

Dr. med. Hugo Henzi

**THE METHANOL HYPOTHESIS
A NEW CONCEPT
OF MULTIPLE SCLEROSIS:**

**The path to causal treatment
Report on 80 cases**

**Juris Druck + Verlag Zürich
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**Dedicated to my beloved wife
Yvonne Henzi-Goldschmid (†)**

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PREFACE

In this work the multiple sclerosis problem has been approached in a manner similar to that developed by Euclid when perusing Alexandria's Library: observation, definition and logical application of existing knowledge. The methanol hypothesis, which evolved and has been deepened and strengthened in more than ten years work has, in a pragmatic sense, almost reached the status of a disease theory. This contention is supported by the success of the rational therapy based on the hypothesis and by the fact that it has become possible to find explanations for hitherto incomprehensible phenomena.

Part A of this book describes the methanol hypothesis – the background, logical development and consequences thereof. Although well based on findings in the literature and on theoretical background, certain chemical proof of the theory is still lacking, and Chapter 9 presents proposals for further research. While Part A is thus to a certain degree speculative, Part B presents details of a therapy, based on the considerations of Part A, which has proven itself in practice. Part C provides the raw data (case histories) demonstrating the usefulness of the therapy. Parts B and C are written so as to be understandable independent of Part A.

The therapy based on the methanol hypothesis allows the progress of the disease to be arrested. It involves no radical or exotic medication.

We feel strongly that delaying introduction of the present therapy simply because certain elements of the underlying hypothesis are open to discussion is unjustified and unfair to the patient.

*David Sargent Ph.D.
Rolf U. Schwyzer*

INTRODUCTION

This book about the aetio-pathogenesis of multiple sclerosis (MS) presupposes knowledge about the clinical picture of the disease. Important for the comprehension of the present work is a familiarity or renewal of acquaintance with the fields of knowledge which have supplied the clues: the bibliography includes books and papers on toxicology, allergology and botany. Further evidence has been drawn from climatology, geography, from the history of the disease itself and, last but not least, from the nutritional sciences and the great changes therein.

The seemingly well established results from specialized multiple sclerosis research have not been neglected. They are adduced to test the new hypothesis, and vice versa. This led to a critical reappraisal done in the light of the paper's central theme – MS as a toxic-allergizing event.

Attention is given to:

- experimental allergic encephalomyelitis (EAE) as a model disease for MS: another model disease is proposed in its place
- cause and origin of the antibodies of the “autoimmune” disease MS
- the slow virus hypothesis, which presumes viruses, or parts of viruses, as antigens of the immune reaction.

In the elucidation of these contentious points, well-based alternative ideas are presented. Painstaking care is given to methodology.

As for the disease itself:

Multiple sclerosis was described in the medical literature for the first time in 1818 and it is likely that the affliction was unknown in previous centuries. In the following 150 years the frequency of MS increased, but its cause remained unknown. In 1968, for the first time, it was pointed out that a substance, methanol, had the characteristics necessary for inducing MS (*Methanol und Nebenfaktoren....*, 28). The book points out the long neglected fact that methanol occurs as a breakdown product of foodstuffs in human metabolism.

In the same year a pilot study with Uehlinger on a group of twelve patients treated only with menadion (no supportive measures) was reported (29). Not until 1976/77 could case histories be presented concerning twenty-three patients submitting to the therapeutic regimen as recommended in the present work (dietary and general measures in combination with medication).

For the English edition the text has been revised and new information added. Most importantly, a case study of fifty-seven patients and a follow-up assessment of the twenty-three patients from the 1976/77 report is included. The section ‘Observations on the “autoimmune” phase’ has been improved and updated in line with results from allergology and immunology.

The methanol hypothesis presents a concept for the causative factors of MS. The effect of the already established medication with corticoids becomes more understandable and the logical general measures – partly rules and regulations, partly absolute restrictions – which are essential for the complete therapy, follow as a matter of course.

It is hoped this successfully tested and safe treatment, involving only modest costs, may be granted to more patients. Treatment can be ambulatory, although this makes higher demands on the individuals' self-discipline.

The book addresses itself to medical doctors, students and scientific readers. The theory of the pathogenesis permits precise reasoning for prognosis of MS as a grave, incapacitating illness.

Abstract

The methanol hypothesis of multiple sclerosis is presented. For the first toxic phase of MS a well studied toxic condition is used as a model. The second phase of MS leading to the formation of plaques is discussed using the insights of immunology and allergology. It is shown how knowledge of metabolic processes and of human eating patterns can explain the appearance of the affliction during the 19th Century and its pathogenesis and geographic/climatic frequency distribution.

The therapy, based on the hypothesis that methanol is the root cause of the disease, is described. Eighty case studies indicating that this therapy is a real hope for stabilization of MS in the relatively harmless early phase are reported.

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PART A

METHANOL AS THE PRIMARY CAUSE OF MULTIPLE SCLEROSIS

Chapter 1: Available Laboratory Tests for Diagnosis. Slow Virus Hypothesis

The author wishes to express his indebtedness to the book of the renowned British researchers McAlpine, Acheson and Lumsden (40). Their work considers most aspects of multiple sclerosis (hereafter referred to as 'MS'), shows the gaps in our knowledge and clarifies sound scientific opinion on the important points of dispute. Particularly valuable are the details demonstrating antibodies against myelin with the myelin toxicity test. The immunofluorescence test also described helps to explain the myelin toxicity test. Unfortunately this test, developed by Lumsden prior to 1972, was not introduced by medical laboratories, although during these years the profession has been limping along with expressions such as "probable" or "possible" MS. Apparently the test was considered as too involved and costly. There is now hope that the gliotoxigenicity test of Berg and Kaellen (see Lumsden (40, pp. 548, 561)), recently also described by Abramsky *et al.* (1), may be easier to introduce as a help for early diagnosis of MS (discussed in Chapter 6.c).*

One of the reasons for this delay in application of research findings may be the fact that most of the MS research effort is guided by the thought that a slow virus, either alone or as an allergizing co-factor, is the cause of the disease. Lumsden (40, p. 532) wrote ... "that models of 'slow virus' each entail distinctive neuropathologies and these all differ both from multiple sclerosis and from perivenous encephalitis".

More recently Adams and Bell (4) endeavoured to define a slow virus and a slow virus disease. They describe possible mechanisms of the production of

* Nonserological screening tests, i.e., computer tomography and the evoked visual potentials method, are a help for assuring an early diagnosis. Rieder and Jegge (55) suggest a more differentiated serological test called isoelectric focusing which can be applied for the same purpose. These newer methods, of course, do not diminish in any way the importance of Lumsden's myelin toxicity test and immunofluorescence test for an understanding of the genesis of the plaques.

clinical disease by slow viruses, but state that these are mainly lines of thought not yet supported by observable fact.

In his speech to the General Meeting of the Multiple Sclerosis Society, Orkney Branch, in 1975, Poskanzer (51) noted that during examinations in the Shetland and Orkney Islands in 1974 he found five cases in which measles did not develop until long after MS had been diagnosed.

After the newer results on slow viruses, the question of the measles virus (Millar *et al.*, 43) can be laid *ad acta*. Thus it appears that the intense work in this field of research has had few tangible results for MS, and Lumsden's opinion is still relevant.

Evidence is also accumulating in epidemiological papers that the aetiological agent in MS may be found outside the main hypotheses hitherto discussed. For example, Nathanson and Miller (45) clarify the types of *viral hypothesis* proposed to date and review those aspects of the epidemiology which they see as demanding explanation by any proposed hypothesis. At the end of the paper they state: "In our view, the data do not show a conclusive fit to any of several versions of the viral hypothesis". A further statement from their paper is particularly relevant to the present work: "A hypothesis could be postulated which suggests that MS has as its underlying cause an environmental factor and that there is no infectious agent involved". Frick (20a) states: "The lack of proof of viral aetiology of MS is more evident than ever; the modern methods of virology – so successful in other diseases, particularly the slow virus infections of the nervous system – have brought only negative results".

Another example is that of Craelius (13), who finds a positive correlation between the epidemiologies of MS and dental caries. He considers the possibility that common environmental and dietary factors may lie behind both diseases.

Chapter 2: The Distinction from Other Demyelinating Diseases

One must consider the question of how MS can be distinguished from other demyelinating diseases. To begin with it may help to remember that the central nervous system, like the skin, originates from the ectoderm. As eczema may be caused by many different factors, demyelination in the CNS seems to have various causes with different pathogeneses. It is therefore not hard to agree with Lumsden's point of view (40, p.320). He makes a clear

distinction between MS and the other demyelinating diseases of man, such as Kuru, postinfectious and postvaccinal encephalomyelitides as well as leuko-encephalopathies associated with anoxic-ischaemic and toxic disturbances on the one hand, and also from the experimental encephalomyelitis and the demyelinating diseases of animals, such as scrapie and visna, on the other hand.

Concentric sclerosis (Balo) and Devic's optic neuromyelitis are considered to be subforms of multiple sclerosis.

Chapter 3: Two Cases of Chronic Methanol Poisoning Point the Way. Pathologic-Anatomical and Histological Results.

The starting point of the working hypothesis was the remarkable similarity of the coeco-central retrobulbar neuritis which occurs in the same form in MS and in methanol poisoning. In a review of the literature on acute methanol poisoning, no cases could be found which showed the other symptoms of MS. However two specific cases of chronic industrial methanol poisoning were found in the Swiss toxicological literature.

A paper by Schwarzmänn (59) describes the case of a technician, R.G., who, during three periods, inhaled vapors from technical formaldehyde while working in the laboratory. For stabilisation of formalin the formaldehyde was mixed with 16% methanol, so that he acquired an inhalatory intoxication. For details the original paper should be consulted. The symptoms which, in the beginning, appeared to be typical of poisoning, later gave the pathological picture of MS.

A second case, described by Dreyfuss (15), is the case history of a garage employee, St.E., who repeatedly swallowed methanol while decanting it into containers. He also had an initial toxic phase and later a pathological picture akin to MS. The case history also records an ethanol abuse during five years.

Both cases could be followed up clinically, and pathologic-anatomical investigations were performed*. No sign of MS was observed in the routine section performed. However, on histological investigation, the case described by Schwarzmänn showed the typical distribution of diseased centres and gave the picture of MS that had run its course.

* I am indebted to Prof. Max Aufdermaur, Lucerne, and Prof. Jürg Ulrich, Basle, for performing the sections and Prof. Ulrich in particular for having undertaken the histological investigation of both cases.

The details of the second case are typical (see also remarks in Chapter 6.f). Evidence was only found on the optical nerve. The myelin sheaths were thinner, which can be interpreted as a result of the methanol poisoning.

The pathologic-anatomical results established in the two cases have been achieved by cooperation among colleagues. The obvious criticism that it is a case of two rare diseases occurring simultaneously is refuted firstly by the case histories of the two patients. A primary toxic phase is followed by a MS phase, indicating the development of the "autoimmune" reaction. The toxic phase would correspond to the premorbid condition which, in the MS literature, is assumed retrospectively after diagnosis. This condition can frequently be traced back to the childhood of the patient. Secondly, the rarity of such reports is certainly due to the lack of histological investigations in cases of chronic methanol poisoning. Thirdly, methanol poisoning is now a rarity: methanol has been in Class 3 of the Swiss law on poisons for twenty years, and its use restricted by stringent regulations. It is now rarely used in the paint industry and otherwise only used in closed circuit systems. A certain risk exists for model aircraft enthusiasts, as methanol is used as fuel. Fourthly, if we assume that the 5000 cases of MS in Switzerland are to be distributed over thirty years and for the same period fifteen cases of chronic methanol poisoning occur, we get the following:

- probability of acquiring MS $= 5000:6,000,000 = 1:1200$
- probability of acquiring chronic methanol poisoning $= 15:6,000,000 = 1:400,000$
- free combination would give a frequency of $1:1200 \times 1:400,000 = 1:480,000,000$.

Based on the above cases, the actual frequency is *at least* 160 times higher. The discrepancy could indicate a causal connection.

Conclusion: Considering the course taken by chronic methanol poisoning and the similarities revealed in histological tests, it is permissible to consider this poisoning to be the temporal and causal origin of MS and the pacemaker of the "autoimmune reaction".

Chapter 4: Methanol Hypothesis of Multiple Sclerosis

a) Introductory comments

The two cases described in Chapter 3 have almost the appearance of experiments to test the effect of repeated absorption of a non-lethal dose of

methanol by the human organism. They are viewed by the author as a pathogenetic model lending strong support to the hypothesis. As first published in 1968, (28) the hypothesis was based on the clinical picture alone. Since then the hypothesis has been substantiated by histological results obtained from the autopsies.

