COMMENTS TO DR. H. PETIT'S COMMUNICATION ON REFSUM'S DISEASE AND REFSUM'S SYNDROME

SIGVALD REFSUM
Department of Neurology, University of Oslo, Norway

The difference between the two clinical pictures, heredopathia atactica polyneuritiformis and "Refum's syndrome" is stressed, together with their individual variability. A review of the literature clearly shows that in none of the cases of "Refsum's syndrome" described so far have any biochemical errors been identified.
The cases with a symptomatology similar to heredopathia atactica polyneuritiformis represent a challenge to further intensive studies.

Accumulation of phytanic acid appears to be specific for heredopathia atactica polyneuritiformis. To my knowledge no case with all the typical symptoms and signs of this disease and without any atypical clinical features, has yet been reported without a concomitant disturbance of phytanic metabolism. Conversely, serum from patients with a wide variety of neurological diseases have all yielded normal (trace) levels of phytanic acid (Try 1969).

The view that the phytanic acid which accumulates in heredopathia atactica polyneuritiformis is of exogenous origin led to attempt a treatment with a phytanic acid low diet (Eldjarn et al. 1966). This has been proved to be beneficial in several cases (Eldjarn et al. 1973).

Concordance between clinical diagnosis and phytanic acid storage has been established in at least 48 cases thus far, according to review of the literature which I made just before this congress (Refsum 1975). Dr. Petit now reports 2 further cases of heredopathia atactica polyneuritiformis with accumulation of serum phytanic acid, and he has kindly called my attention to a recently reported case of heredopathia atactica polyneuritiformis by Gautier et al. (1973). An increased level of serum phytanic acid was found in this patient. A loading test with a large dose of oral phytol was performed in the grandson of the patient and a significantly increased level of phytanic acid was subsequently demonstrated. The authors propose that the grandson is a heterozygous carrier of the disease and that such a loading test may be used to identify heterozygotes.

A total of 51 patients with heredopathia atactica polyneuritiformis and proved increase of serum phytanic acid level has thus been reported up to the present moment.

The term " Refsum's syndrome" — a term about which I am not particularly happy — has been used to designate clinical conditions which fulfill some or most of the clinical criteria for classification as heredopathia atactica polyneuritiformis, but without concomitant disturbance of phytanic acid metabolism.

A much quoted case is the patient reported by Kolodny et al. (1965) and by Baum et al. (1965) in whom no phytanic acid could be demonstrated either in plasma or in liver biopsy. However, this patient presented some unusual features: No night-blindness was noted. He

Proc. 4th Int. Congr. Neurogenet. Neuroophthalmol. (1973)
Acta Genet. Med. Gemellol. (*Roma*), 23: 333-335

had a bilateral corneal dystrophy which to my knowledge previously has never been reported in heredopathia atactica polyneuritiformis. He further presented bilateral ptosis and presented a marked dysarthria as a fairly early sign. The EEG was very abnormal. This patient was republished by Kayden et al. (1973) under the title *Diffuse cerebral sclerosis erroneously reported as Refsum's syndrome.*

At post-mortem the patient did not show any of the stigmata of Refsum's disease (H.A.P., phytanic acid storage disease). The neuropathological finding was a patchy, electively demyelinating form of sudanophilic diffuse cerebral sclerosis.

One girl observed by Skre et al. (1969) manifested several of the usual clinical criteria for a diagnosis of heredopathia atactica polyneuritiformis, but no phytanic acid could be demonstrated in the serum. However, the deep reflexes were of average strength, the protein content of the cerebrospinal fluid was normal, the electrocardiogram was normal, and there was a mild steatorrhea. The sister of the patient suffered from retinitis pigmentosa, but otherwise presented no neurological deficits.

An interesting case, probably belonging to the group Refsum's syndrome, according to the author, because of lack of increase of phytanic acid, has been described by Solcher (1973). The presenting symptom in the 30-year-old patient was bilateral ptosis. Some months later disturbances of sensation of the limbs and "general loss of reflexes" suddenly occurred. A year later again sudden onset of disturbances of sensation, weakness and unsteadiness of gait. Examination revealed: atypical tapetoretinal degeneration, reduced vision, paralysis of vertical conjugate movements, strabismus convergens, bilateral ptosis, neurogenic hearing loss, disturbances of sensation of arms and legs, and ataxia. The patellar and Achilles reflexes were absent. The speech was markedly dysarthric, slow with " Silbenverschlucken ". Striking was the indolence and carelessness of the patient. The protein content of the cerebrospinal fluid was 70 mg/100 ml. There was a progressive enlargement of the heart and increasing arhythmia and the patient succumbed during an Adam-Stokes attack.

