Quebec Cooperative Study of Friedreich's Ataxia

Friedreich's Ataxia 1978 — An Overview

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SUMMARY: *In the present overview an attempt is made to summarize the investigations carried out during the first part of Phase Two of the Quebec Cooperative Study of Friedreich's Ataxia. These investigations delineated the relative importance of various biochemical leads uncovered during the preliminary survey. It is possible to indicate some findings that may be primary and which should be pursued in subsequent investigations. Among these, the observation of an abnormal composition of high density lipoproteins in Friedreich's Ataxia appears to be the most important.*

RÉSUMÉ: *La présente revue générale a pour but de résumer les nouvelles investigations accomplies lors de la première partie de la Phase Deux de l'étude Coopérative de l'Ataxie de Friedreich. Ces études ont permis une délinéation plus détaillée de l'importance relative des diverses indications de nature biochimiques découvertes lors de l'enquête préliminaire. Il nous est maintenant possible de proposer quels pourraient être les défauts primaires et lesquels parmi ceux-ci méritent une étude plus poussée. L'observation d'une composition anormale de lipoprotéines à haute densité dans l'ataxie de Friedreich nous semble le plus important de ces résultats.*

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INTRODUCTION

The usual mechanism of progress in clinical research has been to await the development of a new basic concept and to apply it to various diseases. Less frequently, a chance observation by a clinician has led to major discoveries. It was a gamble when the planning committee of the Quebec Cooperative Study of Friedreich's Ataxia decided to carry out a prospective study of 50 cases of Friedreich's ataxia in the hope of redefining the absolute requirements for the diagnosis, including the minimum constellation of symptoms and signs for early recognition and in the hope of discovering the underlying biochemical substratum. The results of this survey have been published in the Canadian Journal of Neurological Sciences (Vol. 3: 269-397, November 1976).

A number of biochemical leads were uncovered indicating possible defects in the metabolism of glucose, pyruvate, tuarine and β-alanine, calcium, bilirubin and cholesterol. It is not known if any of the biochemical anomalies are primary or secondary to the disease. The purpose of the second phase was to follow in detail each of these leads using the most advanced techniques at our disposal. The present issue reports the results of these researches which are summarized briefly.

I — Clinical and genetic features

Despite criticisms of our restricted criteria for the characterization of typical Friedreich's Ataxia (see table in the Introductory paper of this issue), we have found no reason during our subsequent investigations to broaden the definition. In rare cases the clinical onset may be delayed to the age of 19. Further, the vibratory and/or position sense in the lower limbs may be more accurately classified as decreased rather than absent. We have never encountered normal or brisk tendon reflexes in true Friedreich's ataxia. These cases should be classified as atypical or Marie's spino-cerebellar degeneration. This rigid position has permitted the identification of at least 42 cases of a new syndrome of recessive spastic ataxia in the counties of Charlevoix and Saguenay in Quebec. These patients present many biochemical similarities to Friedreich's ataxia. The age of onset is earlier (1-2 years), the course is slower and less severe without kyphoscoliosis. Posterior column signs and absent evoked potentials are found, as in Friedreich's ataxia, but the tendon reflexes remain brisk except towards the end (Bouchard et al., this issue).

This new syndrome and two families with a recessive form of spino-olivo-ponto-cerebellar atrophy, resembling OPCA type II, composes our knowledge of the spectrum of autosomal recessively inherited disorders with ataxia in Quebec. It is of interest that the clinical features and the localization of neuronal damage are apparently determined by the age of onset. It is as if the selective vulnerability of the parts of the nervous system varied according to the time at which the presumed "toxin" (or metabolic defect) was operative. This observation is of interest in the eventual understanding of the pathophysiology of the clinical phenotype.