In this booklet a number of further points of differing value are presented, along with plausible explanations. The author admits that he experienced difficulty in clearly representing the interconnections between the hypothesis and different facets of the MS problem.

In this chapter a synopsis is given, as if the book had already been read. As the scheme develops in the following chapters the various fragments of information are taken up as to the contribution they make to MS as an understandable process. It was unavoidable to use references to publications in various branches of learning, cross-references between chapters and frequent reiteration of a particular aspect with a different emphasis to achieve this objective. It is hoped that this process will give researchers in various fields the impetus to unearth further evidence, thus clarifying the remaining biochemical questions of the hypothesis.

b) Synopsis

MS appeared only after a basic change in eating habits had occurred early in the 19th Century. Previously, methanol arising from pectins in food which contains plant matter could degrade harmlessly, but now with additional fructose supplied by the sugar-rich foods, a disturbing factor was introduced which, *due to repetitive simultaneous presence of methanol-formaldehyde and fructose-glyceraldehyde in the cells, could lead to an allergic reaction*. The allergen is protein (in the myelin) which has been altered by formaldehyde. The degradation of the altered myelin results in plaque formation.

Thus methanol from pectin is assumed to be the temporal and causal primary aetiological agent of MS. Methanol is also sometimes found in minute quantities in certain fruit juices. Constipation prolongs the time for hydrolysis of pectins in the intestines (influenced perhaps also by variations in pH, which may range from 5.9 to 8.8 in different individuals).

Toxicological findings indicate that methanol permeates the central nervous system and crosses the blood-brain-and blood-liquor-barriers. Its solubility in lipoproteins explains the affinity to the white substance and especially myelin. The lipid-containing membranes and synapses are similarly easily

crossed, interfering with their function. Where it escapes from the venules it may alter the blood-brain barrier and acts like a local anesthetic. These areas are obviously also the *locus minoris resistentiae* where methanol can continually act on the developing plaques. Additional modification of hitherto normal polypeptides at the periphery of the plaques explains their steady growth.

Methanol is also found in muscle, degradation occurring slowly over approximately four days.

Methanol passes the cell membrane and binds the Fe^{2+} -containing cytochromes, preventing their normal functioning in electron transport in mitochondria. Cellular respiration is impaired, glycolysis favoured: the level of pyruvic acid rises. As the second phase of glucose degradation is hindered, less ATP is formed per molecule of glucose. This may explain the adynamia and quick tiring of MS patients.

Based on experiments with animals by Stuhlfauth and Neumaier (61) and Gilger *et al* (23), and clinical observations on humans, we can assume that fructose enhances the toxicity of methanol. Formaldehyde, the degradation product of methanol, and glyceraldehyde, the degradation product of fructose, are both metabolized by alcohol dehydrogenase, and competitive inhibition occurs. Formaldehyde thus blocked in breakdown can bind to the NH_2 groups of amino acid side chains, forming a so-called Schiff base. Polypeptides altered in this manner are allergens for the "autoimmune" reaction (see Chapter 6.c), triggering the relapse with demyelination. Simultaneous intake of fructose with methanogenic pectins seems to be the *conditio sine qua non* for the development of MS.

This toxic-allergizing (sensitizing) phase occurring in the CNS precedes the clinical beginning of the disease and the beginning of formation of new plaques.

Chapter 5: Model Diseases of Multiple Sclerosis

As a preliminary to the intricate chapter of aetio-pathogenesis the author wishes to illustrate the first phase of the MS process by a model disease.

If a model is to have clarifying and heuristic value, it has to correspond in as many aspects as possible with the disease to be elucidated, in this case MS. Discrepancies have to be explained and accounted for.

a) Excitatory phase of ethanol intoxication (EPE)

Instead of EAE (see below), I propose the excitatory phase of ethanol intoxication as a model disease of the toxic first phase of MS, following the concepts of the methanol hypothesis. Ethanol is the second member of the series of aliphatic monovalent alcohols, methanol being the first.

The following symptoms are observed in this phase of ethanol intoxication: nystagmus, diplopia, impaired speech, static and dynamic ataxia, disturbed sensitivity, mood changing from euphoric to depressive. In chronic ethanol abuse the typical coeco-central retrobulbar neuritis is also observed. All these symptoms are found simultaneously or successively in MS patients. In the two cases of chronic methanol poisoning referred to at the beginning of Chapter 3, the same syndrome was present. There are, of course, differences, e.g., in the excitatory phase of ethanol intoxication we have a case of acute poisoning, whereas in the other diseases referred to chronic poisoning occurs. Such differences can, however, be readily reconciled. As an exception to Richardson's law, methanol is more toxic for man (and presumably other primates) than ethanol. Inversely, the narcotic effect of methanol is less intense than that of ethanol. A quantity of an alcoholic beverage corresponding to 50 ml is required for the excitatory phase of ethanol intoxication. Intake of the same quantity of methanol would produce acidosis masking all other symptoms and could well lead to death within 48 hours. The degradation of methanol occurs via formaldehyde to formic acid, that of ethanol via acetaldehyde to acetic acid. Formic acid is degraded into CO_2 and H_2O , whereas acetic acid enters the citric acid cycle. The acetaldehyde has no protein-altering potency, in contrast to formaldehyde. Thus the symptoms of the acute ethanol intoxication have no lasting effect in the CNS, whereas methanol poisoning leads via demyelination to MS.

b) Experimental allergic encephalomyelitis (EAE)

There appears to be some sort of consensus among MS research workers that the study of EAE can contribute valuable clues to the solution of the MS problem.

In EAE, laboratory animals (usually guinea pigs) are given an intramuscular injection of a brain extract (generally bovine) formed by maceration and subsequent delipidation with methanol/chloroform. Freund's adjuvant is sometimes present. Demyelinated centres are found in the brain of the experimental animal after about three weeks.

c) Pathocclisis

The term "pathocclisis" is introduced as it is a useful concept in discussion.

I follow the description by Orthner (48, p. 70) (my translation). "...It is a well known fact that each irritant, whether organic or not, will damage certain organs or parts of organs preferentially.

"The locus of the first and most pronounced damage is in many cases satisfactorily explained by the manner in which the injurious matter enters the body and then disseminates in relatively well defined pathways. For other types of pernicious conditions this explanation is unsatisfactory. The nervous system in particular is often afflicted by diseases which are more or less strictly confined to definite parts without it being possible to explain this solely on the basis of the dissemination pathways. If the body always reacts only at well defined loci to the penetration by certain irritants ('agents') some form of closer connection between agent and locus may be presumed. Thus the agent of reaction may, for reasons unknown, be especially concentrated at the loci, or the local tissue may be more intensely altered there than elsewhere."

C. and O. Vogt (cited in Orthner, 48, p. 71) explained that the local differences of reaction must be due to physico-chemical disparity of the tissue (topistic) units. For this they coined the expression "pathocclisis". According to the Vogts the local vulnerability is due to a particular mode of reaction of the irritant with the physico-chemical structure of the locus, thus causing a disturbance of the local biological processes. Ultimately there are thus unknown affinities between agent and tissue which lead to the pathocline selection of damage.

In other words, *pathocclisis* indicates the preferential binding of a toxic substance to definite loci and the production there of signs and symptoms.

d) Comparison and evaluation

aa. The excitatory phase of ethanol intoxication (EPE)

This is a model that illustrates precisely the observable beginnings of MS, namely,

- 1) oral ingestion by man
- 2) representative symptoms identical to MS.

It is also easy to demonstrate the similarity between the pathocclisis of ethanol, as demonstrated in the excitatory phase of intoxication, and the pathocclisis of chronic methanol intoxication and the pathocclisis of MS.

As described in Chapter 6, formaldehyde, the first degradation product of methanol, does not circulate as such, but can only occur in the CNS due to

methanol infiltration. Formaldehyde is known to alter the native substance of an organism. For example, Spatz has proved that the gradually increasing acidity of formalin (which contains formaldehyde and 16% methanol) during the conservation of organic preparations is caused by the production of formylated proteins rather than of formic acid (cited in Orthner, 48, p. 59). The modified protein has an acidic reaction as the side chain amino functions are blocked following hydroxymethylation, while the acidic carboxyl groups remain reactive. In living systems such modified protein can act as an antigen and, in the case of MS, could lead to demyelination by the induced humoral antibodies.

Thus, starting with the model disease EPE and continuing with the known properties of methanol and its degradation product, formaldehyde, the whole causal chain leading to MS can be justified theoretically and demonstrated chronologically.

bb. Experimental allergic encephalomyelitis (EAE)

EAE fails to illustrate in any way the beginning of the disease MS: it does not contribute one iota to the question of pathogenesis and pathocclisis. Even what appears to be the strong point of the EAE model, the fact that it does cause demyelination, is marred in that it is a lymphocyte-mediated demyelination instead of a humoral one. To utilize EAE as a model is, as it were, putting the cart before the horse, as the demyelination appears at the end of a chain of events altogether different from that known to precede MS.

Lumsden (40, p. 522) considers EAE to be a model disease for parainfectious perivenous encephalitis. The cases found in Japan following vaccination against Lyssa should be considered as well. The analogy is obvious: in both afflictions an intramuscular injection of allergenic foreign material is administered and an allergic effect on the brain of the subject results.

One might add that it seems inappropriate to describe EAE as a model disease when one considers that such an intramuscular introduction of foreign protein, with or without Freund's adjuvant, is not a factor in MS. EAE should not be used as a model of an autoimmune disease because it really demonstrates an allergic reaction to foreign antigens. Based on these arguments the status of EAE as a model disease of MS is voided.

Appendix: Basic Protein

An interesting "basic protein" has been found as a sequel to work with EAE. The supporters of the EAE model believe the substance, which is found in the intraperiod line of myelin, to be the antigen of EAE against which the

antibodies are directed. Such a conclusion cannot be extrapolated to MS as soon as it is realized that EAE is not a viable model disease.

Chapter 6: Aetio-Pathogenesis

a) Introductory comments

At this point it is desirable to discuss the individual causative components of the pathogenesis. The information on pectins and methanol and its degradation makes comprehension of the synopsis easier (see also Chapter 4).

In the subsection "Glucose. Methanol. Fructose as a disturbing factor" the interaction of fructose and methanol is shown.

The subject matter of the ensuing stage of the disease, the "autoimmune" phase, demands comprehensive treatment (Chapter 6.c). This section is an exercise in the application of the insights of immunology and allergology to MS.

Thereafter follow inspection of the quantitative and temporal conditions (Chapter 6.d). To explain the incidence of MS reference is made to its character as a multifactorial disease (Chapter 6.e). The history of MS, its first occurrence and increasing incidence parallel the rapid growth of sugar consumption. The picture is rounded off with a summary of the instructive geomedical facts.

At the end of this chapter the essential points are summarized and the methodic parallelism to Koch's rules for infectious diseases demonstrated (Chapter 6.g).

b) Observations on the toxic allergizing phase of multiple sclerosis

aa. Pectins

Regarding pectins, Herrmann (33) states:

"The technologically most important polysaccharides of fruits are pectins which, in fruits, occur together with cellulose. The pectins are found as 'glue' in the inter-lamellar substance of plants, and in the cell membranes. A fermentation process hydrolyzes this substance into soluble pectins during the ripening process.

"The soluble pectins occurring in nature are polymer-homologue mixtures of 1,4-D-glucosidic-coupled molecules of D-galacturonic acid of linear structures of various lengths. The carboxyl groups are esterified with methanol to a large extent. The degree of esterification diminishes in many fruits and

vegetables on ripening, such as, for example, from 89% to 43% in pears, whereas in peaches there is hardly any change."

This higher degree of esterification with methanol in unripe fruit explains the geographic distribution of the incidence of the disease. In the latitudes near the 15°C July isotherm (15°C January isotherm in the Southern Hemisphere) and similarly in alpine regions, the duration of sunshine and average temperature do not permit full ripening of the harvest on the trees and in the fields. The psychological reaction of farmers and particularly small land-holders is to tend to recover as much as possible and to make good use of it in foodstuffs. The general rule for fruit is: the less ripe, the more sugar is added to preserves, jams, etc.

According to Kertesz (36), polygalacturonic acids esterified with methanol are pectinic acids and are described as pectins (in the technological sense) if, together with sugar, they are capable of jellying fruit.

