; one patient developed abnormalities in the mesencephalic corticospinal tracts at the age of 11 years, and after more than 6 years of dietary therapy. Two patients developed thrombocyte counts below $10 \times 10^9/l$ without concomitant haemorrhagic diathesis.

Discussion

Treatment with the GTO/GTE ("Lorenzo's oil") dietary therapy induced normal or near normal plasma concentrations of C26:0 in 19 of the 22 patients (86%) we studied. Despite this significant biochemical response we were unable to detect a clinically relevant beneficial effect during a median follow up period of 2.5 years. Disability increased mildly but significantly in the 16 patients with neurological symptoms. One "Addison only" patient developed AMN (F), and another demyelinating lesions in the corpus callosum (C). One patient with AMN developed occipital demyelination (I), another (N) adrenocortical insufficiency, and three others (F, G, and S) hypogonadism. Furthermore, we did not find improvement in the electrophysiological studies, endocrine function, and cerebral MR imaging.

Non-randomised studies in the United States,¹⁵ Italy,^{17,18} Japan,¹⁹ and Germany²⁰ showed that the treatment with "Lorenzo's oil" did not alter the downhill course in the phenotypes with cerebral demyelination despite the effective lowering of plasma VLCFA concentrations.

However, much less is known about the efficacy of the GTO/GTE diet in adult neurologically symptomatic patients. Cappa *et al* reported stability of neurological abnormalities in 11 patients with AMN studied for a mean period of 2.0 years, and improvement of bladder function in two of these patients.¹⁸ Asano *et al* noted amelioration of spasticity in one patient with AMN followed up for 3 years.¹⁹ On the other hand, Aubourg *et al* found clinical deterioration in nine of 14 AMN patients over a 2.5 year period, although there was some improvement in peroneal nerve conduction and in posterior tibial nerve SEP; the clinical status of five symptomatic heterozygotes did not change.²¹ Korenke *et al* studied three AMN patients for 1.5 years: two men with AMN showed progression of neurological symptoms,

and the third AMN patient deteriorated mentally.²⁰ Preliminary results of a study in 100 patients with AMN by Moser *et al* in the United States do not indicate an amelioration of clinical progression.³³

Regrettably, the worldwide decision to conduct non-randomised studies has hampered the assessment of the efficacy of the dietary treatment tremendously. In retrospect, it is all too easy to argue that it was unethical to withhold from the patients a placebo controlled double blind study. However, there are several extenuating circumstances. When "Lorenzo's oil" was introduced it seemed unethical to withhold this apparently promising therapy from patients with the crippling and debilitating X-ALD.³³ Other therapeutic options were lacking, and treatment with the GTO oil apparently induced a lowering of plasma VLCFAs and a statistically significant improvement in peroneal nerve conduction, suggesting that the oil might be efficacious to the central white matter as well.⁹ Furthermore, the prevalence of X-ALD was relatively low, and the phenotypic expression highly variable.^{5,7} As dangerous as it is to use historical controls, it would have been even riskier in the trials with "Lorenzo's oil", because the natural course in untreated patients was not exactly known. Until recently it was assumed that about 50% of all patients with X-ALD would eventually develop cerebral variants,^{6,9} but in a survey of 30 Dutch kindreds we found a lower risk of about 30%, and predominance of the milder AMN phenotype (46%).⁷ Nevertheless, we tried to compose a representative control group, but this was in vain: the patients who discontinued the dietary treatment were more severely affected, and those who rejected treatment were not keen on regular consultations or investigations.

The aggregate of the available data on the efficacy of "Lorenzo's oil" in adult patients with X-ALD and neurological symptoms suggests that the oil is not efficacious. Our results are in concordance with the findings of Aubourg *et al*²¹ and the preliminary results of the study by Moser *et al*.³³ Even if treatment with "Lorenzo's oil" would be beneficial, several groups of investigators, including ours, were unable to detect these effects.

The accumulation of VLCFAs in brain lipids is associated with myelin instability and the inability of brain macrophages to remove the excess of VLCFAs. The accumulation of VLCFAs in lipids of the central white matter initiates a severe inflammatory reaction in the cerebral variants of X-ALD, resulting in demyelination.³⁴ Therefore, it was reasoned that demyelination might be slowed down or halted if oleic and erucic acid reached the brain. Indeed, in 1989 Rizzo *et al* reported increased concentrations of erucic acid in the brain lipids of a patient with CCALD treated with "Lorenzo's oil" in comparison with an untreated patient,¹⁵ but Rasmussen *et al*³⁵ and Poulos *et al*³⁶ recently were unable to detect increased concentrations of erucic acid in the brain tissue of three patients with CCALD and two with AMN. This raises the question

whether the dietary oils are able to pass the blood-brain barrier.