From these observations and considerations we would like to propose a new functional nosological classification of recessive progressive ataxias (Table 1) to be used in our further studies. Some of the clinical aspects, neglected in the literature, have been ocular concomitants of the vestibular component of heredit-

TABLE 1 NOSOLOGY OF INHERITED RECESSIVE ATAXIAS

GENETICS	TENDON REFLEXES	TYPE	AGE OF ONSET	MAIN PATHOLOGY	ASSOCIATED SYMPTOMS	KNOWN ENTITIES
Progressive Recessive Ataxia	Hyperreflexic	I	Congenital (0-6m)	Brain Cerebellum	-Mental retardation -Eye symptoms -Congenital defects -Spasticity	a) Marinesco-Sjoegren Syndrome b) Congenital ataxia, aniridia and mental retardation (Gillespie)
		II	Infantile (0-6y)	Brain Cerebellum Post. Column	-Spasticity -Mitral valve prolapse -Foot deformities	a) Charlevoix-Saguenay Syndrome b) Troyer Syndrome c) Ataxia-telangiectasia
	Areflexic	III	Childhood (6-16y)	Cerebellum Post. Column Cortico spinal	-Scoliosis -Pes cavus -Cardiomyopathy	a) Friedreich's Ataxia b) Refsum's disease c) Bassen-Kornzweig Syndrome
		IV	Juvenile (16-25y)	Post. Column Cortico spinal Peripheral nerves	no scoliosis slow progression	a) Recessive Roussy-Levy Syndrome
	Normo-Reflexic	V	Adult (> 25y)	Cerebellum Brain stem	Dysarthria	a) Recessive type II OPCA (Fickler-Winkler type)

ary ataxias. Monday et al. (this issue) carried out a thorough investigation of vestibular function in 16 patients with typical Friedreich's ataxia, using electronystagmography and caloric tests. They observed a number of defects, but most abnormal findings were related to ocular dysmetria, disorganized pursuit and square waves which were found in a significant number of cases.

The genetic aspects of inherited ataxias recently received a marked impetus with the tentative localization of the presumed ataxia gene on the sixth chromosome, near the HLA loci, in a family with OPCA — type I (Jackson et al., 1977). Unfortunately, in another similar family with autosomal dominant inheritance from the Gaspé peninsula, we failed to find evidence for association or linkage to the HLA or C4 complement loci (Wastiaux et al., this issue). We also did not find any association with HLA genotypes in 19 patients with the Charlevoix-Saguenay syndrome or in 16 patients with typical Friedreich's ataxia. Thus, the question of the localization of the ataxia gene remains open. Study of much larger numbers of cases, analyzed by a computer program, will probably be required to draw firm conclusions.

II — Biochemical Features

(a) Calcium metabolism

In the only autopsy available to us, Sanchez-Casis et al. (1976) demonstrated granular deposits of calcium salts and iron in the muscle cells of the heart. Friedreich's ataxia is almost always associated with a cardiomyopathy. In view of our findings of a possible taurine defect in this disease (Lemieux et al., 1976), it is of interest that Huxtable and Bressler (1974) had observed abnormal cardiac concentrations of taurine in congestive heart failure. We asked Huxtable (this issue) to review the possible pharmacological links between these observations. He concluded that the evidence leads to the suspicion that the lungs may be strongly involved in the development of the right heart disease common in Friedreich's ataxia. An underlying genetic defect in the heart, plus an insult to the right side could account for the asymmetrically developing hypertrophy. Huxtable also postulated a possible toxic origin to many of the metabolic changes found in Friedreich's ataxia and indicated how calcium fluxes play a fundamental role in these mechanisms. Taurine in the heart has been shown to have a modifying influence on calcium kinetics. It increased the retention of calcium by the heart, the extra calcium being held in a bound form (Huxtable, 1976). Furthermore, Izumi et al. (1977) have shown that when the experimental milieu mimics the situation of a hyperpolarized membrane, taurine again modifies the binding of calcium to microsomes, making more free calcium available. On a resting membrane, taurine has no effect on microsomal calcium. If calcium and taurine interplay significantly in the heart to produce a cardiomyopathy, a number of therapeutic approaches become possible. For example, Jasmin et al. (1975) have prevented the cardiomyopathy of the Syrian hamster with the calcium mobilizing drug, verapamil. Such possibilities deserve study in Friedreich's ataxia.