The conditions are best explained by the formulae that follow (G-COOH indicates a single anhydrogalacturonic acid moiety):

G-COOH	G-CO-O-CH ₃	G-CO-O-CH ₃
G-COOH	G-COOH	G-CO-O-CH ₃
G-COOH	G-CO-O-CH ₃	G-CO-O-CH ₃
-----	-----	-----
-----	-----	-----
polygalacturonic acid	pectinic acid (pectin in the technological sense)	ideal (completely esterified) pectinic acid

Kertesz writes (36): "There are various ferments attacking pectins: the pectin methylesterase (formerly called pectase) changes pectins into pectic acid by cleaving the methyl groups; the pectinase hydrolyzes the polygalacturonic chains." Von Fellenberg (17), who searched for an explanation for the occurrence of methanol in fruits, vegetables and wines, was the first to demonstrate the presence of the methyl group in pectins. The methyl groups can easily be hydrolyzed from pectinic acid using basic substances.

bb. Methanol: properties and effects in the body

Methanol is a poisonous, colorless, water-soluble liquid with a boiling point of 65°C. As it is the best solvent for lipoproteins, it easily crosses the blood-brain and the blood-liquor-barriers and also the membranes and synapses, and penetrates the mitochondria.

Carla Egg (16, p. 6) notes that methanol contains the OH-group and thus a highly coordinated oxygen atom. She also wrote: "The fundamental importance of the heavy-metal (particularly Fe^{2+}) catalysis has recently been demonstrated by O. Warburg, Meyerhoff and others. I have found the ferro ion to be complexed by methyl alcohol in a form which precludes its function as catalyst in typical oxidation processes."

In this connection Warburg's discovery of cytochrome oxidase (cytochrome a3) comes to mind. The relationship between methanol and the divalent iron atom offers the explanation why the retina, the organ with the highest iron content, is affected in methanol poisoning.

In the Swiss Poison Control Law, methanol is placed in Class 3, which contains those substances having an LD_{50} * of between 50 – 500 mg/kg body weight, corresponding to 3 – 30 g ingested for a 60 kg person.

Death has occurred following ingestion of only 8 g, so that the average *acute* lethal dose probably lies nearer 3 g than 30 g. As far as the ophthalmotoxicity goes, one may cite the case of an American labourer who spilt 4 l of methanol over his pants but did not change his clothing and became blind as a result.

In contrast to other opinions, Möschlin (44, p. 207) considers a *chronic* methanol poisoning probable on inhalation or oral uptake of smaller amounts. The previously mentioned cases of Dreyfuss (15) and Schwarzmänn (59) were cited by Möschlin.

According to Richardson's law, the narcotic effect and toxicity of monovalent alcohols in animals increases with increasing number of carbons. However methanol is more toxic for man (and presumably other primates as well) than ethanol. As Röe (56) has already emphasized, this fact must be taken into account in all conclusions based on experiments with animals but extrapolated to humans. In particular, it applies to the methanol hypothesis.

* The LD_{50} is that dose which, when administered to animals over a 24 hour period, causes death of half the animals within 5 days.

Methanol can be taken up by inhalation, orally or through the skin (the latter mainly in cases of occupational poisoning). Oral, alimentary uptake is virtually the only route of importance in MS. Von Fellenberg (17) carried out experiments on himself on the production of methanol during digestion, and reported:

"... With a pectin-free diet very small amounts of methyl alcohol are excreted in the urine, and even this small amount is reduced by about half when fasting. With food containing moderate amounts of pectin the content in the urine increases many times. Whether pectin originates from vegetables or fruit, and whether the food is taken raw, in pectase-containing form or cooked, is of no consequence.

"Methyl alcohol is not only released from pectin by pectase [now called pectin methylesterase] contained in the food, but also by the digestive juices of the animals themselves. The question of whether enzymes are involved, or whether the basicity of the intestine is enough to cause cleavage, remains open." (17, p. 112).

It is of interest that he suggests that, in the interest of public health, the question of the banning of drinks containing methyl alcohol should be considered.

No further attention has been paid to the methanol content of foods since von Fellenberg's publication of 1918*.

Aside from a short section on methanol-containing spirits in only one of many dietary textbooks consulted, there has been just as little reference to methanol in basic and luxury foodstuffs in biochemistry texts. Although Kertesz (36, p. 392) treats the metabolic fate of pectin and the galacturonic acids, which are not digested or resorbed, he neglects the toxic methanol.

cc. On the question of toxicity

The usual concepts such as " LD_{50} " or "toxic dose" and the statement that the uptake of methanol in food is two or three orders of magnitude less than the toxic dose are only valid for purely toxic effects. As soon as allergic reactions – as is maintained in this article – come into play, however, then even minute doses of methanol or formaldehyde must be considered. In mass balance experiments one usually assumes that that part of an ingested

* The neglect of von Fellenberg's findings was one of the incentives for the further development of the methanol hypothesis. It was possible to reach significant conclusions using only the relatively simple methods of the 1930's.

substance that is not excreted either unchanged or in bound form has been degraded. Such experiments may be misleading when, as is the case with formaldehyde where reaction with native protein may occur, a substance effectively side-steps the analysis.

While seeking information on the toxicity of methanol in the presence of fructose, a search through the literature revealed two experiments:

- i) Stuhlfauth and Neumaier (61) found a reduced rate of survival when rats poisoned with methanol were given fructose as well. Their tentative conclusion was that, contrary to ethanol poisoning the giving of fructose in methanol poisoning is contra-indicated. However, the objection was dropped as, due to the number of animals involved, test results did not permit definite statements to be made.
- ii) Gilger, Potts and Farkas (23) set out to clarify the ophthalmic toxicity of methanol. In a first test five young rhesus monkeys weighing 2 to 4.9 kg were given methanol and ethanol concurrently. To control vomiting animal no. 3 received sucrose and no. 4 glucose. All animals survived without damage to the eyes.

In a second test the animals received methanol only. Animals no. 1, 2, 4 and 5 (no. 5 weighed 3.2 kg and received in addition 105 ml 5% sucrose in water) died within 18 to 38 hours after ingestion. An acidosis had developed, even in animal no. 4, which had received glucose in the first test and died after 36 to 38 hours. Animal no. 3 weighed 2.3 kg and received in addition to methanol a total of 270 ml 5% sucrose solution over a 48 hour period, corresponding to 3.4 g fructose per day or 1.5 pro mil of the body weight per day. This animal remained ill and died 18 days later without developing an acidosis. Eye symptoms were noticed in animals no. 3 and no. 4.

The observations of Gilger *et al.* conducted with primates (rhesus monkeys) can be understood as the outcome of the known and surmised interference effects discussed under 6.b.dd (see also Chapter 9).

dd. Degradation of methanol

"The catalase-hydrogen peroxide system plays a large role in the oxidation of methanol. The ferment catalase, after forming a complex with hydrogen peroxide acts, at low H_2O_2 concentrations, as peroxidase (Keilin and Hartree, in 67). It will transfer hydrogen from a substrate about to be oxidized – in this case methanol – to H_2O_2 , forming two molecules of H_2O in the

process. The catalase which is set free can again combine with H_2O_2 and thus oxidize further substrate. The hydrogen peroxide required arises, for example, in reactions catalyzed by unspecific aldehyde oxidase (xanthine oxidase = Schardinger enzyme). Further hydrogen peroxide can be provided by oxidation of thiol compounds (Aebi)." (See in 67.)

The oxidation product of methanol is formaldehyde, which does not circulate freely in the body. The effects of formaldehyde are described by Orthner (48, p. 58ff.) as follows:

"Proteins are precipitated by formaldehyde. This is the basis of formalin fixation, in which the amino acids are transformed by hydroxymethylation into "formylated proteins". The discrepancies of the syndromes after ingesting formalin or methyl alcohol are explainable by the fact that formaldehyde cannot penetrate deeply from inner or outer surfaces due to its ability to precipitate proteins. Methanol, on the other hand, is easily absorbed by mucous membranes and flows nearly uniformly through the body and, just like ethanol, does not find much resistance at the blood-brain or blood-liquor barriers. Methanol penetrates all cells and has, as have all other narcotics, an initial, slight narcotic effect as a complete molecule (Kochmann). If we assume that, in contrast to ethanol, it is not degraded rapidly into H_2O and CO_2 (Bernhard), but is slowly oxidized to formaldehyde, then the specific phenomena occurring after a latent period become understandable: slow hydroxymethylation of amino acids is poisoning the cells from the inside, so to speak." In more precise terms, formaldehyde attaches itself to the NH_2 groups of the side chains of the amino acids, e.g., to arginine and possibly also to lysine. The material so changed becomes "nonself" tissue.

Peters (49, p. 527) recorded an observation of interest in this context: "In formol fixation (of CNS-sections of MS patients) changes which are invisible or hardly recognizable can be made visible."

According to Wolf (67), degradation of formaldehyde can occur in three ways:

- "a) direct oxidation to formate
- b) transfer to hydrofolic acid (coenzyme F) with formation of formyl-tetrahydrofolic acid (activated formic acid). This compound is, in the presence of vitamin B_{12} , a donor of labile methyl groups, such as are present, for example, in methionine and choline. A reaction path also exists from formyl-tetrahydrofolic acid to formate.
- c) disproportionation of the formaldehyde to yield methanol and formate: in this process alcohol dehydrogenase is participating as a ferment (Abeles and Lee)."

The potential role of alcohol dehydrogenase in such cases is emphasized by Pietruszko (49a), who notes that "...Its broad substrate specificity makes the enzyme eminently suitable for a protecting role against toxic alcohols, aldehydes, and ketones ingested in foodstuffs."

In the mostly somewhat older literature on acute methanol poisoning one finds reports of rather varying sensitivity to methanol. The explanation of these observations lies presumably in the presence of various interference phenomena.

- 1) Interference of ethanol with methanol. Wolf gives the following explanation: "For the observed retardation of methanol degradation we have at the time of writing two possible interpretations: competition for the position in the catalase- H_2O_2 -complex or inhibition of the formaldehyde disproportionation reaction and thus reduction of the breakdown to formate." In the presence of ethanol interference (the recognized antidote), methanol is excreted as such, which is why ethanol is used therapeutically to treat acute methanol poisoning. An ethanol: methanol ratio of 1:16 already causes complete blocking of methanol degradation, and a slow excretion of methanol results.
- 2) Interference between glyceraldehyde and formaldehyde. This possibility can be pointed out in the flow chart for fructose degradation by Leuthardt (38) (Fig. 1). Glyceraldehyde is reduced to glycerine in the presence of NADH and alcohol dehydrogenase. Because formaldehyde is being disproportioned to methanol and formate by this same enzyme (see above), competition could occur, thereby explaining the deleterious effect of fructose.

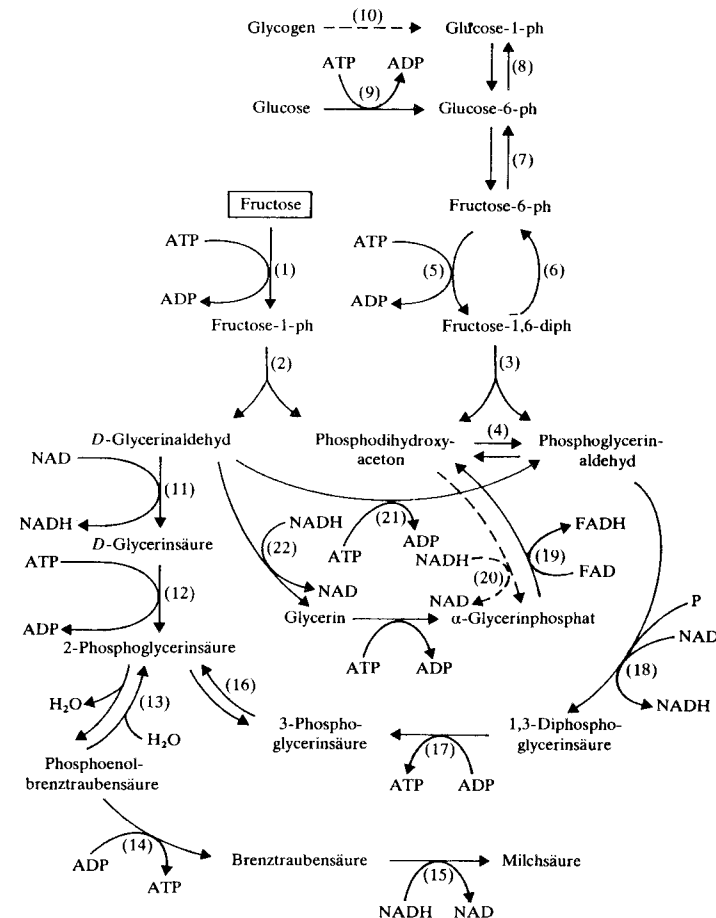
Considerations based on enzyme kinetics also lead in this direction. Pietruszko (49a) lists the Michaelis constant, K_m , for methanol (formaldehyde) as 24 mM for human alcohol dehydrogenase ("ADH"), whereas a value of 20.4 mM is given for horse ADH acting on glyceraldehyde (unfortunately the K_m values for both substrates are not available for either enzyme). Although the K_m values for the two substrates appear to be similar, the concentration of glyceraldehyde is probably higher, so that it will be preferentially metabolized. Formaldehyde will be degraded less quickly than would otherwise be the case and thus the probability of its reacting with proteins is higher. Re enzymes see also Chapter 9, p. 44/45.

