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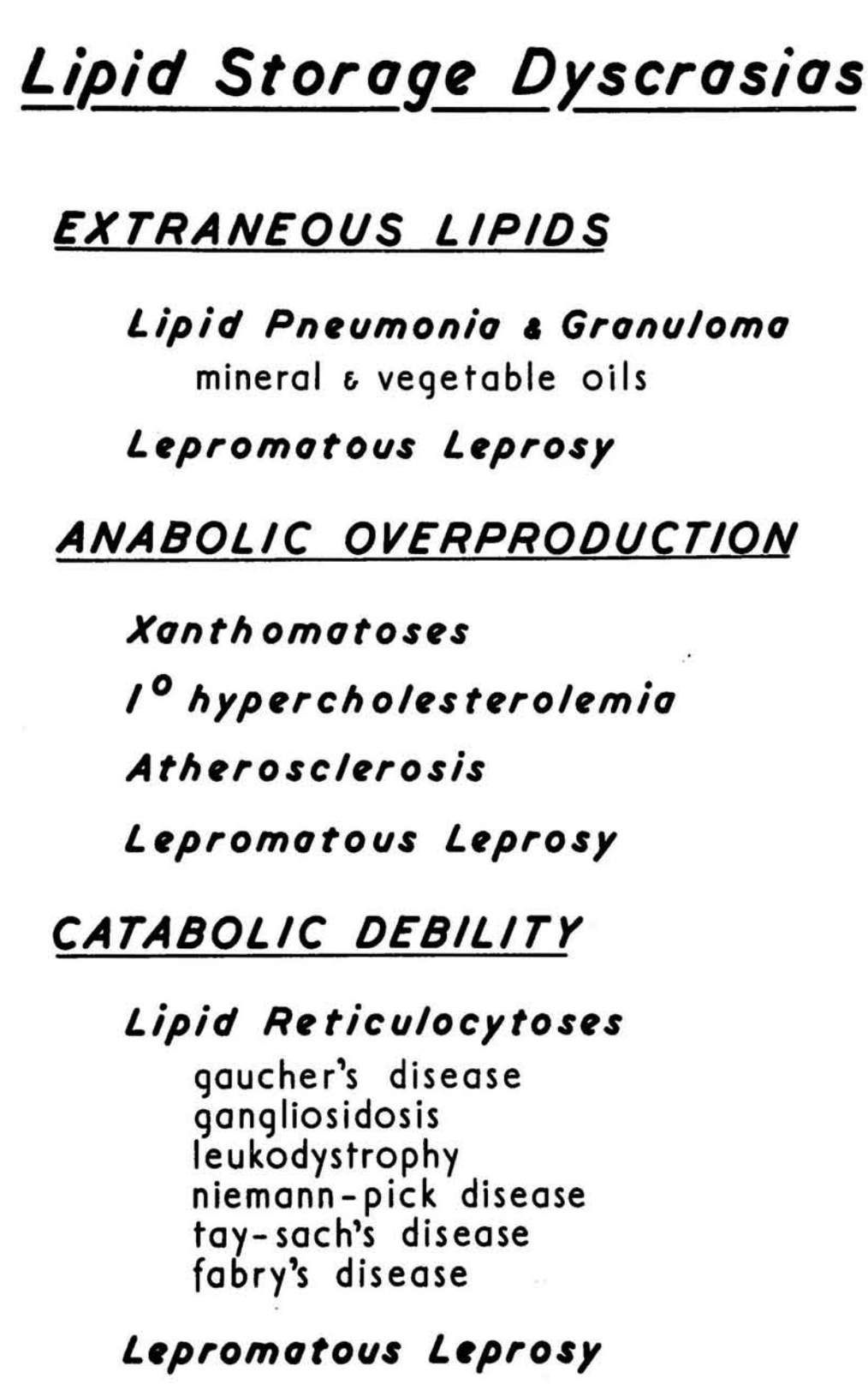
EDITORIALS

Editorials are written by members of the Editorial Board, and occasionally by guest editorial writers at the invitation of the Editor, and opinions expressed are those of the writers.

Leprosy and the Lipidoses

The foam cell of lepromatous leprosy has long been recognized as a unique phenomenon among the infectious granulomata despite the fact that several disseminated, and then often fatal, protozoal and mycotic infections present parasitism of the reticuloendothelial system similar to that seen in lepromatous leprosy.[1]

Though Virchow first thought that the vacuolization of the foam cell was a hydropic change, it was soon recognized that the contents of the vacuoles consisted of lipids. The lipid accumulation persists in the cells for some time after bacilli have disappeared. This is not so with tuberculoid epithelioid cells. The contrast is so striking that Davison and associates,[2] utilizing Sudan III and IV staining of frozen sections from skin biopsies of 129 patients across the leprosy spectrum, found a correlation between leprosy type, bacterial positivity and lipid accumulation. They suggested that the correlation was good enough to be helpful, though not definitive,