Although cortisol, lithium and taurine, on their own, have no effect on basal prostaglandin (PG) production, these substances can block the effect of prolactin, or zinc, upon the mobilization of dihomo-γ-linolenic acid which increases the synthesis of PG E1 (Horrobin et al., this issue). These authors, using a smooth muscle model, have shown that prostaglandin PG E2 probably regulates entry of calcium from extracellular fluid, whereas the release from intracellular stores depends on the interplay between Thromboxande (TX A2, PG E1) and prostacyclin. Again, the important role of calcium fluxes at the membrane is underlined, and again one can imagine a number of hypotheses on the pathophysiology of disordered calcium fluxes as well as eventual therapeutic approaches. This may have direct bearing upon the pathology of Friedreich's ataxia, since calcium defects may be involved in demyelination and nerve conduction. To date, calcium transport defects have only been hinted at in Friedreich's ataxia.

Calcium, prostaglandins and hormones interplay at the site of receptors in membranes. Their transport requires a number of nucleotides to supply energy. Draper et al. (this issue) carried out a detailed investigation of nucleotide synthesis, interconversion and degradation and found no difference between subjects with Friedreich's ataxia and

normal controls. It appears improbable that this disorder is related to a primary defect in purine metabolism.

(b) Oxygen Transport

Because of the abnormal pulmonary function seen in patients with Friedreich's ataxia (mild degree of hypoxia with low diffusing capacity, a progressive fall in total lung capacity and in vital capacity, and a late decrease in residual volume and functional residual capacity) (Bureau et al., 1976) and the hypertrophic cardiomyopathy (Côté et al., 1976), it was reasonable to suspect an abnormality in the oxygen-hemoglobin dissociation curve. This hypothesis was tested in 12 subjects with Friedreich's ataxia. Both the hemoglobin and P50 were found to be normal. This normal oxygen transport system most likely excludes an abnormal oxygen dissociation curve as an important contributing factor to the pathophysiology of the cardiomyopathy or neuropathy of this disease.

(c) Bilirubin metabolism

One of the most unexpected findings of the first phase survey was that some patients with Friedreich's ataxia had total and unconjugated bilirubin values above normal limits (Barbeau et al., 1976a). This suggested there were two sub-groups of ataxics, one with associated hyperbilirubinemia, one without. Conversely, all patients might have the same biochemical defect which was picked up only under certain metabolic conditions. To test the latter hypothesis, patients with typical Friedreich's ataxia and matched controls were exposed to the combined metabolic stresses of fasting and the intravenous injection of 50 mg nicotinic acid (Hamel et al., this issue). This experiment led to the delineation of two sub-groups of responses. The high bilirubin ataxics maintained abnormally elevated levels of bilirubin, while normal bilirubin ataxics behaved like the normal controls. This suggests that the hyperbilirubinemia is not an integral part of the disease, but is more likely to be a chance association, or linkage, of the Gilbert's disease gene with that of ataxia. The other possibility is that there are two phenotypically similar forms of Friedreich's ataxia, one of which is linked closely to an abnormality in bilirubin metabolism. A similar high incidence of hyperbilirubinemia has been found in 42 cases of the Charlevoix-Saguenay syndrome of spastic ataxia, but not in 30 cases of O.P.C.A. type I (Bouchard et al.; Wastiaux et al.; this issue). We think this defect is a secondary manifestation and not a primary factor in Friedreich's ataxia.