The flow chart also shows a connection via glycerine and α -glycerophosphate to the glycerophosphate cycle (Bücher cycle). A possible influence on phosphatide metabolism is worth considering.

Figure 1

Metabolic reactions starting with fructose

from F. Leuthardt, Intermediär-Stoffwechsel. Walter de Gruyter. Berlin. New York. 1977. p. 442.



- 1 Fructosekinase, 2 Ketose-1-phosphataldolase, 3 Aldolase, 4 Triosephosphatisomerase, 5 Phosphofructokinase, 6 Hexosediphosphatase, 7 Glucosephosphatisomerase, 8 Phosphoglucomutase, 9 Glucokinase, Hexokinase, 10 Phosphorylase, 11 Aldehyddehydrogenase, 12 Glycerinsäurekinase, 13 Phosphopyruvathydratase, 14 Pyruvatkinase, 15 Milchsäuredehydrogenase, 16 Phosphoglyceromutase, 17 Phosphoglycerinsäurekinase, 18 Phosphoglycerinaldehyddehydrogenase, 19 Mitochondriale α -Glycerophosphatdehydrogenase (Meyerhof-Green-Enzym), 20 Cytoplasmatische α -Glycerophosphatdehydrogenase (Baranowski-Enzym), 21 Triosekinase, 22 Alkoholdehydrogenase

ee. Glucose. Methanol. Fructose as a disturbing factor

Sucrose consists of equal portions of glucose and fructose. It is not necessary to consume sucrose to sustain life. The sugar selected in the course of evolution for the metabolic process in man is glucose, which is derived mainly by degrading starch. Glucose is oxidized in the tricarboxylic acid cycle (Krebs cycle) and the respiratory chain, whereby the necessary ATP is produced. Surpluses of glucose are stored in the form of glycogen in the liver and muscles.

Fructose occurs mainly in fruit. Intake from eating fruit is quite modest and thus with the type of diet prior to the industrial revolution only small quantities had to be processed by human metabolism. But now with the ingestion of sugar, i.e., sucrose, this has changed. In spite of the fact that excessive intake of fat and sugar is blamed for a number of diseases, the particular problem of the repercussions in metabolism of the high fructose intake does not appear to have been thoroughly studied. The consumption figure in Switzerland, with an annual sugar intake of 49 kg per head, is representative for MS countries.

In the preceeding section I referred to the possible competitive blocking problem between the fructose derivative glyceraldehyde and formaldehyde, both being degraded by the alcohol dehydrogenase complex. Thus high fructose intake appears to be an important factor in the toxic allergizing phase of MS.

One aspect of the fructose degradation process has to be emphasized. Pletscher (50) found in his experiments that pyruvic acid, a labile but important intermediate in carbohydrate degradation, occurs in load tests with fructose at a higher level than in the tests with glucose. His comment was: "The momentary concentration in the blood depends on the rate (quantity per unit time) of occurrence and rate at which the further reaction proceeds. No reason exists which permits the assumption that the high pyruvic acid level on fructose loading may be induced due to delay in further processing of this keto-acid."

However, if the organism has to degrade methanol and fructose simultaneously the situation specifically excluded by Pletscher for the normal case can come about. Due to the narcotic effect of methanol on the cytochromes the processing of pyruvic acid tends to slow down. Thus we have an explanation of the high pyruvic acid level of MS patients. It can be understood as a sequel of high fructose consumption by an individual in whose metabolism methanol slows down mitochondrial electron transport and thus indirectly reduces

normal degradation in the tricarboxylic acid cycle. Lumsden discusses the high pyruvic acid level of MS patients and gives interesting information which should be read in the original report (40, p. 442–444).

Evidently one of the main dietary measures must be to prohibit sugar completely for MS patients. In this manner the additional fructose (i.e., additional to the fructose ingested by consumption of fresh fruit) is eliminated. The nourishment is then similar to what was customarily eaten at the time when MS did not occur, i.e., before 1800 (see Chapter 8).

A factor just as constantly present as high sugar consumption in areas with a high prevalence of MS is pectin as a source of methanol in fruit and vegetables, and methanol itself in small quantities in fruit juices.

The fact that man has adapted to the methanol in fruits and vegetables and can harmlessly metabolize this poisonous alcohol and its degradation products is discussed in Chapter 6.b.dd. Compared with the time during which human metabolism evolved and adjusted to the naturally available foodstuffs and thus also to the toxic methanol, however, the time since MS has been recognized is very short and an adaptation to the high intake of fructose has not been possible. A special factor is involved in unripe fruit and presumably vegetables: the pectin of such sources is, to a large extent, made up of pectinic acids (polygalacturonic acids esterified with methanol). This methanol is reduced in the process of ripening.

Unripe fruit is rarely eaten in the sunny southern latitudes. Near the 15°C-July isotherm in northern Europe, however, where fruits often ripen poorly and are hard, poor tasting, rich in methanol and low in sugar, such fruit is prepared by the addition of sugar in preserves, jams (e.g., gooseberry-fool in England), etc.

Unripe, methanol-rich fruit plus added sugar corresponds exactly to the pathogenic model of MS according to the methanol hypothesis. The poor taste, hardness and lack of aroma, all danger signs, can be hidden by the addition of sugar. The dangerous, high pectinic acid content is even useful for jellying of the preserves. Summary: ripe fruit contains little methanol and much sugar; unripe fruit has much methanol and – still – little sugar. One situation that does not occur in nature – rich in both methanol and sugar – can only be arranged by man: a protective mechanism is bypassed.

The Shetland Islands show a special twist. Fruit and berries do not grow there: the inhabitants eat some citrus fruits. On the other hand, the veget-

ables available are beets, carrots and members of the cabbage family. The sugar consumption, according to a local authority, is maximal and results in wide-spread obesity and a high incidence of tooth decay (cf. Chapter 1). In setting up a diet based on the methanol hypothesis, it turned out to be necessary to ban the cabbage family (because of their high pectin content) and carrots (due to the presence of a plant pectin methylesterase: turnips may well also contain this enzyme). It is just these vegetables that are generally eaten in the Shetlands. The factors for the development of MS when sugar consumption is excessive are all present in pronounced form.

The following description of the local diet in earlier times is from Nicolson (46). Cabbages were brought to the Shetlands in the 17th Century, and potatoes introduced in 1730. The main grain crops were barley and oats, which were used to make bread and porridge. Fish was a dietary staple. Birds' eggs and young birds were caught in the early summer. Lamb was available mainly at harvest time. Milk was in good supply, and was used to make butter and a type of soft cheese. The liquid remaining from the cheese-making, known as "blaand", was the most common drink at the end of the 19th Century. Beer was rarely made. "...Generally speaking the people of Shetland had better food and a more varied diet than did the common people elsewhere in England" (46, Nicolson, p. 69). Obviously the same gross changes in diet occurred in Shetland as elsewhere, but exactly when this change took place has not been possible to determine.

The prevalence of MS in the Shetlands was demonstrated on four different occasions (from Poskanzer, 52):

Date	Prevalence (probable plus possible) (rate/100,000)			
	1954	1962	1970	1974
Shetland Islands	134	165	177	184
Orkney Islands	111	178	233	309

A further suggestive comparison is given by the prevalence of MS in Norway, which is lower in the coastal regions than further inland (38 per 100,000, compared with 80 (1959), according to McAlpine). MS seems to have appeared on the Faroes for the first time in 1943 (Nathanson and Miller (45), based on Kurtzke and Hyllested's work). Only a few new cases have occurred since 1960. In 1966 Fog and Hyllested (18) report a prevalence of 54/37 for all/probable cases. It is not known if these cases might be among immigrants. The source of the methanol will have to be tracked down by local authorities.

Regarding sugar consumption, it is worth mentioning that Danish statistics show great variation in the amount of sugar imported: e.g., 1920 – 732,000 kg (?), 1922 – 225,700 kg, 1939 – 225,000 kg, 1940 – 353,900 kg. No data is available during the occupation in Word War II, but sugar is said to have been imported from England. In 1946, 751,500 kg were imported, and from 1954 on an average of 1300 tons (about 1,200,000 kg) per year. With this the yearly *per capita* consumption has reached the 40 kg level.

In the above cases a lower prevalence of MS is found where necessity and custom have resulted in the Faeroe Islanders and coastal Norwegians eating mainly fish. It is, of course, nonsense to conclude that a diet of fish works wonders against MS. It is indeed generally accepted that fish protein is less balanced than that from meat. If "eating fish" helps, then probably only because less methanogenic food is included in the general diet.

c. Observations concerning the autoimmune phase of MS

In the literature discussing the aetiology of MS the term "autoimmune reaction" is frequently met. On the other hand, when studying papers dealing with autoimmune diseases, it is found that MS is not referred to or is mentioned in an indefinite manner, such as: MS is perhaps or possibly caused by an autoimmune reaction.

In immunology and allergology various authors differ as to the particular sense they attach to a number of expressions. The following discussion with references to the literature tries to recapitulate what has been clarified in existing work and then to connect it with aspects which are important for the methanol hypothesis.

Of all the sources there can be not doubt that the meticulous work of Lumsden, Aparicio and Bradbury at the Pathological Institute of the University of Leeds is of central importance for the present discussion.

Scientists reading the part by Lumsden in "Multiple sclerosis, a reappraisal" (40), published in 1972, are prompted into thoughtful analysis of present knowledge and deplore the loss to MS research caused by Lumsden's death in 1974.

aa. Nomenclature

Is the term "autoimmune reaction", as used when discussing the etiology of MS, in line with the definitions in allergology? In discussing nomenclature I will follow a recent review by Brunello Wüthrich (68) who writes:

“What von Pirquet wrote in 1906 has remained relevant: ‘The term *immunity* shall be reserved for those processes in which the introduction of alien substances into the organism does not give any clinical reaction, i.e., where there is complete insensitivity.’

Further: ‘A foreign body which, after being implanted once or more, changes the organism’s reaction, is an *allergen*. The expression is chosen as it overlaps to some extent with antigen, which denotes a substance which is capable of inducing the production of antibodies.’

Then: ‘For this general concept of altered ability to react I wish to propose the expression *allergy*. *Allos* denotes: deviation from the original state’.”

von Pirquet’s reasoning forces the conclusion on us: the antigen-antibody reaction in MS does not follow the model of immunity but the one of allergy. In other words MS should not be described as an “autoimmune” disease but as an allergic disease caused by introducing an external factor which then alters body tissue. If, in line with the methanol hypothesis, we call introduction of an external factor causing alteration (*allo*) of native body tissue (*auto*) resulting in an allergic reaction (*allergy*), we get the expression *allo-auto-allergy* which, as an exact new concept, should take the place of the rather vague term “autoimmune” disease.

In our hypothesis we have found in formaldehyde a compound which attaches itself directly to the side chains of amino acids, e.g., arginine or lysine*. Methanol is transported by the blood while formaldehyde, which is not transported but appears only in the tissue after degradation of methanol, is the altering agent and thus the agent initiating antibody formation. It could thus be called an *allergenogen*. Following von Pirquet’s clear definition we must call an allergen-antibody reaction showing clinical symptoms an allergy.

The clinical reaction, the demyelination, can be classified into one of the four basic types of allergic antigen-antibody reactions considered by Coombs and Gell (see 68). Classification as type II cytotoxic (modified for MS to myelinotoxic) is easily possible. For this type it is assumed that there is a complement-dependent “cytolysis” with IgG-(IgM)-antibodies of variable reaction time.

