Epilepsy and alcohol : the influence of social alcohol intake on seizures and treatment in epilepsy

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Epilepsy and Alcohol

*The influence of social alcohol intake
on seizures and treatment in epilepsy*

Omslagtekening: Anneke Höppener-Rutten

Epilepsy and Alcohol

The influence of social alcohol intake on seizures and treatment in epilepsy

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE
GENEESKUNDE AAN DE RIJKSUNIVERSITEIT LIMBURG,
OP GEZAG VAN DE RECTOR MAGNIFICUS PROF. DR. W. H.
F. W. WIJNEN, VOLGENS BESLUIT VAN HET COLLEGE VAN
DEKANEN IN HET OPENBAAR TE VERDEDIGEN OP VRIJDAG
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RENÉ HÖPPENER

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Prof. Dr. H.A. Valkenburg

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Ook werd voor het tot stand komen van deze thesis een donatie verstrekt door het Ariëns Kapper Fonds van de Nederlandse Vereniging voor Neurologie.

Aan Anneke
Alice
Edmond
Joris

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1 Reasons for investigating the relationship between the social use of alcohol and epilepsy

People suffering from epilepsy are often confronted with restrictions, resulting from their seizures, such as exclusion from various professions, not being allowed to drive a car, swim, etc.

In contemporary western society the use of alcohol is very common and during receptions, birthday parties, etc. almost universal.

Therefore, when advising patients about the use of alcohol, one has to be very careful because prohibiting or discouraging the use of alcohol exaggerates the anomalous position in which the patient finds himself in various social circumstances.

As in literature no studies can be found which provide a basis for advising about use of alcohol in epilepsy, an experiment was undertaken to study the influence of social use of alcohol on seizure frequency, blood serum levels of antiepileptic drugs and epileptic activity in the EEG.

When introducing the concept 'social use of alcohol' the question of the limit between social use of alcohol and alcohol abuse always comes under discussion.

The alcoholic is preoccupied with drinking, is secretive and often hides his or her supplies of liquor.

Nevertheless for purposes of the present study a social drinker is taken to be one who is not regularly consuming more than 2 to 3 glasses per day. Whatever value judgments are made concerning the definition of social use of alcohol, it is an inescapable reality.

The medical profession adopts various attitudes:

- 1 Some doctors accept this social use of alcohol.
- 2 Others in their relations with patients apparently project their own personal ethical objections to drinking.

Inevitably our advice to patients is somewhat coloured by personal views but so far as possible the patient should have access to informed advice concerning the medical consequences of taking alcohol.

Specifically:

- 1 To what extent is abstinence from the social use of alcohol a handicap for the individual concerned.
- 2 What influence will the social use of alcohol have on the patient's epilepsy.

An important consideration in the support of any person with epilepsy is to achieve as far as possible social integration and in particular to minimize the stigma felt by him or others.

Since social use of alcohol is the norm in our present society, an epileptic patient may feel, rightly or wrongly, excluded or 'special' if he has to refuse when offered an alcoholic drink. The admittance that one is not allowed to drink due to epilepsy is often seen as yet another stigma by the patient who is often very sensitive on this subject. Rejecting an alcoholic drink with some poor excuse, is often experienced as frustrating and it also creates embarrassing situations. The total abstainer finds himself in a different situation, because the refusal of alcohol is based on a free choice, in which indeed he may take some pride.

When this problem is discussed by people who are supporting epileptic patients, the view is often advanced that because of the above considerations social use of alcohol should be permitted. Others feel that one should advise against the use of alcohol as it may have a provocative effect on the seizures.

Before a decision can be made whether or not to advise against, it is necessary to determine the consequences of the social use of alcohol in epilepsy.

Is there a significant influence on the frequency of the seizures or the numbers of epileptiform discharges in the electro-encephalogram and what is known about the influence of alcohol on the blood levels of anti-epileptic drugs.

Without this information it is impossible to reach any reasonable decision concerning the relative importance of the psychological factors considered above and the harmful physical effects of a person with epilepsy taking alcohol.