(d) Pyruvate metabolism

An important result of our survey was the observation of an in vivo slowing of pyruvate oxidation, particularly evident after a glucose load. Preliminary studies by our group (Barbeau et al., 1976b) and by Blass and collaborators (1976) indicated that the defect could be at the level of the third component of the pyruvate dehydrogenase complex (PDH), i.e. the E_3 or lipoamide dehydrogenase (LAD) step. The complex mechanism of regulation of the PDH complex and of LAD in particular was elucidated in rat brain by Ngo and Barbeau (this issue) and shown to involve a non-classical 3-site "ping pong" mechanism.

It was discovered (Barbeau et al., 1976b) that ataxic subjects were different from the control group in their pyruvate response to glucose. This slow pyruvate oxidation is not found in all types of spinocerebellar degenerations. It is normal in dominant OPCA, but is abnormal in the Charlevoix-Saguenay syndrome and in recessive Roussy-Levy. This indicates that a common factor, not found in OPCA, would be involved. Perhaps slow nerve conduction is the factor. Experiments by Butterworth et al. (1977) indicated that ataxia produced by 3-acetyl-pyridine, which causes lesions of the olive and cerebellum only, was not accompanied by decreased PDH in the muscles. Ataxia produced by acrylamide, which attacks the peripheral nervous system, was always accompanied by a decrease in the active proportion of muscle PDH. Furthermore, not all patients with Friedreich's ataxia responded similarly to a glucose load. Familial patterns in pyruvate responses (high responders, normal responders) can be isolated, indicating that this may be an inherited trait perhaps independent of the disease.

Kark et al. (1974) had reported low muscle pyruvate oxidation in a sub-group of patients with Friedreich's ataxia (but not in all cases) and in other neuropathies. We tried (Barbeau et al., 1976b) to locate a similar PDH defect in white blood cells and platelets of Friedreich's ataxia (Filla et al., this issue), but could not find an anomaly. We could not confirm the decreased PDH in fibroblasts (Blass et al., 1976) of patients with Friedreich's ataxia. In three separate experiments (Melancon et al., this issue) we found normal pyruvate oxidation in Friedreich's fibroblasts. The only consistent abnormality (Filla et al.; Melancon et al.; this issue) was a decrease in serum lipoamide dehydrogenase activity (LAD).

It is our conclusion that the defect in pyruvate oxidation found in vivo (glucose load or LAD determination), but not in vitro (fibroblasts, leukocytes or platelets) in the majority of typical cases of Friedreich's ataxia is not primary to the disease. It may be the result of abnormal regulation of the third component (E_3-LAD) of the PDH complex, perhaps reflecting another metabolic defect found in Friedreich's ataxia (insulin, taurine, bilirubin, calcium or pyridoxal phosphate?). When present, this defect in the regenerating component of the PDH complex could disturb this pathway, and the eventual production of acetyl-CoA could be responsible for some of the symptoms (Gibson et al., 1975). This conclusion should not be interpreted as meaning that there may not be rare cases of ataxia where a PDH defect is primary. This is certainly the case in some forms of infantile intermittent ataxia (Blass et al., 1970).

(e) Amino Acid Metabolism

In the previous survey, Lemieux et al., 1976 demonstrated a marked

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increase in the urinary excretion of taurine and β-alanine and an increased renal clearance rate of taurine, β -alanine and aspartic acid. These findings could be due to overflow amino aciduria, a defect in the tubular reuptake of the amino acids, or an abnormal tubular secretion. Normal or low blood levels eliminate the first option. It is known that taurine and β-alanine share the same transport system (Goldman and Scriver, 1967). We looked for a possible generalized defect in taurine transport in other organs. Filla et al. (this issue) measured the uptake of ^{14}C-taurine in platelets of 20 ataxia patients and 20 age-matched normal control subjects. No significant differences were found in uptake or kinetics of taurine between the two groups. If a transport defect in taurine exists in Friedreich's ataxia, it is not present in all tissues. Further studies of CSF taurine and aspartic acid values, with a modified gas-chromatographic technique (Lemieux et al., this issue), revealed that the levels of these amino acids were not decreased as previously thought.