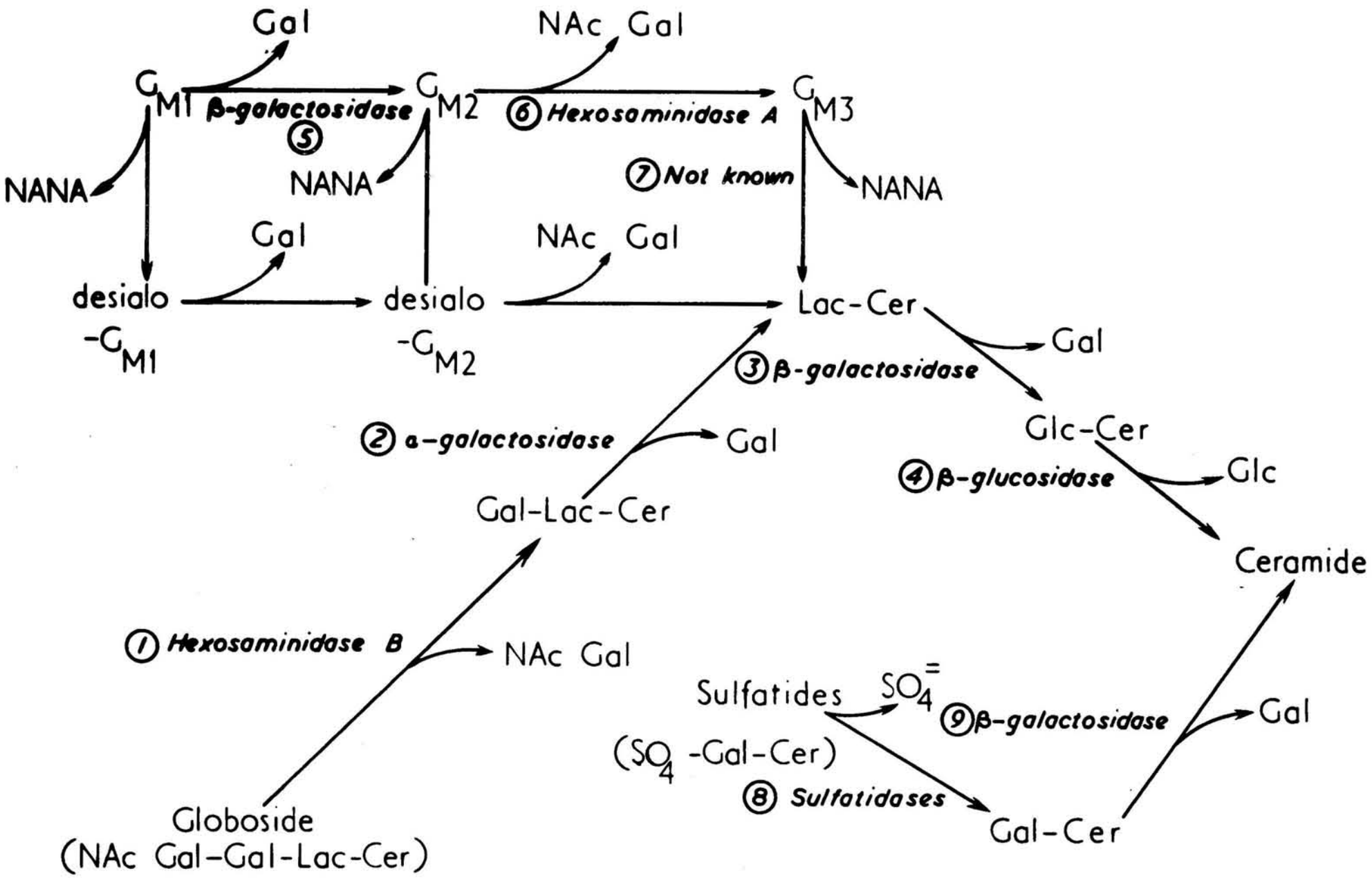
[1] Skinsnes, O. K. Comparative pathogenesis of mycobacteriosis. Ann. N.Y. Acad. Sci. **154** (1968) 19-31.

[2] Davison, A. R., Kooij, R. and Wainwright, J. Classification of leprosy. II. The value of fat staining in classification. Int. J. Lepr. **28** (1960) 126-132.