The brain showed extensive status spongiosus, diffuse glial proliferation and in the brain stem some glial nodules. The authors emphasized that such an extensive brain involvement is not yet known in heredopathia atactica polyneuritiformis. The frontal pole was examined post-mortem by Professor Klenk with regard to phytanic acid, but with negative result.

From clinical point of view there are objections to the diagnosis of heredopathia atactica polyneuritiformis. Ptosis is extremely unusual in heredopathia atactica polyneuritiformis and has hardly been reported in any biochemically verified case. The same is the case with paralysis of vertical conjugate movements. Whether or not night-blindness was present is not mentioned. Mental changes appear to have been prominent in this patient.

In reviewing all the described cases of " Refsum's syndrome " which have not showed any disturbance of phytate metabolism, it seems clear to me that none of them have presented the complete and typical clinical picture of heredopathia atactica polyneuritiformis. All of them have also presented additional atypical or unusual features even if the symptomatology sometimes appears to have been very similar to heredopathia atactica polyneuritiformis. In only two such cases have post-mortem examinations been performed (Kayden et al. 1973, Solcher 1973). In none of these cases did the histological changes correspond to the ones recorded in heredopathia atactica polyneuritiformis.

In none of the cases of " Refsum's syndrome " have, to my knowledge, as yet any bio-

chemical errors been identified. The cases with a symptomatology similar to heredopathia atactica polyneuritiformis therefore represent a challenge to further intensive studies, and clinical, genetic, physiological, pathological, and biochemical studies ought to be reported in detail.

REFERENCES

Baum J.L. Tannenbaum M. Kolodny E.H. 1965. Refsum's syndrome with corneal involvement. Am. J. Ophthalmol., 66: 699-708.

Eldjarn L., Try K., Stokke O., Munthe-Kaas A.W., Refsum S., Steinberg D., Avigan J., Mize C. 1966. Dietary effects on serum-phytanic acid levels and on clinical manifestations in heredopathia atactica polyneuritiformis. Lancet, 1: 691-693.

Eldjarn L., Refsum S., Stokke O., Try K. 1973. Heredopathia atactica polyneuritiformis. Dietary treatment and pathogenetic role of phytanic acid. Excerpta Medica, Int. Congr. Ser. No. 296, p. 127.

Gautier J.C., Laudat Ph., Rosa A., Gray F., Lhermitte F. 1973. Maladie de Refsum. Test de charge en phytol chez un descendant. Nouv. Presse Med., 2: 2029-2032.

Kayden H.J., Reagan T.J., Mize C.E., Herndon J.H. Jr., Steinberg D. 1973. Diffuse cerebral sclerosis. Erroneously reported as Refsum's syndrome. Arch. Neurol., 28: 304-307.

Kolodny E.H., Hass W.K., Lane B., Drucker W.D. 1965. Refsum's syndrome. Report of a case including electron microscopic studies of the liver. Arch. Neurol., 12: 583-596.

Refsum S. 1974. Heredopathia atactica polyneuritiformis. Phytanic acid storage disease (Refsum's disease). In Vinken and Bruyn (eds.). Handbook of Clinical Neurology, Vol. 21 (in print).

Skre H., Eldjarn L., Stokke O., Try K. 1969. A new case of heredopathia atactica polyneuritiformis (Refsum's disease). A review with special emphasis on dietary treatment. Excerpta Medica, Int. Congr. Series No. 175, pp. 710-722.

Solcher H. 1973. Ueber Hirnveränderungen bei Heredopathia atactica polyneuritiformis (Refsum). Acta Neuropathol. (Berl.), 24: 92-95.

Try K. 1969. Heredopathia atactica polyneuritiformis (Refsum's disease). The diagnostic value of phytanic acid determination in serum lipids. Eur. Neurol., 2: 296-314.

Prof. Sigvald Refsum, Neurologisk Avdeling, Rikshospitalet, Oslo 1, Norway.