The functions of taurine and of aspartic acid in the cerebellum and spinal cord are still not clearly known. The study of animal models of ataxia (Butterworth et al., this issue), using the single intraperitoneal injection of 3-acetyl-pyridine in rats, produced pathological damage to the medulla oblongata and to the climbing fibers of the cerebellum. This produced a clearer delineation of the selective vulnerability of neuronal systems within the cerebellum. Three-acetyl-pyridine decreased glutamic acid in the cerebellum, medulla, cortex, striatum, hippocampus, retina and olfactory bulbs. More specifically, it reduced the concentrations of taurine in the cerebellum and medulla oblongata. Aspartic acid levels were not modified by 3-acetyl-pyridine, but were specifically decreased in alloxan diabetes (Butterworth et al., this issue). The specificity of low aspartic acid levels in some forms of ataxia (Robinson, 1968) is challenged.

Another aspect of the possible CNS functions of taurine was uncovered in the course of these studies (Collu et al., this issue). The administration of small amounts of taurine did not modify pentobarbital-induced sleep and pituitary hormone release. The marked increment in plasma growth hormone values, induced by morphine administration, was completely blocked by the IVT injection of the amino acid. This indicates that taurine may play a role in hypothalamic functions.

(f) Lipid Metabolism

In the previous survey, Butterworth et al., 1976 found some of the typical Friedreich's ataxia patients had relatively low levels of cholesterol, compared to the normal population. None of the subjects investigated had acanthocytosis, as would be seen in the Bassen-Kornzweig syndrome. This observation stimulated an investigation of plasma lipids and lipoproteins in Friedreich's ataxia and familial spastic ataxia (Davignon et al., this issue). A study of plasma lipids and lipoproteins was carried out in 11 cases of Friedreich's ataxia and 6 cases of the Charlevoix-Saguenay syndrome. No differences were noted in the fatty acid profile of the total lipid fraction, in the total cholesterol and phospholipids, or in the percentage distribution of the individual phospholipid classes. The triglycerides were higher in Friedreich's ataxia, but within the normal range. Although no systematic abnormalities could be detected in the electrophoretic pattern of plasma lipoproteins or in the apolipoprotein profile on polyacrylamide gel electrophoresis, major differences were found in the high density lipoprotein (HDL) fraction. Their total amount was reduced and their composition was abnormal in both neurological diseases. In Friedreich's patients, the relative proportion of cholesterol and triglycerides was increased, while the relative protein content was greatly reduced. In Charlevoix disease, a similar abnormality was seen except for the excess of triglycerides. The proportion of phospholipids in HDL was the same in the three groups of patients. In addition, the low denstiy lipoprotein (LDL) fraction (β -lipoprotein) was slightly reduced in both diseases. This slightly low β -lipoprotein level was confirmed using another determination method by Wastiaux et al. (this issue).

The significance of this anomaly of the HDL fraction (α -lipoproteins) is not understood, but it could indicate that the HDL apolipoprotein moiety has a greater affinity for cholesterol and triglycerides in Friedreich's ataxia than in its normal counterpart. Because the cholesterol content of membranes is dependent on the surrounding milieu (Cooper et al., 1975), and can be exchanged with the lipoproteins of the milieu, the eventual significance of the HDL defect could be a modification of membrane structure or fluidity in Friedreich's ataxia. This hypothesis is now being investigated.

III — Therapeutic approaches

The above observations can lead to a number of possible therapeutic approaches. Verapamil could be tested in the prevention of the cardiomyopathy of Friedreich's ataxia. Taurine, cortisol or lithium could be used to modify possible abnormal calcium fluxes in membranes. Finally, the postulated acetyl choline synthesis defect in ataxia (Gibson et al., 1975) could be corrected with physostigmine (Kark) et al., 1977) or with choline or phosphatidylcholine (Barbeau, this issue). These avenues are being explored.