For the explanation of auto-allergy in blood diseases which are also classified with type II, Burnet (12) refers to the opinion on N.R. Shulman:

* The attachment of formaldehyde to free NH₂ groups capable of reaction occurs also on toxoiding diphtheria and tetanus toxin; these materials have the character of antigens and are used for active vaccination. Thus we can say that the attachment to the NH₂ groups causes the protein to become “foreign” matter without causing an impediment to their antigenic effect.

“He and others suggest that what is normally classed as haemolytic anaemia caused by autoimmunity or as thrombocytopenic purpura is really a reaction against other antigens”.

bb. Is MS an autoimmune disease?

1) Antigen

For the theory of autoimmune diseases I follow Grob (25). He summarizes the possibilities for autoimmune reactions as follows:

- i) Cross-reacting antigens
When bacteria adapt their structures to mimic those of man there is just enough contrast between native and foreign substance that the bacteria act as antigenic stimulants but the antibody may direct itself against the native substance as well.
- ii) Denatured antigens
Normal constituents of native tissue can be altered to such an extent that they act as antigens and cause immunological reactions. Possible mechanisms are:
 - denaturation through viral infection
 - chemical influences
 - somatic mutation.
- iii) Sequestered antigens
Here it is assumed that there are substances which, albeit native, come into contact with the immunological apparatus too late to be considered as “self”. Thus they have the effect of antigens.
- iv) Aberrant immune system
In the cases i) to iii) the immunological apparatus has an essentially normal response. A further possibility is that a substance originally considered as native is suddenly considered to be foreign and is attacked, i.e., the immunological system has become unable to recognize self. During recent years increasing importance has been attached to this possibility.

Lumsden and other researchers hold the opinion that MS is an “autoimmune” disease. There is good cause to believe that their opinion favours (iv) above, i.e., they consider it to be a case of an aberrant immune system. Lumsden does not mention alterations in myelin or oligodendrocyte membrane, which he assumes to be the antigen*. However in the description of the immunofluorescence test, which completes and essentially makes the

* Lumsden writes (40, p. 585): “...the writer must be content to reaffirm that there is, at the moment, no evidence whatsoever for an underlying biochemical cause for multiple sclerosis”.

myelin toxicity test understandable, there is the enigmatic remark that healthy myelin is not attacked*. The statement's logical conclusion, that where the antibodies have to be traced, i.e., in the plaques, there must be diseased myelin, is not explicitly stated. So the answer to the question as to whether native or altered myelin or oligodendrocyte membrane is assumed to be present is unfortunately not resolved. The opinion of other MS researchers that unaltered body substance is present and MS thus represents a case of an aberrant immune system, seems to emerge.

From a theoretical point of view the model of the aberrant immune system for MS is least convincing. If wayward antibodies which do not respect sound, healthy tissue are assumed, how can it be explained that the scars typical of MS occur only at certain specific sites? The model has to be abandoned as no corresponding pathoclisis** can be demonstrated. Further, the concept is difficult to accept as it questions the role of the immune system as the guardian of the organism's self, thus violating the principle of immune tolerance***.

Regarding the methanol hypothesis on the other hand, the formaldehyde-attacked protein of myelin permits one to classify the antigen-antibody reaction according to Grob (ii) (denatured antigens). There is no difficulty at all in recognizing the pathoclisis of the substance causing MS as that of aliphatic monoalcohols such as methanol or ethanol (cf. Chapter 5).

Possibilities i) (cross-reacting antigens) and iii) (sequestered antigens) have never been postulated as models for MS and there is no reason to do so now.

2) Antibodies

To the question of antibodies we have independent contributions by Bornstein and Murray (11), and Lumsden (40 p. 561). The latter demonstrates demyelination upon adding diluted MS serum to myelinated nerve fibres *in vitro*. Whatever the cause, immunoantibodies of globulin structure (IgG and perhaps some IgM) are responsible for demyelination. Lumsden surmises that the antigen is in the myelin or in the oligodendrocyte membrane. The reaction of the antibody in the serum of MS patients with the antigen

* "...There is no such deposition of immunoglobulins in the normal areas of white matter" (ibid, p. 572).

** See Chapter 5.c.

*** Immune tolerance is the characteristic of the organism not to produce antibodies against native substances. As a rule therefore the native substance occurring at birth has no antigenic effect.

(allergen) destroys the myelin. The development can be followed through the microscope by taking readings after 3, 6 and 24 hours. This myelin toxicity test is done with serum containing complement and cannot be done with inactivated serum. The test would permit the early diagnosis of MS*.

Lumsden expressed the fairly definite opinion that this is a case of a humoral-mediated antigen-antibody reaction, there being far too few lymphocytes in the brain to be capable of causing demyelination. He suspects that the immunoglobulin-G antibody is produced outside the brain. An indirect proof of this premise is the lack of response to application of antilymphocytic serum in MS therapy.

Thus the question as to which type of autoimmune disease MS represents can be answered in the following manner: The possibility that an aberrant immune system is responsible has to be doubted due to lack of proof. More convincing arguments favour the concept of an autoimmune reaction (Grob, type ii, Chapter 6.c.bb) against altered body substance. For this the term *allo-auto-allergy* has been proposed.

To recapitulate: The immune system, in its defensive role, notes that a new (modified native) substance has appeared and treats it as an allergen. Its performance is thus "correct", albeit injurious to the tissue attacked: although it seems senseless that very slightly modified native material is attacked, it nevertheless occurs, leading to the plaque and the sickness MS. The allergen directly induces and steers the process.

In contrast to antigen-antibody reactions in the skin and the lungs, in MS the reaction causes a destruction of the tissue containing the allergen, thus inducing invalidism.

d) Quantitative considerations and temporal relationships

Review of the original papers on two cases of industrial methanol poisoning to which I briefly referred in Chapter 3 makes one realize that presumably St.E., who ingested methanol orally, assimilated more of the poison than R.G. did by inhalation, and both of them more than appears to be possible when ingesting foodstuffs.

* Abramsky *et al.* (1) obtained positive results with their gliotoxicity test on sera from both MS and SSPE (subacute sclerosing panencephalitis) patients, whereas Lumsden found no antibodies in two SSPE sera. Thus the myelin toxicity test appears to be more specific.

In considering the temporal relationship we can start with the opinion, remarkably noncontroversial amongst workers, that the first imperceptible onset of the disease can often be traced back to the youth of the patient. In light of the methanol hypothesis and based on the two aforementioned cases, the duration of this imperceptible phase can be determined to be of the order of magnitude of years: the duration is certainly also dependent on the quantity of methanol ingested. The prephase of MS is composed of the time interval in which the intoxication is operative, plus the allergizing phase.

According to Lumsden's findings, the time required for formation of new plaques is 6 to 8 weeks. Due to the persistence of the axons it can be assumed that the function is but little affected initially, especially with respect to the speed of nerve signal transmission.

The papers by Wüthrich and Rieder (69), and Rieder, Wüthrich and Ritzel (54) show that the maximum number of relapses occurs in the first months of the calendar year. This may be correlated with the time of possibly increased sugar intake around Christmas.

Finally, it is pertinent that the elimination of methanol takes about a week, i.e., the same duration as is normal for transient relapses.

e) Prevalence: multiple sclerosis as a multifactorial disease

Sucrose, which occurs in cane and beet sugar, became available as an inexpensive commodity during the 19th Century due to better strains of beet and sugar cane, and improved agricultural and industrial technology. This resulted in new methods of utilizing foodstuffs and a profound change in dietary habits*. Keeping this point in mind and referring also to what has been said in Chapter 6.b.bb. and 6.b.dd. I shall try to arrive at pertinent statements regarding prevalence (total number of afflicted persons) and incidence (frequency of new occurrences) of MS as a multifactorial disease.

* As said earlier, it may be assumed that during evolution the human species adapted to poisons in the natural diet. The assumption thus appears justifiable that the degradation of methanol – when a cleavage from pectins occurs – usually happens in a fluctuating, balanced manner so that the poisonous formaldehyde is quickly degraded to formic acid without inflicting damage. At this critical stage in methanol degradation, depending on an individual's metabolism, the breakdown of formaldehyde by the alcohol dehydrogenase complex could be disrupted by glyceraldehyde stemming from the fructose component of sucrose. This metabolic disturbance could allow formaldehyde, with its ability to alter protein, to initiate the allergic phase of MS.

The strong correlation between high sugar consumption and high incidence of MS is very suggestive. One could maintain the view that MS should be classified as a disease of civilization (discussed in detail in Chapter 8.c).

The following individual factors have been identified as being of importance in the primary toxic-allergizing phase of the pathogenesis:

- 1) Ethanol in diet: as an antidote for methanol it protects from MS at the price of risk of alcoholism.
- 2) Simultaneous intake of fructose and foodstuffs or beverages containing methanol: competitive inhibition of the alcohol dehydrogenase complex.
- 3) Pectin degradation in the intestine: resorption of methanol is dependent on pH of intestine and constipation.
- 4) Lack of, or damage to, naturally occurring substances or menadion, which help to degrade methanol: menadion damage by light and heat (e.g., insolation or hot bath) can have adverse results.

Prevalence of MS in Switzerland

The relatively low prevalence of approximately 50:100,000 allows one to consider classification as a multifactorial event. Viewed pragmatically we can make the following assumptions for MS and conditions in Switzerland: the people in the age groups from 15 to 55 are, due to one reason or another, susceptible to the disease.

This involves 3,500,000 out of a total of 6,000,000 inhabitants.

As discussed, acquiring the disease is a multifactorial event, in which ethanol consumption has a retarding influence and simultaneous consumption of methanol-containing foodstuffs and fructose, constipation and insolation are promoting factors.

The following calculation is an attempt, based on these various assumptions, to illustrate how the number of MS cases in Switzerland may arise. The influence of the various factors, which we now have to assign, can be estimated to be near 10% for the promoting factors and near 20% for the retarding one.

Calculations:

total population of Switzerland	6,000,000
susceptible age group (15-55 years)	3,500,000
ethanol consumers (20%)	<u>700,000</u>
Remainder	2,800,000

Factor:	excessive sugar consumption (interference between glyceraldehyde and formaldehyde).	(10% of 2,800,000)	280,000
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Factor:	constipation (formation of methanol from hydrolysis of pectins).	
	(10% of 280,000)	28,000
Factor:	insolation (damage to a substance which degrades methanol).	
	(10% of 28,000)	2,800

This figure corresponds within an order of magnitude to the number of MS patients in Switzerland.

f) Comments on the induction of MS

Lumsden (40, p. 597) makes a remark which harmonizes in this context with the methanol hypothesis: it is necessary to distinguish between ...“the primary sensitization events that initiate the multiple sclerosis process as distinct from the multiple sclerosis plaque.” In Switzerland about 150 new MS cases occur annually. The formal genesis of MS in accordance with the methanol hypothesis has already been described in detail and considered from various points of view, but a short recapitulation will be useful.

Causal to the incidence of MS is a change in dietary habits. Since the beginning of the 19th Century it has become feasible to add fructose (as sucrose) to foodstuffs to sweeten them and also to make unripe or not fully ripened fruit palatable (before that time it was hardly done as sugar was too expensive). Methanol stemming from pectin-containing foodstuffs, i.e., fruit and vegetables or processed food containing these, will in itself be degraded harmlessly. But if, in the presence of fructose, methanol degradation is impeded the disease process can get underway. Methanol as the undegraded molecule already has an effect – it causes the adynamia of MS sufferers – as a narcotic impeding cell respiration. Formaldehyde, the first degradation product of methanol, leads to an allergic reaction if it binds to proteins in the myelin. An increased level of formaldehyde may arise from the competitive inhibition due to simultaneous fructose and methanol degradation and lead to the allo-auto-allergic disease MS.

In connection with incidence we wish to consider the temporal conditions. Generally it is assumed that MS begins during the patient's youth but remains unrecognized. Retrospectively certain early symptoms of a general nature (vertigo, adynamia, short-termed disturbance of coordination) are considered to have been caused by MS. Reference is made in McAlpine's review (42, p. 50) to the papers by Dean (14) and Alter and Kurtzke (6). They have been studying MS in migrants and assume a latent interval of 13 and 9 years

respectively. Perhaps these estimates appear high, but the observations in the case described by Schwarzmann (59) supply corroborating evidence. The engineer who contracted chronic methanol poisoning which later developed into MS worked for three years in the poisonous environment before distinct signs and symptoms occurred.

Thus the phase preceeding observation of clinical symptoms, i.e., the so-called *premorbid phase* of MS, is certainly of the order of magnitude of years.

