tion and for the duration of the drug effect, the patient reported no auditory hallucinations and he showed a transient improvement in cognitive organization. Of the remaining schizophrenic patients, four showed no change and five, a slight worsening with apomorphine. The frequency distribution of the apomorphine-induced change in psychosis ratings (Fig. 2) does not appear to be a normal distribution. While these data are suggestive of a bimodal response, neither age, sex, diagnosis, or type or dose of medication predicted the apomorphine-responding group. Because of some difference in pharmacokinetic handling of the drug, some patients may not have received the critical dose. Alternatively, these data may indicate an apomorphine-responsive subpopulation of schizophrenic subjects who have a common link in pathophysiology.

Before the discovery of the antipsychotic properties of phenothiazine drugs, apomorphine was administered to schizophrenics when temporary relief from psychotic symptoms was necessary. Case reports in the older literature describe its beneficial action as a short-acting "tranquilizer" (*12*). More recently, clinical studies of a number of neuropsychiatric disorders suggest that DA agonists may be useful in treating those illnesses in which dopaminergic function is thought to be augmented. Specifically, the involuntary choreiform movement disorders, including tardive dyskinesia, Huntington's chorea, and L-dopa-induced dyskinesias, have been reported to improve with various DA agonists, notably apomorphine (*13*). It is tempting to postulate that apomorphine diminishes schizophrenic symptoms and certain involuntary movements by inhibiting dopaminergic transmission through a predominant action at presynaptic DA receptors. This hypothesis is consistent with the neurochemical theories of schizophrenia and hyperkinetic extrapyramidal movement disorders, as well as with the results of preclinical studies of DA neuronal mechanisms. Alternative interpretations of the present results might be cited. Apomorphine could act as partial agonist at the postsynaptic receptor, diluting the concentration of the natural neurotransmitter in the synapse. A pharmacologic action of apomorphine not related to dopaminergic transmission could mediate the psychosis-remitting properties, possibly a residual pharmacologic action of apomorphine at the opioid receptor. These possibilities seem much less compelling, however, since there is no biochemical evidence that apomorphine acts through either of these mechanisms. Although the observations reported here need to be replicated and their mechanism elucidated, we propose that they can best be understood as a consequence of presynaptic DA receptor activation.

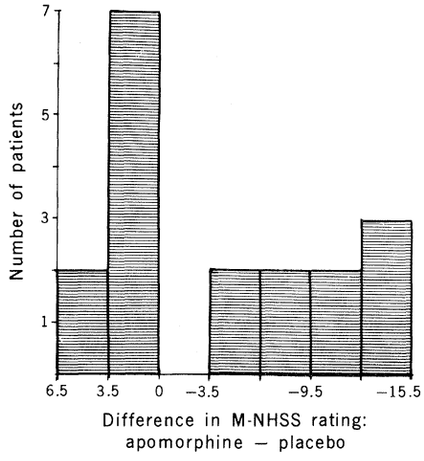

Fig. 2. Distribution frequency of the change in scores on the M-NHSS after administration of apomorphine. The values on the abcissa represent the net change in the M-NHSS score after apomorphine minus the net change in score after placebo. Those patients with a positive score had increased psychotic symptoms, while the group with negative scores sustained a decrease in their psychosis. The distribution appears to be bimodal and may suggest a nonhomogeneous schizophrenic population.

Given that apomorphine produces its transitory antipsychotic effect through activation of presynaptic DA receptors with a consequent decrease in DA synthesis, apomorphine at low doses may represent a new class of antipsychotic agents whose antischizophrenic properties derive from this presynaptic DA receptor action. The development of presynaptic agonist drugs in long-acting oral preparations may prove practical and effective as pharmacotherapy for schizophrenia. An optimal drug combination that includes presynaptic receptor activation with postsynaptic receptor blockade may maximize treatment of some schizophrenic and choreiform disorders. Furthermore, drugs that activate presynaptic DA receptors might lower the incidence of tardive dyskinesia by decreasing the requirement for neuroleptic drug.