CONCLUSIONS

The second phase of the Quebec Cooperative Study of Friedreich's ataxia has permitted a clearer delineation of the possible biochemical defects in this disease. All the leads uncovered during the Phase One survey have been followed. Some (like oxygen transport, purine metabolism) have been eliminated from consideration. Others have been found most likely to be secondary to the disease or to other regulatory metabolic factors, or to be coincidental (hyperbilirubinemia, pyruvate oxidation). However,

TABLE 2 SUMMARY OF PERTINENT BIOCHEMICAL FINDINGS IN FRIEDREICH'S ATAXIA

(FEBRUARY 1978)

NORMAL FINDINGS	INCIDENTAL OR SECONDARY FINDINGS	POSSIBLE PRIMARY FINDINGS
1. Oxygen transport	1. Possible defect in regulation of membrane calcium fluxes (Taurine or prostaglandin controlled).	1. Abnormal composition of high density lipoproteins
2. Purine and Nucleotide metabolism	2. Accumulation of calcium in heart tissues.	2. Possible membrane structural defect.
	3. Urinary loss of taurine and ß-alanine, but no generalized transport defect of taurine.	
	4. Unconjugated hyperbilirubinaemia.	
	5. Sub-group of patients with slow oxidation of pyruvate and low LAD in serum.	

these latter findings may be responsible for some of the symptoms of the disease. Finally, we are left with a series of observations which may bear directly upon the pathophysiology of Friedreich's ataxia and deserve further studies (Table 2). These relate to the new finding of an abnormal composition of high density leipoproteins (α-lipoporteins) in Friedreich's ataxia, and possible consequent membrane defects. This observation is consistent with the reports of abnormal lipoproteins in Bassen-Kornzweig's disease (a - Beta-lipoproteinemia), a recessive disorder, and the low-Beta-lipoproteins in a dominant kinship (Mars et al., 1969). It is noteworthy that all these diseases present with the clinical phenotype of Friedreich's ataxia (Aggerbeck et al., 1974), suggesting that membrane lipid or protein constituents may be the common pathogenic link.

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REFERENCES

AGGERBECK, L. P., McMAHON, J. P. and SCANU, A. M. (1974). Hypobetalipoproteinemia: Clinical and biochemical description of a new kindred with Friedreich's ataxia. Neurology, 24, 1051-1063.

BARBEAU, A., BRETON, G., LEMIEUX, B. and BUTTERWORTH, R. F. (1976a). Bilirubin metabolism in Friedreich's ataxia — Preliminary investigation. Can. J. Neurol. Sci., 3, 365-372.

BARBEAU, A., BUTTERWORTH, R. F., NGO, T., BRETON, G., MELANCON, S., SHAPCOTT, D., GEOFFROY, G. and LEMIEUX B. (1976b). Pyruvate metabolism in Friedreich's ataxia. Can. J. Neurol. Sci., 3, 379-388.

BLASS, J. P., AVIGNAN, J. and UHLENDORF, B. S. (1970). A defect in pyruvate decarboxylase in a child with an intermittent movement disorder. J. Clin. Invest., 49, 423-432.

BLASS, J. P., KARK, R. A. P. and MENON, N. K. (1976). Low activities of the pyruvate and oxoglutarate dehydrogenase complexes in five patients with Friedreich's ataxia. New Engl. J. Med., 295, 62-67.

BUREAU, M. A., NGASSAM, P. LEMIEUX, B. and TRIAS, A. (1976). Pulmonary function studies in Friedreich's ataxia. Can. J. Neurol. Sci., 3, 343-348.

BUTTERWORTH, R. F., IZUMI, K., LANDREVILLE, F. and BARBEAU, A. (1977). Dosage de la pyruvate déshydrogénase musculaire dans deux modèles expérimentaux d'ataxie. Union Med. Can., 106, 468-471.