Patients with X-ALD who might still benefit from "Lorenzo's oil" are those without neurological deficits. Four of the six (67%) neurologically asymptomatic patients with X-ALD we studied remained free of neuroinvolvement during the observation period (median follow up 2.1 years), and it seemed that the five "Addison only" patients on whom we unfortunately had limited data did not develop cerebral demyelination during a median follow up of 5.8 years. However, this observation period is too short to draw firm conclusions about the efficacy of "Lorenzo's oil" in these patients. Cappa *et al* reported that CNS demyelination occurred in only two of 11 asymptomatic patients during a follow up of 2 years.¹⁸ Asano *et al* found no neurological involvement after 2.5 years of dietary therapy in two asymptomatic patients,¹⁹ Aubourg *et al* were unable to detect neurological deterioration in five patients over an identical period,²¹ and Korenke *et al* observed no neuroinvolvement in seven patients over a 2 year period.²⁰ Moser *et al* studied 53 neurologically asymptomatic patients with a mean age of 7.5 years at the start of treatment with "Lorenzo's oil". Preliminary analysis after a mean follow up of nearly 39 months showed that only 10% of the patients had signs of cerebral demyelination or had died, and that the others remained asymptomatic.³⁷ These figures look promising, assuming that the risk for developing cerebral demyelination in X-ALD is high. However, the assessment of the efficacy of treatment with "Lorenzo's oil" in these patients is hampered as well by the absence of an untreated control group and our ignorance of the risk for developing each of the different phenotypes. At present, investigators in Europe (including members of our study group) and the United States are studying whether "Lorenzo's oil" can delay or prevent the onset of symptoms in a large group of neurologically asymptomatic patients with X-ALD. This study is supported by the BIOMED 2 programme of the European Commission and the United States Food and Drug Administration.

Data on the changes in endocrine function of the adrenal cortex and testis are sparse. In 1994 we reported that GTO and GTO/GTE therapy in all five patients with AMN improved neither adrenocortical nor gonadal function.³⁸ In the present study we found no significant improvement in endocrine function of the adrenal cortex and testis, organs that probably are more easily accessible to oleic and erucic acid in the absence of a protective mechanism such as the blood-brain barrier. Many patients with X-ALD,^{27, 39} had extremely low concentrations of DHEA-S, the most abundantly produced adrenocortical hormone. This hormone seems to be involved in the modulation of the immune response,⁴⁰ a response that is so excessive in the cerebral forms of X-ALD.³⁴ The interaction between DHEA-S and the immune response in X-ALD deserves further research. For testis function, we recently found that most men with X-ALD (77%) have clinical or

subclinical testicular insufficiency, even in the absence of neurological deficits or adrenocortical insufficiency.²⁷ The possible role of treatment with androgens in patients with X-ALD and testicular insufficiency merits further study.

Although treatment with "Lorenzo's oil" did not seem to be beneficial, we often found side effects such as mild increases in liver enzymes (55%), thrombocytopenia (55%), gastrointestinal complaints (14%), and gingivitis (14%). Furthermore, there was a decrease in Hb concentration and leucocyte count, and an increase in the plasma AP concentration. The reduction in platelets fortunately did not result in haemorrhagic diathesis. We recently reported that the thrombocytopenia may be due to platelet activation, resulting from an increase in the erucic acid concentration of lipids in the platelet membrane.⁴¹ In patients with counts below $80 \times 10^9/l$ we lowered the GTE dose by 50 to 75%, and again added GTE carefully until normal or near normal concentrations of C26:0 were achieved. Low platelet counts have often been found by others as well.^{19-21, 42-44} Lymphocytopenia⁴⁵ and severely depressed natural killer cell activity⁴⁶ were also reported. We do not know whether some of the side effects may have been due to low concentrations of essential fatty acids, or induced by reduction of the dietary fat intake; we are studying this at present.

The results of our study with "Lorenzo's oil" raise the question whether this therapy is efficacious at all, and whether a marginal therapeutic effect counterbalances the side effects. As other therapeutic options are virtually lacking for patients with X-ALD and impending neurological deficits, we still prescribe the GTO/GTE diet to neurologically asymptomatic patients with X-ALD, and to those with neurological symptoms who prefer to adhere to it. Bone marrow transplantation seems to be effective, but only in young boys with mild signs of cerebral demyelination.^{31, 32} Other therapies such as immunosuppression,^{47, 48} β -interferon,⁴⁹ and intravenous immunoglobulins⁵⁰ were ineffective. The efficacy of "Lorenzo's oil" can only be assessed by a randomised, placebo controlled, double blind study. At present it seems very unlikely that such a trial will ever be conducted. Fortunately, Lu *et al* recently developed an X-ALD mouse model by gene targeting.⁵¹ The X-ALD mice exhibit biochemical defects equivalent to those found in patients with X-ALD, thus providing a manageable system for testing present and future therapeutic interventions.