This is an allergizing process, namely a reaction to an allergen which is in itself altered substance. It is clearly established that the “type II” (Coombs and Gell) allergic reaction to a foreign substance can take years to develop.

The change in conformation of the protein molecule due to binding of formaldehyde to the side chains of amino acids (arginine and lysine) is minute. The reason for the apparent localization of the reaction of formaldehyde with protein in myelin remains to be clarified. It may be that protein in myelin, as a product of the oligodendrocytes, which have a low average metabolic activity (Norton, 47), is less quickly replaced than other exposed protein. The antigen so formed would be what Burnet (12) calls a “poor antigen”. Thus an accumulation over a considerable period will be required before an allergen-antibody reaction is properly underway and the disease process, i.e., the MS process, has been induced.

Thus we have a more plausible explanation than the assumption of a slow virus for the origin of the allergic reaction and why the reaction is “slow”. With this, the basic mechanism of the “sensitization event” to which Lumsden refers can now be visualized.

Here we can review the conditions as they presumably existed in the two cases of industrial methanol poisoning which were referred to in Chapter 3. R.G. was practically a teetotaller. He was the owner of an orchard and consumed a lot of sugar. He was the type to acquire a methanogenic MS.

St.E. was a worker in a brewery and consumed 5 to 6 bottles of beer per day during a period of 5 to 6 years, long before the methanol poisoning episode. His different reaction can be explained as follows (von Wartburg, 66): “...With this considerable ethanol consumption we must presume that he had the changes in the liver normal in alcoholics. Amongst other changes this means that the microsomal ethanol oxidizing system (MEOS) had been induced (increased enzyme activity). In this system catalase and other enzymes oxidize alcohol and, in contrast to alcohol dehydrogenase, these are

induceable enzymes. MEOS oxidizes methanol as well as ethanol. Thus it is likely that St.E. oxidized methanol rather faster than individuals in whom the MEOS had not been induced.”.

At the time the poisoning occurred (when he was employed in the garage) his drink at work was sugared tea. From the original paper one gathers that a MS syndrome was apparent and that it was tentatively diagnosed as such. Obviously only the narcotic effect of methanol on tissue prevailed and caused symptoms of MS.

It would be very wrong to conclude from the examination of the protecting effect of ethanol in cases of methanol poisoning and the scrutiny of the course that the poisoning took in the case of the formerly tippling St.E. that ethanol would be a suitable and reasonable prophylactic for MS. MS patients cannot cope with ethanol, as in the organism ethanol easily reaches the old centres where damage has occurred and also the new ones which are starting to develop. Ethanol is apparently capable of interfering with the possible remyelination of the plaques.

g) The methodic aspect of MS aetio-pathogenesis

The methanol hypothesis (see Chapter 4.b) is a model which explains a multitude of facts. The methodologically important points are summarized as follows:

- 1) Methanol is a substance which appears capable of being the temporal and causal primary inducer of MS.
- 2) It is possible to illustrate the characteristics of the pathoclisis of MS with a corresponding model disease (Chapter 5.a.).
- 3) There exist pathologic-anatomical and histological results of a case of MS which occurred due to inhalation of methanol (Chapter 3).
- 4) The methanol hypothesis can explain why the disease is known only since the early part of the 19th Century and why the incidence increased rapidly after 1850 (Chapter 8, The history of MS and of sugar consumption).
- 5) The geomedical conditions can be explained with the methanol hypothesis (Chapter 7, Geomedical facts).

Points 1) to 3) appear to be of utmost importance. They are, for a toxic-allergic induced disease such as the “autoimmune” disease MS, methodologically parallel to Koch’s rules for infectious diseases. These are:

- 1) Demonstrating the causative agent of the disease
- 2) Isolating the causative agent
- 3) Reproducing the disease by the suspected agent in a suitable animal.

With reference to Chapter 1, the impression is gained that the methanol hypothesis is the one approach in the field of MS research capable of meeting the demands of classical medical methodology.

Chapter 7: Geomedical Facts

a) Frequency distribution with latitude and altitude

The view widely held today, that the frequency of MS increases from the equatorial region towards the poles can, in the case of Western Europe, be stated somewhat more precisely. In Europe’s climatic zone (so called temperate rain climate) the greatest frequency of MS occurs on or near the 15°C-July isotherm (average surface air temperature) (see also Chapter 6.b.ee). In Western Europe this isotherm traverses Ireland, the south of Scotland and crosses Scandinavia in southern Norway. According to recent investigations, the prevalence of MS in the Orkneys is 309*, while in the Shetland Islands a little to the north, it is 184. According to an older source eastern Norway has 80, and Denmark 64 patients per 100,000 inhabitants.

The distribution in the Southern Hemisphere can be described with the same 15°C isotherm rule. Tasmania and the South Island of New Zealand have a higher prevalence than Australia or the North Island of New Zealand. The same pattern is to be found in Chile.

In a mountainous country like Switzerland the isotherm follows the height above sea level and is generally found at 1100m, or in the Canton Wallis at 1200m. Bärtschi-Rochaix (9) in his book “Multiple Sklerose im Wallis” (1977) has interesting results which are based on his investigations in the years 1971/72: the prevalence of MS in Lower Wallis is lower than in Upper Wallis, and in the latter region is greater above 1200m than at lower altitudes. The calculated prevalence in Upper Wallis above 1200m is 68.2, i.e., approximately the prevalence in Denmark. The 15°C isotherm rule is confirmed whether the temperature is caused by latitude or by altitude.

That the prevalence at the critical altitude of 1200m is dependent upon methanol as a factor is probable. That sugar consumption is also of importance can be judged from the information on dental health: of 51 patients investigated, 21 have at least a partial denture and only one has a healthy set of teeth.

* Recent deaths have reduced proportions in the Orkneys (temporarily at any rate) to a lower rate than that in Shetland (written communication by Dr. E.J.M. Shearer, Kirkwall).

Considering the history of MS and of sugar consumption, it is regrettable that the work of Bärtschi-Rochaix is just a cross-section of today's situation. It would have been interesting to learn how long MS has been found in Wallis and how the prevalence has grown, and similarly for the sugar consumption. (Obviously the time of exclusive consumption of brown bread made from locally grown rye is a thing of the past.)

b) Higher frequency of MS in agricultural areas?

In the work discussed above, 57.1% of the patients have an agricultural background, whereas only 15% of the population are agriculturally employed.

In my paper of 1968, reference is made to investigations in Lower Franconia (Western Germany). Bammer (8) has found that 65% of the patients have an agricultural background. The author states: "...As a side-line many inhabitants in the Spessart have a small holding to grow their own food."

Sällström (58) in Sweden draws the following conclusion: "...It is of interest to note that figures of agriculturists who have MS and patients whose parents have an agricultural background, correspond."

In Norway, Swank found 78% of MS cases in farming areas. In that country the coastal fishing population has a lower prevalence of MS than that of the inhabitants of the interior. Georgi (22) and his team of researchers investigated East Africa and Ethiopia in 1957 and found no cases of MS. The situation here is obviously different, however. Quite generally the statement can be made: populations in the Third World which subsist rather barely on rice, millet, etc., have a lower sugar consumption than populations in the affluent countries, where the high frequency of MS is observed.

c) MS prevalence among various races

For this aspect we can refer to a paper by Alter *et al* (5), dealing with the prevalence of MS among the various races of man living on Hawaii, namely: 1) Caucasians (Whites), 2) Japanese, 3) Chinese, 4) Philipinos, 5) Negro, 6) people of mixed race. The authors report that, among those born in Hawaii, there is no significant difference between Caucasians with 10.5 and Orientals with 8.8 patients per 100,000. However the prevalence among immigrants, half of whom were Caucasian and 96% of these were over fifteen years of age when entering Hawaii and hailed from the USA or from other temperate regions, is much higher (17.1 per 100,000).

Without considering place of birth, the prevalence for Chinese is 9.6, Japanese 6.5 and Caucasians 24.0. The authors have the opinion that it is no longer justifiable to accept that the disease is less frequent amongst Orientals than among Caucasians, when considering the aetiology of MS. Environmental influences should be considered rather than racial or ethnic factors.

In groups 4) to 6) above only very few cases were found. These people live presumably on a traditional subsistence diet, whereas groups 1) to 3) are accepting more and more the American dietary habits.

d) Migration problem

The significantly higher frequency among immigrants from high risk areas than people of the same race born in the country was shown for the first time by Dean (14) for South Africa and later by Alter *et al* (6) for Israel.

If one follows the train of thought in this paper it is easy to recognize the immigrants as being sensitized for methanol/formaldehyde. These individuals remain sensitized throughout their life span, and therefore even in a country with low MS frequency, such as Israel or South Africa, succumb to MS, because the primary prerequisite, the sensitization, already existed upon immigration. Other factors (simultaneous sugar and pectin consumption, constipation, insolation, etc.) can also be present in the country to which they migrate. The old sentence by Horace "*Qui trans mare currunt, caelum non animum mutant*" has *ceteris paribus* validity here.

Chapter 8: The History of Multiple Sclerosis and of Sugar Consumption

a) The history of multiple sclerosis

In a paper presenting a hypothesis involving amalgam, Baasch, a MS researcher from Zurich, gave a short history of MS and raised a pertinent question (7, p. 8). The following is a translation of this part of his work:

"In a paper 'The Centenary of Multiple Sclerosis' Tracy J. Putnam quotes Carswell and Cruveilhier and points out that in earlier works (Bonet 1679, Morgagni 1761, Haslam 1798) no reference to a case of MS can be found.

"From other sources there is also no reference to any case of MS, which is remarkable as MS can mimic various other diseases. I have to emphasize, however, that as there is no specific symptom MS cases could have been grouped with other paralyzing diseases.

“The first certain cases of MS in 1818 cannot have been caused by a quasi-random mutation, as after its first appearance in Paris, the disease was soon also recognized in Britain, Germany and the USA. Even if, which is probable, rare cases occurred in earlier times, it is incontestable that the incidence increased from approximately the second half of the 19th Century at an alarming rate to today’s prevalence of 25 to 100 per 100,000 inhabitants in the countries of the temperate zones. For the last 20 – 40 years the incidence seems to have remained more or less constant although, due to the increased longevity of patients, the prevalence still appears to increase somewhat.

“What new exogenous factor occurred during the 19th Century which could explain this development? So far I have not found a paper which has systematically tackled this problem.”

Baasch’s answer to the question was the amalgam hypothesis, which had then to be abandoned, but the question remains to be answered.

b) The history of sugar consumption

Linné (1707–1778) called sugar cane *Saccharum officinarum*, the “officinarum” indicating that sugar was a traditional medical remedy. The generic term *saccharum* has forms in various languages. Philologists trace the root of these forms to the Sanskrit “çarkarâ” and the Pali “sakkharâ”, denoting gravels, grit, sugar. The expression for sugar cane in Sanskrit is, however, “ikshú” indicating that sugar was processed and presumably traded in India in very ancient times. The Arabs brought the cane to Sicily in the 9th Century and from there it reached Madeira and the Spanish and Portuguese Colonies in the Americas in the early 16th Century, where it was soon intensely cultivated. The consumption outside medical use grew very slowly as sugar remained far too expensive to be within reach of most people. Beet sugar was first commercially produced in 1802 when a sugar factory opened in Silesia (Achard). In the 19th Century improved strains of beet root and cane and large scale agricultural and industrial technology made sugar an inexpensive commodity used by everyone and in an astonishing number of preprocessed foodstuffs.

Table I below shows the *pro capita* consumption (kilograms of unrefined sugar) during the periods indicated.