BUTTERWORTH, R. F., SHAPCOTT, D., MELANCON, S., BRETON, G., GEOFFROY, G., LEMIEUX, B. and BARBEAU, A. (1976). Clinical laboratory findings in Friedreich's Ataxia. Can. J. Neurol. Sci., 3, 355-360.

COOPER, R. A., ARNER, E. C., WILEY, J. S. and SHATTIL, S. J. (1975). Modification of red cell membrane structure by cholesterol-rich lipid dispersions. J. Clin. Invest., 55, 115-126.

COTE, M., DAVIGNON, A., ELIAS, G., SOLIGNAC, A., GEOFFROY, G., LEMIEUX, B. and BARBEAU, A. (1976). Hemodynamic findings in Friedreich's ataxia. Can. J. Neurol. Sci., 3, 333-336.

GIBSON, G. E., JOPE, R. and BLASS, J. P. (1975). Decreased synthesis of acetyl choline accompanying impaired oxidation of pyruvic acid in rat brain minces. Biochem. J., 148, 17-23.

GILLESPIE, F. D. (1965). Aniridia, cerebellar ataxia and oligophenia in siblings. Arch. Ophthal., 73, 338-341.

GOLDMAN, H. and SCRIVER, C. R. (1967). A transport system in mammalian kidney with preference for ß -amino compounds. Pediat. Res., 1, 212-213.

HUXTABLE, R. and BRESSLER, R. (1974). Taurine concentrations in congestive heart failure. Science, 184, 1187-1188.

IZUMI, K., BUTTERWORTH, R. F. and BARBEAU, A. (1977). Effects of taurine on calcium binding to microsomes isolated from rat cerebral cortex. Life Sci., 20, 943-950.

JACKSON, J. F., CURRIER, R. D., TERASAKI, P. I. and MORTON, N. E. (1977). Spinocerebellar ataxia and HLA linkage. New Engl. J. Med., 296, 1138-1141.

JASMIN, G., SOLYMOSS, B. and EU, H. Y. (1975). Effect of thyroparathyroidectomy and of a low calcium diet on the cardiomyopathy of the Syrian hamster. In: The Metabolism of Contraction, University Park Press, Baltimore (edited by P. E. Roy and G. Rona), pp. 717-729.

KARK, R. A. P., BLASS J. P. and ENGEL, W. K. (1974). Pyruvate oxidation in neuromuscular diseases — Evidence of a genetic defect in two families with the clinical syndrome of Friedreich's ataxia. Neurology, 24, 964-971.

KARK, R. A. P., BLASS, J. P. and SPENCE, M. A. (1977). Physostigmine in familial ataxias. Neurology, 27, 70-72.

LEMIEUX, B., BARBEAU, A., BERONIADE, V., SHAPCOTT, D., BRETON, G., GEOFFROY, G. and MELANCON, S. (1976). Amino acid metabolism in Friedreich's ataxia. Can. J. Neurol. Sci., 3, 373-378.

MARS, H., LEWIS, L. A., ROBERTSON, A. L., BUTKUS, A. and WILLIAMS, G. H. (1969). Familial hypo-ß -lipoproteinemia — a genetic disorder of lipid metabolism with nervous system involvement. Am. J. Med., 46, 886-900.

ROBINSON, N. (1968). Chemical changes in the spinal cord in Friedreich's ataxia and motor neurone disease. J. Neurol. Neurosurg. Psychiatr. 31, 330-333.

SANCHEZ-CASIS, G., COTE, M. and BARBEAU, A. (1976). Pathology of the heart in Friedreich's ataxia: Review of the literature and report of one case. Can. J. Neurol. Sci., 3, 349-354.

SJOGREN, T. (1947). Hereditary congenital spinocerebellar ataxia combined with congenital cataract and oligophrenia. Acta Psychiat. Scand., Suppl. 46, 286-289.