Furthermore, two novel therapeutic approaches were described recently, and may be used in future trials. According to Singh *et al*, lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor used for the treatment of hypercholesterolaemia, also decreases plasma concentrations of VLCFAs in patients with X-ALD, and should be further evaluated.⁵² Kemp *et al* reported that 4-phenylbutyrate, used against urea cycle disorders, lowers VLCFA concentrations by increasing β -oxidation in cultured cells from

patients with X-ALD and the X-ALD knock-out mice.⁵³

In conclusion, we were unable to detect a beneficial effect of treatment with “Lorenzo’s oil” in patients with neurologically symptomatic X-ALD. On the contrary, the dietary therapy often caused adverse effects. We think that the oil should not be prescribed routinely to patients with X-ALD who already have neurological symptoms. However, it remains to be determined whether “Lorenzo’s oil” can postpone neurological involvement in neurologically asymptomatic patients with X-ALD.

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NEUROLOGICAL STAMP

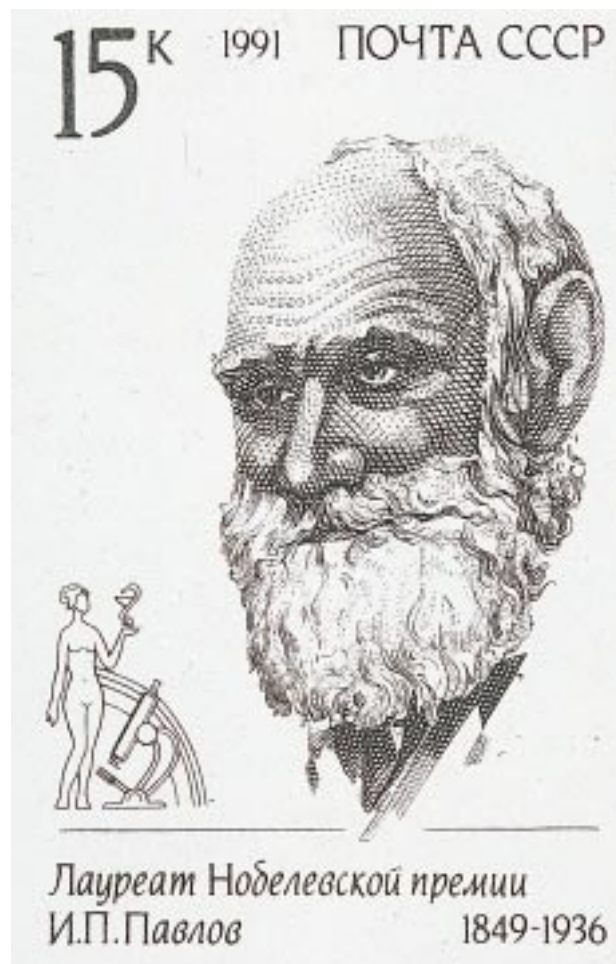
Ivan Petrovich Pavlov (1849-1936)

Although trained as a physician Pavlov always worked as an experimental laboratory scientist. He only had contact with patients at the end of his career. Under the influence of the well known clinician Sergei Petrovich Botkin he developed a commitment to nervous, as opposed to humoral explanations for bodily functions. By 1883 he had developed his theory of "nervism" which he defined as a physiological theory which tries to prove that the nervous system controls the greatest possible number of bodily functions. With the development of aseptic methods of surgery at that time, Pavlov was able to develop surgical methods for physiological research. One of his teachers, Heidenham, had previously made a stomach pouch from which he could obtain pure gastric juice free from food but in the formation of the pouch Heidenham had destroyed the nerve supply to the pouch. Pavlov had a great skill as an experimental surgeon. He developed a small part of the stomach, the "Pavlov pouch" as well as chronic external salivary, biliary, and pancreatic fistulae for his fundamental study of gastric physiology, publication of which won him the Nobel Prize in 1904. Pavlov demonstrated that secretory nerve fibres of the pancreas and stomach were in the vagus nerve.

With his later work on conditioned reflexes (1912), the effect sensory or psychic stimuli have on reflex actions, Pavlov showed that stimuli such as a musical note, a bright colour, a strong odour, skin stimuli, or an electric shock if previously associated with the sight of food, caused salivation. At the sound of a given note this would cease if the note was raised or lowered even by a quarter tone. Pavlov thought that the conditional or acquired reflexes were associated with different areas of the cerebral cortex. This led to a new psychology oriented school of physiology and stimulated ideas of many aspects of human behaviour being the result of conditioning. In his acceptance of the Nobel Prize for his work on digestive physiology in 1904, Pavlov chose to speak on his work on conditioned reflexes.

Pavlov further extended this sphere of his research interest into human psychophysiology and psychopathology. In the late 1920s he began making observations on patients in a psychiatric hospital and attempted to explain disorders that he saw in terms of his work on conditioning.

Pavlov criticised communism and in 1922 requested and was refused permission to move his laboratory abroad. After expulsion of priests' sons from the Medical Academy,



Pavlov, who was also the son of a poor village priest and himself a former seminary student resigned in protest from the Chair of Physiology but his research continued to be supported by State funds.

Pavlov has been philatelically honoured on several occasions. He is shown here on a Russian stamp of 1991 (Stanley Gibbons 6253, Scott 5999) in a series commemorating Russian winners of the Nobel Prize.

L F HAAS