Table I

Summary of Sugar Consumption

	18th Century	1870–74 (from Meyer’s Lexicon 1906 Edition)	1903–04	before 1939 (FAO Rome)	1962
(Kilograms of unrefined sugar pro capita and annum)					
Great Britain	8	22.6	46.4(?)	36.8	56.3
USA		17.6		47.0	47.6
Switzerland	4	6.7	20.7	41.0	49.4
France		7.8	20.1	24.7	32.5
Denmark		12.0	29.3	55.3	56.8
		1920	1930		
(from Ziegler (70), pp. 53–56)					
Europe:					
Belgium/Luxemburg				29.3	31.3
Denmark		44.8	54.5	55.3	56.8
Finland		8.3	28.0	28.1	41.4
France		20.2	23.5	24.7	32.5
Ireland				39.3	48.0
Norway				30.7	42.2
Sweden		38.8	35.3	49.3	45.7
Switzerland		35.1	37.9	41.0	49.4
West Germany		15.1	25.2	25.2	31.0
Greenland				38.3	69.0
For comparison:					
Italy				7.9	25.7
Portugal				10.0	18.5
Spain				12.4	18.7
Other countries:					
Australia		54.1	53.9	51.1	52.3
Canada		42.2	46.8	40.8	48.0
Chile				25.8	32.3
Japan				12.3	15.8
New Zealand				50.2	52.3
South Africa				19.4	38.4
Turkey				4.9	13.4
USA		41.3	50.5	47.0	47.6
Cuba				37.0	70.7

c) The relationship between sugar consumption and MS

MS has characteristics that place it among the afflictions of civilisation. It thus appears to be an undesirable sequel of in themselves praiseworthy efforts to improve food supplies and forestall malnutrition by applying agricultural-industrial production methods. Modes of transport and distribution have also brought astonishing changes. The analysis of MS presented in this treatise indicates that the disease belongs to the group of disorders caused by excessive sugar consumption, a factor so frequently met in the industrialized countries. In many of these countries average consumption has risen five to ten fold since 1800. Moreover, individuals with a sweet tooth consume two to three times the average. Thus many individuals consume twenty to thirty times the quantity of fructose – a critical factor in the methanol hypothesis (see Chapter 6.b.ee) – as when the human metabolism adjusted to its food supply.

Another of the group of afflictions with a connection to sugar is the abnormal growth rate of children. This has been analyzed by Ziegler (70, 71) under the title “acceleration” in a comprehensive and convincing manner. He lists the countries with the highest sugar consumption in the years 1920 to 1962 (70, pp. 53–56). Most of these countries have a high MS morbidity, while no country with a low sugar consumption has an elevated MS morbidity. The exceptions to this rule are understandable in the light of the methanol hypothesis (certain subtropical or tropical countries (e.g., Cuba) where pectin-containing fruit and vegetables ripen so well that low esterification with methanol occurs; also Greenland, where the harsh climate prescribes a fish diet, thereby eliminating pectin as a source of methanol).

Morbidity figures for the 19th Century are lacking. The first MS descriptions were made in 1818 and 1823, followed in 1868 by a clear characterisation of the new disease (Charcot's classical monograph). In 1961 Georgi *et al.* (22, p. 16) published a synopsis of the major MS investigations (completed according to McAlpine and Hyllested). None are known before the 1920's*. The first regional survey was started in Switzerland in 1918 and was followed by another country-wide one 38 years later. Denmark also gathered data in 1921 to 1927 and again in 1949. These data are compared with the average sugar consumption ten years previously (beginning of the disease) in Table II.

* Ackermann (3) wrote in his 1931 publication: “...With this paper the statistical figures concerning MS in Switzerland have been completed. Comparisons with other countries are not yet possible, due to lack of corresponding investigations.”

Table II. Prevalence of MS in Switzerland and Denmark compared to sugar consumption

	data gathered	published	prevalence of MS per 100,000 population	sugar consumption
Switzerland				
1) Northwestern Switzerland. Bing & Reese (10)	1918/22	1926	36	
2) Remaining portion of Switzerland. Ackermann (3)	1918/23	1931	20	
3) Switzerland. Bing & Reese (10) Ackermann (3)	1918/23		23	29.6 kg (1910*)
4) Switzerland. Georgi, Müller & Hall (22)	1956/57	1961	50	41.2 kg (1949*)
Denmark				
1) Fraction of population with health insurance. Gram (24)	1921/27	1934	29	38.0 kg (1910**) 44.8 kg (1920**)
2) Hyllested (35)	1949	1956	64	55.3 kg (1934/38**)

* Ziegler (70, p. 58)

** Ziegler (70, p. 56)

*** Ziegler (71, p. 52)

Based on a) the methanol hypothesis (Chapter 4) and especially the presentation of MS as a multifactorial disease (Chapter 6.e), and b) what Ziegler (71) calls the "sugar climate", defined as "the course of the mean of the yearly average sugar consumption of the population", the Summary of Sugar Consumption (Table I) appears to provide the answer to Baasch's question about the cause of the appearance of MS in the 19th Century and its subsequent development. However, it should be clear that the appearance of new cases of MS or of relapses depends less on the total sugar consumption of the individual patients than on the interplay of various pathogenic factors with the consumption of foodstuffs containing high levels of fructose and methanol.

One may thus venture the following general forecast for the appearance of MS in the MS zones of both hemispheres:

average sugar consumption (per capita and annum)	level of MS
up to 5 kg	unknown
5–15 kg	comparatively rare
above 15 kg	a high prevalence of MS must be expected, depending on climate and dietary habits

The hard fact is that the diet of our great-grandfathers was such that children and young adults were not sensitized for this allo-auto-allergic ailment.

The frequency of the disease is increasing. Baasch's remark (7, p. 8) "...the incidence seems to have remained more or less stable in the last 20–40 years" may no longer be considered valid. This is shown clearly by the following examples:

- a) Between 1954 and 1974 the number of cases increased 40% on the Shetland Islands and almost tripled on the Orkneys (see Chapter 6.b. ee). (According to a local authority the sugar consumption of the inhabitants of these islands is markedly higher than on the mainland.)
- b) A newspaper report listed thirteen afflicted persons in Johannesburg in 1958, whereas the present number is two hundred (Rand Daily Mail, January 29, 1979).
- c) Although the Japanese used to be thought to have been spared the disease, this has recently been shown to be false when the conditions regarding sugar consumption are met (Chapter 7.c).

These increases cannot be simply an apparent change caused by increased longevity, as Baasch proposed.

It is hoped that future work will clarify these complex relationships.

Chapter 9: Proposals for further research

Some research centres have been contacted with the aim of having the chemical reactions which are the cornerstones of the hypothesis checked *in vitro* or *in vivo*. Positive results in such tests would obviously lend support to the concept which evolved essentially as a working hypothesis for clinical use.

Organisations funding MS research have brought neither proof nor disproof of the methanol hypothesis. MS societies have voiced vague disapproval and avoided factual discussion of the ideas expressed. On the other hand, logical rigour has led to objections to models such as EAE, a pathologically aberrant immune system, and the slow virus hypothesis. These are clearly defined in this paper.

To achieve progress an interdisciplinary research program with suitable priorities is needed. The following may serve as a basis of discussion.

a) Biochemical studies

Reference is made to the findings in the toxicological literature: Orthner (48), Roe (56), Lehninger (37, p. 97) and Lindner (39).

1. In aerobic conditions pyruvic acid is quickly oxidized (Lehninger, 37, p. 97) in the presence of intact mitochondria.

Proposal: The methanol concentration at which the degradation of pyruvic acid is disturbed or stopped should be determined (binding of methanol to the Fe^{++} ions of the cytochromes).

2. It was suggested in the methanol hypothesis that the enzyme alcohol dehydrogenase mediates the interference by glyceraldehyde of formaldehyde degradation.

Proposal: The competition of glyceraldehyde and formaldehyde as substrates for alcohol dehydrogenase should be tested *in vitro*.

b) Studies on tissues

1. The formylation of proteins during formalin fixation (Orthner, 48), and observations on the use of formol fixation in CNS-sections of MS patients, (Peters, 49) was mentioned in Chapter 5.d.aa and 6.b.dd, respectively.

Proposal: The binding of formaldehyde to the NH_2 -group of amino acids *in vivo* should be demonstrated. It appears most suitable to utilize tissue cultures of myelinated nerve fibres, as they were used by Lumsden for the myelin toxicity test. This has the advantage of providing homogeneous material but the disadvantage that the material from rats does not comply with the demand made in this paper of accepting results only if tests were made with primates. Human myelin-containing tissue, *ex post mortem*, freshly used, may possibly be satisfactory. In this paper the opinion is expressed that myelin is only altered where it is in actual contact with methanol/formaldehyde. Apart from this zone large quantities of normal myelin are present.

2. Lindner (39, pp. 56 – 61) discusses damage to skeletal muscle in acute and chronic ethanol poisoning. In dogs and rats it could be shown that, after oral feeding of ethanol, changes in mitochondria occur. A reduction of mitochondrial oxygen consumption and a reduced level of the energy-rich phosphates is found. This observation corresponds exactly to the assumption in this paper based on Egg (16) of damage to muscles by methanol binding to the Fe^{++} ions of the cytochromes, with the corresponding effect. (For further references see Lindner (39)).

Proposal: The effect of methanol on muscle metabolism should be tested.

3. In a continuation of his work on a histochemical mapping of the enzyme activity of normal brain, Friede (72) studied a freshly obtained brain of a victim of progressive MS. In the border-zone of progressive plaques he found an increased activity of the oxidative enzymes NAD-diaphorase and succinic dehydrogenase and of acid phosphatase. The number of mitochondria increased. Peak enzymatic activity occurred in the region of acute myelin breakdown. The number of oligodendroglia cells increased near the demyelinated region (border-zone). The demyelinated areas, in contrast, showed reduced activity of the oxidative enzymes in the glia cells: the mitochondria disappeared and the number of glia cells decreased abruptly at the boundary of the plaques*. The accumulation of neutral fat was generally associated with the loss of activity of the oxidative enzymes. Axons, blood vessels and the ependyma were not affected.

From these studies, Friede concluded that "... demyelination represents a damage to certain functions of glia cells at a very specific biochemical

level, using lipids for the construction of the sheath." In particular, "... damage to the mitochondria and the mitochondrial enzyme systems, entailing loss of the ability of the cells to utilize metabolites via the citric acid cycle" is involved.

Two of these findings – change in myelin and loss of mitochondrial function – have been met in the present work in conjunction with the methanol hypothesis. The concept put forward, i.e. slowing down of pyruvic acid processing by blocking of the Fe^{2+} ions of the cytochromes, correlates with Friede's observations.

The histochemical research approach gave no direct pointer to a mechanism that could explain the degradation/breakdown of myelin as a result of damage to the enzyme system.

The methanol hypothesis on the other hand – keeping in mind that methanol is an excellent solvent of lipoproteins – suggests the following possibility: Primary damage of myelin sheath by intracellular action of methanol and consequent anomalies of enzyme activity, occurrence and activity of acid phosphatase and the observed accumulation of neutral fat.

Further studies to identify the primary cause and clarify the cause and effect relationships among the changes Friede observed are urgently needed.

c) Animal experiments

The first tests to clarify the toxicity of methanol in primates were undertaken in 1956 by Gilger, Potts and Farkas (23). They tested both the acute toxicity and the protecting effect of ethanol in methanol poisoning, and also the ophthalmic toxicity.

In view of various proposals to use methanol for energy production McMartin *et al.* (42a) have undertaken further tests. They used cynomolgus monkeys, which are apparently just as useful as rhesus monkeys for studying the effect of methanol poisoning, but are easier to obtain. Their research aimed to clarify the role of formate in metabolism and the influence of folic acid deficiency of monkeys being poisoned by sub-lethal doses of methanol (0.5 g/kg). Similar tests to clarify conditions as they are proposed for the pathogenesis of MS would have to use much lower doses. The long duration of such tests (at least one year and if possible much longer) and the fact that monkeys will not readily take a diet rich in either sugar or methanol-rich food (unripe fruit) present special difficulties.

* Friede mentions in this context that "a similar distribution of cytochrome oxydase in plaques has been described by Roizin".

PART B

THERAPY OF MULTIPLE SCLEROSIS

a) Limiting factors

Factors which limit effectiveness of therapy are:

- i) existing glial scars
- ii) the lifelong predisposition to the allo-auto-allergic reaction caused by methanol and formaldehyde
- iii) the active foci present at the commencement of therapy. In favourably developing cases there is a regeneration or, in cases where demyelination is already considerably advanced, development into scars.

The basic therapy applies to all stages and degrees of severity of the disease. Its effectiveness is lower the more the formation of plaques has advanced and the more marked the antibody reaction is. It appears that the latter factor increases with duration and gravity of the affliction.

Adjustments are made to the therapy according to the stage of the disease: corticoids during relapses or exacerbations, menadion only during remission, recommended diet at all times. The therapy can be described as causal as it tries to reduce the production of allergens as much as possible by a suitable diet.

The therapy has to counteract two conditions:

- i) the toxic-allergizing phase (most important, the first phase of methanol intoxication as prophylaxis against relapse)
- ii) the "autoimmune" reaction (allo-auto-allergy) during exacerbations and real relapses.