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Niemann-Pick Disease Experimental Model

Sakuragawa *et al.* (*1*) recommend compound AY-9944, an inhibitor of cholesterol biosynthesis, as an appropriate tool to create an animal model of the inherited sphingomyelinosis of man. While such experimental models are in demand, we would warn of being optimistic about the validity of the approach presented by Sakuragawa *et al.* (*1*). Undoubtedly, AY-9944 induces generalized accumulation of phospholipids, but the increase does not at all selectively affect

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sphingomyelin; and the apparent reduction of sphingomyelinase may be due to factors other than inhibition of the enzyme or of enzyme synthesis.

AY-9944 is just one of a whole series of cationic compounds with pronounced amphiphilic character that all induce generalized phospholipid storage regardless of their main biochemical or therapeutic actions. Among them are some other hypocholesterolemic drugs, several tricyclic antidepressants, neuroleptics, anorectics, antimalarials, antihistaminics, and coronary dilators (*2*). Some 20 drugs from the above groups induce generalized cytological alterations identical with or very similar to those observed after application of AY-9944 (*3*): cytoplasmic inclusions with lamellated or crystalloid patterns as the hallmarks of intralysosomal deposition of excessive amounts of undigested polar lipids (*2, 4*). For several compounds the induced lipid storage has been substantiated also by biochemical methods (*2, 5*).

Neither AY-9944 nor any other of the lipidosis-inducing amphiphilic drugs so far reported can cause an increase of only one single type of phospholipids, but rather elevate a whole spectrum of phospholipids. Alterations of the distributional patterns may vary slightly, depending on the drug and on the organ investigated (*1, 5*). Unfortunately, the report of Sakuragawa *et al.* is focused entirely on sphingomyelin, although in animals treated with AY-9944, it represents no more than a fraction of 6.8 percent (3.0 mg/g)—as compared to 5.6 percent (1.6 mg/g) in controls—of the total hepatic phospholipids, which are increased from 28.7 to 43.9 mg/g. The authors state that there was also "a 20 percent elevation of phosphatidyl inositol," while "the distribution of other phospholipids such as phosphatidyl choline, phosphatidyl ethanolamine, and phosphatidyl serine was unchanged. . . ." This statement obviously distracts from the simple conclusion to be drawn from the presented data: The elevation of minor fractions such as sphingomyelin and phosphatidyl inositol by factors of 1.88 and 1.2, respectively, cannot account for the 1.5-fold increase of total phospholipids. Thus the absolute amounts of major fractions such as phosphatidyl choline and phosphatidyl ethanolamine must increase considerably irrespective of whether their distributional patterns are changed or not.

In summary, it appears that the lipidosis induced by a variety of cationic amphiphilic drugs including AY-9944 indeed mimics the inherited lipidoses as far as the cytological events are concerned, but the experimental and the inherited conditions profoundly differ from each other with respect to the underlying pathogenetic and biochemical mechanisms.

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As we pointed out in our report (*1*), the concentration of phospholipid per gram of liver increases in the treated animals. We also stated that there is a large reduction in the weight of the livers in these animals. The cogent observation that we report was the *differential* increase in sphingomyelin, in particular sphingomyelin C (+292 percent). This molecular species of sphingomyelin is precisely the predominant lipid that accumulates in patients with Niemann-Pick disease. This rise is reasonably explained by the 89 percent reduction of sphingomyelinase activity in the livers of the treated rats. The added importance of this finding lies in the specificity for this enzyme since the activity of 13 other lysosomal enzymes actually increases in tissues of animals receiving the drug (*1, 2*). Such an increase in ancillary enzyme activity is frequently observed when a particular enzyme is deficient (*3*).

My colleagues and I emphasize that the pathogenesis of the drug-induced animal model differs from that in the human disorder where there is probably an alteration of the genetic code for the enzyme (*1*). The accumulation of sphingomyelin produced by AY-9944 is likely to be a temporary phenomenon. However, in the absence of an animal with the heritable genetic mutation, the pharmacological model with depleted sphingomyelinase activity has obvious utility for a number of important experiments including attempts at replacement of the deficient enzyme.

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