CHO Enzyme Defects in the Lipidoses

① G_{M2} (Tay-Sachs)
② Fabry's disease
③ Ceramide lactosid lipidosis
④ Gaucher's disease
⑤ G_{M1} gangliosidosis
⑥ G_{M2} (Tay-Sachs)
⑦ G_{M3} gangliosidosis
⑧ Metachromatic leukodystrophy
⑨ Krabbe's disease

Note: G_{M1} =Gal-NAc Gal-Gal-Glc-Cer
NANA



—Adapted from Bhagavan, Biochemistry, 1974

Gal = galactose
Glc = glucose
NAc Gal = N-Acetyl-Galactose-2-Amine
NANA = N-Acetyl Neuraminic Acid (a sialic acid)
Lac = lactose (galactosyl(β-1→4) glucose)
Cer = ceramide
desialo = without a sialic acid (NANA) residue

in classification. The nature of the lipid accumulation has been studied by histochemistry and chromatographic analysis and the results referenced and reviewed previously.[3,4] It is generally conceded that most of the

[3] Sakurai, I. and Skinsnes, O. K. Studies on lipids in leprosy. 1. Histochemistry of lipids in human leprosy. Int. J. Lepr. **38** (1970) 389-403.

[4] Sakurai, I. and Skinsnes, O. K. Studies on lipids in leprosy. 2. Chromatographic analysis of lipid in leprosy. Int. J. Lepr. **39** (1971) 113-119.

stored lipids are of bacillary origin. This would account for the storage phenomenon seen in lepromatous leprosy and not in the other disseminated infectious granulomata.

Contemplation of this phenomenon suggests considerable morphologic similarity between the foam cells of leprosy and a considerable variety of other conditions under which macrophages store lipids. These are summarized in the simplified categorization of the accompanying table in terms of lipids having extraneous origin or arising from anabolic overproduction or from catabolic debility. Lepromatous leprosy has features fitting with each of these categories in that the pathogen originates extraneously, presents overproduction of lipid through bacillary proliferation and death, and reflects catabolic debility of the host macrophages in digestion, not only of the bacilli but of their lipid residue.

In those categories involving lipid catabolic debility it is tempting to presume that this lipid storage phenomenon points to lysosomal enzyme deficiency related specifically to some lipid degrading enzyme or enzyme complex. It is tempting also to think, relating to leprosy, that this might be related to the handling of the waxes of the leprosy bacilli. If so, it would seem that these wax complexes must be different from the waxes of the tubercle bacilli, which have been far more extensively studied and categorized, since lepromatous leprosy patients show no deficiency in their response to the latter bacillus.

A comparative review of the nature of the lipidoses and current understanding of their metabolic defects is instructive.[5] These are summarized in the attached figure which has been adapted, with permission, from Bhagavan.[6] In every instance the associated enzyme defect lies with enzymes of carbohydrate metabolic pathways. The recently reported determination that the lepromatous macrophages appear to be deficient in β-glucuronidase was facilitated by the recognition that if there were a carbohydrate related enzyme deficiency in these cells it would probably not lie in any of the areas associated with the lipidoses since there is no increased incidence of any of these lipidoses in patients with leprosy. This recognition eliminated the necessity of histochemical or other biochemical studies in a large area of carbohydrate metabolism and was partially instrumental in leading to the reported studies[7,8] of the relationship between *M. leprae* and the acid mucopolysaccharides.

If these observations are confirmed and extended, it would seem almost inevitable that they are significant to considerations of the immune defect in lepromatous leprosy and probably point to a primary defect in antigen preparation by the deficient macrophages. The defect need not be exclusively related to carbohydrate metabolism since there may also be associated, as yet undetermined, deficiency in lipid metabolism. Or, on the other hand, the lipid storage phenomenon in lepromatous leprosy may be the result of insoluble lipid/carbohydrate complex formation resulting from abnormality of carbohydrate metabolism.

The problem is by no means solved, but the findings reinforce the concept that in CMI there is in the macrophage a meeting of the processes of enzymology and immunology and that the leprosy spectrum provides a unique model for the study of this relationship. The ultimate determination of the complete enzymatic defect in lepromatous macrophages may well be fundamentally as significant as *in vitro* cultivation of *M. leprae* since the prime difficulty in the treatment and eradication of leprosy, particularly the more contagious lepromatous form, is the host's deficiency in resistance to this pathogen.

—OLAF K. SKINSNES

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[5] Brady, R. O., Pentchev, P. G. and Gal, A. E. Investigations in enzyme replacement therapy in lipid storage diseases. Fed. Proc. **34** (1975) 1310.

[6] Bhagavan, N. V. *Biochemistry, A Comprehensive Review,* Philadelphia: J. B. Lippincott Co., 1964, p 662.

[7] Skinsnes, O. K. and Matsuo, E. Acid mucopolysaccharide metabolism in leprosy. 1. Storage of hyaluronic acid and its possible significance in leprosy. Int. J. Lepr. **42** (1974) 392-398.

[8] Matsuo, E. and Skinsnes, O. K. Acid mucopolysaccharide metabolism in leprosy. 2. Subcellular localization of hyaluronic acid and β -glucuronidase in leprous infiltrates suggestive of a host-*Mycobacterium leprae* metabolic relationship. Int. J. Lepr. **42** (1974) 399-411.