Remark. This basic therapy deals only with the damage initiated by methanol/formaldehyde and excessive sugar consumption. Severe conditions such as, spasticity, bladder dysfunction, infections, etc., as have often been encountered with previous therapeutic methods, should be treated according to the general procedures found in textbooks and the specialized literature. A critical discussion with a view to preventing harmful applications will be presented below.

b) The toxic-allergizing phase

aa. Diet

With methanol stemming from fruits and vegetables man ingests a toxic substance. The MS patient has become sensitized to it. For this reason the dietary regimen strives to eliminate the source of methanol as much as possible. The reasons for prohibiting sugar have already been given (see 6.b.ee).

The diet described below eliminates sugar over and above that ingested with fruit and this helps with weight control. In spite of eating the same type of meal, 300 – 500 Calories (1250 – 2100 kJ) are eliminated from the daily intake and a drop in weight usually results. This is an advantage for MS patients, who have to contend with the problem of reduced strength.

The diet recommended is based on toxicological considerations and is for MS patients only. No discrimination against the use of the stipulated foodstuffs for the non-MS population is to be construed.

When a patient starts with the therapy it is recommended to have an eight day period during which no fruit or vegetables are permitted. Milk and milk products are allowed and, as vitamin C and “vitamin B complex” are given, there is no danger of avitaminosis.

The following are prohibited in the general diet:

- i) Beverages which contain even minute quantities of methanol, e.g., (Lüthi, 41),
 - black currant (200 to 700 mg per liter depending on pretreatment with enzymes)
 - cloudy apple juice (20 to 60 mg methanol per liter plus 150 to 200 mg pectin/l)
 - clear apple juice (100 mg methanol/l)
 - grape juice (200 mg/l)
 - all juice or cordials made of citrus fruit
 - juice of carrots or tomatoes (contains pectin methylesterase)
- ii) Unripe fruit in the form of compotes, i.e., using added sugar. For example: compote made utilizing windfallen fruit or compote made with unripe gooseberries (gooseberry-fool). (Hegi (27, p. 648) writes: “Excessive consumption of unripe gooseberries may lead to serious consequences and even death.”) Unripe fruit contains relatively large amounts of pectinic acid, i.e., yields methanol on hydrolysis.
- iii) Fruit and vegetables which contain pectin methylesterase. Kertesz (36, p. 365) gives a list – which he considers to be incomplete – of food plants which contain this enzyme:
 - black and red currants (*ribes nigrum* and *r. rubrum*)
 - gooseberries (*r. grossularia*)

- cherries (*prunus cerasus*)
- citrus fruit (high activity in albedo and flavedo)
- carrots, aubergines (egg-plant), tomatoes
- sprouting vegetables (asparagus)
- peaches (high content of pectinic acid)
- all varieties of cabbage (high content of pectin)
- artichokes (contain inulin, a storage form of fructose).

- iv) All foodstuffs containing fructose, i.e., practically all sweetened foodstuffs. Orange marmalade is probably particularly harmful: rind and pulp are used together with sugar, so that pathogenic factors are combined. No honey is allowed.

Following this list of restrictions, it may be useful to know which foodstuffs may be enjoyed. General rules: All non-proscribed foodstuffs such as meat, carbohydrates (others than sugar) dairy products, etc., are allowed as long as no contra-indications are known and rules for weight control are followed. Only well-ripened fruits should be taken, and early vegetables should be avoided.

For Switzerland, for example, the following list applies:

- drinks – coffee, tea, milk, unsweetened mineral water, alcohol-free beer
- fruits – strawberries, blackberries, prune, plums, pears, apricots, tart apples, kaki
- vegetables – spinach, fennel, leak, beans, peas, mushrooms, peperoni, members of the lettuce family, red and yellow chicory, cress, onions, garlic, all spices, herb vinegar, sunflower oil or olive oil.

The list of prohibited foodstuffs has been prepared for conditions in Switzerland. It is probable that local customs of food processing, sugared fruit preserves and juices (in the USA) or orange marmalade (very rich in pectins and fructose) or gooseberry-fool* play a role in starting the disease. Exacer-

* Historical aside (see Hyams, 34). Gooseberry-fool is a British specialty made from unripe gooseberries. The history of this titbit again throws light on changing food habits. The gooseberry is so named because the fruits (presumably wild berries) were eaten cooked with roast goose. There is no record of gooseberry cultivation in England before the 16th Century. A 17th Century medical publication refers to a preparation of unripe gooseberries conserved with sugar to be given against fever and indigestion.

Hyams notes that in the late 18th and early 19th Century the berry became a sort of cult object for amateurs tending gooseberry bushes in cottage gardens in the industrial Midlands and North. They ran gooseberry clubs competing for large berries, producing single fruit as large as plums.

Thus the 17th Century apothecaries' remedy, which only the sick in wealthy households ate in any quantity, became by the early 19th Century a food product which the cottage housewife prepared for her larder.

bations of short duration (transient relapses) have been recorded among my patients after ingestion of black currants, gooseberry pie, and orange juice (effect of methanol). The benefit of the prescribed diet, which is low in methanogenic pectin, can, as a rule, be noted only in extended therapy.

bb. Menadion therapy

Menadion (methyl-2-naphtoquinone-1,4; menaphton; vitamin K₃) is an oily synthetic compound with vitamin K activity. Menadion was introduced into MS therapy by Tomasziewicz (63). In the analysis of its effects it proved to be antagonistic to the effect of methanol.

Characteristics:

- i) It impedes glycolysis, as it reacts with SH enzymes.
- ii) According to Sribney (60), biological testing indicates that it might stimulate the formation of sphingomyelin in the myelin sheath.
- iii) Thurmman (62, p. 233/4) reports that menadion speeds up the NADPH-dependent methanol oxidation by rat liver microsomes, and that the process is inhibited by light. (Light converts the white menadion sodium bisulfite into the ineffective, yellow menadion-3-sulfate.) This observation is a possible explanation of the effect of menadion on MS patients and also of the deterioration due to insolation, hot baths, etc.

Menadion is given for 14 days in the form of gelatine capsules (0,01 g, 3 times a day), alternating with a pause of 14 days. Sufficient vitamin C (250 mg daily as effervescent tablets) should be given as well. Tomasziewicz (63/64) states that he had given menadion intramuscularly.

Menadion should not be given during a relapse. One of the reasons for this is the influence menadion has on the metabolism of the retina where, apart from respiration, anaerobic and aerobic glycolysis are taking place. Menadion as a glycolytic inhibitor is therefore contra-indicated.

No other side effects are known. The warning regarding embolism and thrombosis in *Documenta Geigy* (21, p. 421) has been dropped. In no cases referred to in this paper did thrombosis occur.

c) Measures against the "autoimmune" phase (allo-auto-allergy)

If transition to this therapy occurred during a relapse, the patient received Synacthen-retard, 0.6–0.8 mg intramuscularly, during five weeks, starting with five injections per week and reduced by one each week.

Prednisolone for four weeks, starting with 30 mg daily mornings in the first week, followed by 25, 20, 15 mg for the second, third and fourth week proved also to have a dampening and shortening effect on the relapse. In order to stimulate the adrenal corticoid production three injections of ACTH on the first, third and sixth day after the prednisolone medication are necessary. This prednisolone/ACTH treatment may be given twice yearly, independent of the presence of relapses. Compared to ACTH it has the advantage that it has no depressive side effects. Both have a physiological function.

Azathioprine may be tried with the necessary caution (19, 20).

d) General regimen

No ethanol. Sufficient vitamin B complex. Regularization of bowel movement. Avoidance of overstraining (applies to physiotherapy as well). No insolation, no hot baths, no sauna. Care should be given to assure enough folic acid and vitamin B12 (see 6.b.dd and 42a), especially during pregnancy.

e) Other therapeutic measures

It is necessary to comment here on some measures currently proposed and used for treatment of MS.

aa. Hot bath or sauna

The following statement from Halliday and McDonald (26, p. 25), sums up the best opinion: "... While heating has an exacerbating effect on clinical symptomatology (Simons, 1937; Guthrie, 1951; Edmund and Fog, 1955; Nelson and McDowell, 1959), cooling may have an ameliorative effect (Boynton et al., 1959; Watson, 1959).

"Heating the patient may lead not only to worsening of existing symptoms but to the development of new ones."

bb. Physiotherapy and riding therapy

Physiotherapists usually insist that only a patient in remission shall be subjected to treatment. In any such programme for an MS patient it is, however, necessary to consider the metabolic effect of the aliphatic alcohols, especially methanol. The enervating effects of methanol were discussed in Chapter 4.b.

Patients suffering from paraplegia, postapoplectic and posttraumatic conditions, and rheumatism show a training effect when subjected to physiotherapy. This is not the case for MS patients. The rapid tiring caused by their metabolic condition cannot readily be corrected. Overtiring is harmful: rational advice to MS patients is to use their energy for the essential daily exertions. It remains to be seen to what extent the usual physiotherapy can be useful for a patient who has adhered to a low methanol diet for some time.

cc. Ultrasonic therapy

Stated in simplified terms, an organism can maintain its "self" against intruded or locally developed "nonself" matter in three ways:

- i) the immune system: γ -globulins combined with the complement system, lymphocytes, plasma cells
 - ii) the monocyte-macrophage system
 - iii) the polymorphonuclear leucocyte system.
- In the case of MS only the first two seem to be involved.

An allergen-antibody reaction has been demonstrated by Lumsden (40, p. 561) and others, and these results are hardly contested. In the plaques, phagocytic cells are also found, i.e., from the macrophage system. A question to be answered by allergology is why the debris material in the plaques does not act allergenically, i.e., cause the formation of antibodies.

According to unpublished reports, in the treatment of MS ultrasonic therapy helps dispose of detrital matter via the lymph system which, according to these researchers, is present in the CNS as well. If that is so the question posed above would be academic. The process would help in the formation of scar tissue rather than of shadow plaques.

f) Thoughts on the healing process

The first aim of the therapy must be to reduce or avoid the occurrence of formaldehyde-modified protein (in the myelin sheath or oligodendrocyte membrane according to Lumsden), i.e., avoid formation of allergen. If the supply of methanol to existing, still active foci is avoided, the self-healing forces of the organism may set things right.

According to Sribney (60), menadion induces the formation of sphingomyelin, a component of myelin. Thus it may be that menadion would help in the self-healing process. Even if the myelin thus formed has only substitute characteristics, a repair of some functional effectiveness can be expected to

occur. Ulrich (65) and others believe the shadow plaques to be loci where some healing has taken place.

A diet low in methanol makes sense and is of undoubted value. Whereas consumption of foodstuffs containing or inducing the formation of methanol must be reduced to the very minimum, ethanol intake must be completely prohibited. Both alcohols are lipid-soluble and easily cross the blood-brain-barrier. Thus they can reach the diseased foci to exert their harmful effects. Methanol aggravates the affliction and ethanol impedes the organism's self-healing process.

g) Closing remarks

Treatment based on the methanol hypothesis is a difficult task for the doctor. Much patience is needed to guide the patients, especially during the first year, during which relapses or exacerbations may still occur. As has already been said, deterioration should be combatted by the application of corticoids early on and in sufficient quantity.

Many patients are not ready to accept a maintenance of the status quo as "success", other have the misguided opinion that the diet and menadion treatment, on the one hand, and corticoids, on the other, are alternative methods. One must steer clear of such misunderstandings.

With the introduction of the diet regimen the treatment resembles that of diabetes, where success or failure depends largely on the patient's attitude. It is well known that treatment and adherence to treatment touching the basic drives is extremely difficult with some patients.

EPILOGUE AND ACKNOWLEDGMENTS

In retrospect the attempt to understand the MS problem seems like a passage through a maze with many alleys all holding promise for investigation. It was a great help and very time-saving to have become aware of several dead ends.

The author is conscious of other authors' long years of efforts behind the books and papers he has perused. He cannot do justice to them except by stating that their work, discussions with friends and signals from adversaries all helped to shape the book.

The outcome has the merit that when MS is diagnosed at an early stage patients can now hope to lead a near normal life. The management of the disease runs at a fraction of the cost of what was normally spent. This is the typical situation when treatment of a disease which was not understood could be replaced by a regimen that comes as a result of a concept of the mechanism of the disease.

In my efforts I found encouraging interest from Professor Robert Schwyzer, Institute of Molecular Biology, ETH, Zurich. In the same vein Dr. Georg Constam was a great help. Valuable hints also came from Dr. Brunello Wüthrich for allergological problems.

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Appendix:

72. Friede, Reinhard L. Enzyme Histochemical Studies in Multiple Sclerosis. *Archives of Neurology*, Vol. 5 p. 103-113 Oct. 1961.

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