2 Some interviews with patients concerning their experiences on alcohol advice

From personal experience of out-patient treatment of people with epilepsy it seemed that abolishing the absolute prohibition of use of alcohol did not influence the frequency of the seizures.

This view was supported by LIVINGSTON (1972) who wrote in 'Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence' that to his opinion permitting moderate use of alcohol by more than 5.000 adolescent patients, had not adversely influenced the frequency of the seizures. In Holland most patients who came for policlinic treatment have been advised not to use alcohol. This advice is understandable, since most textbooks on epilepsy assert that alcohol is a stimulating factor and should be avoided absolutely.

By illustration we will now discuss how some out-patients accepted their alcohol prohibition and what this meant to them. It is just a random sample and should absolutely not be regarded as representative of the experiences of other patients.

1 *Patient A* is a 33 years old central heating fitter, suffering from partial seizures with complex symptomatology.

Had been advised against use of alcohol

At home this never led to any problems. However, in his social life he frequently had to listen to comments of others. One night at a party, some youngsters sitting at another table asked him if he usually drank dishwater (he had apple juice). This annoyed him and he tried to teach them a lesson. He went over to their table and showed them his evening medication, 5 pills, and proposed that the person who swallowed his pills, could have as many drinks as he wanted for the rest of the evening at his expense. They had no answer to this and did not take up the challenge.

There after he took 1 or 2 alcoholic drinks if he went out in the evening. He no longer attracted so much attention in his social life and avoided questions and comments.

2 *Patient B* is a 16 years old student with primary generalized epilepsy.

Had been advised against use of alcohol

During the last year this caused conflicts between the patient and her

parents, as she ignored this absolute prohibition and did take some alcoholic drinks at parties or when going out with friends, which was noticed by her parents on her return. Until then there had always been a good relationship between her and her parents. However, they now had irreconcilable attitudes, which they were not able to discuss. This led to a deterioration of the relation between parents and child. The absolute prohibition was withdrawn and the parents were then able to discuss the matter and to support their daughter.

- 3 *Patient C* is a 46 years old head of a personnel department, with primary generalized epilepsy.

Had been advised against use of alcohol

If the patient had been allowed to use alcohol, he would not have wished to do so anyway and therefore the restriction was not experienced by him as an impediment. His daughter also suffered from epilepsy, had more trouble with the alcohol prohibition. He did not think it desirable to allow her alcohol as he did not believe that she would keep to the prescribed limits.

- 4 *Patient D* is a 28 years old technical designer, suffering from partial seizures with complex symptomatology.

Had been advised against use of alcohol

At first the patient did not take alcoholic drinks at birthday parties of friends and family. He found this very distressing and a source of emotional problems. Indeed the stress of enforced abstinence during a social evening would often lead to an attack the following morning. He ignored the prohibition, limited his use of alcohol to 2 or 3 glasses per evening, had more pleasure in going to parties and no longer attacks the following morning.

- 5 *Patient E* is a 33 years old speech-therapist with primary generalized epilepsy.

Had been advised against use of alcohol

She had no trouble following this advice, although she had used alcohol in the past. However, when the restriction was lifted she found the occasional social use of alcohol very pleasant.

The above samples illustrate only a few of the experiences of patients in relation to counselling on alcohol use.

One should be aware that many patients like patient C, who will even after abolishment of the alcohol prohibition chose not to indulge in intoxicants.

However, it is then a voluntary choice and neither a burden nor an unacceptable restriction of personal freedom.

3 Review of the structure of the thesis

In determining the aims of the thesis a primary consideration was whether the study should be confined to the influence of the social use of alcohol on epilepsy or whether it was necessary to consider more generally on the basis of published literature the social handicaps experienced by people with epilepsy and the means by which these can be overcome. Considering that pharmacotherapy forms only a part of the total multidisciplinary approach, a structure was selected which included a general review of the various social aspects of epilepsy, supported by review of literature.

In this context the lack of quantitative data was striking, despite which many opinions have been expressed which are certainly hardly justified by the available evidence.

What prejudices exist against people with epilepsy and what are the facts on which those prejudices are based?

How extensive is the public knowledge about the various causal factors of epilepsy and the different types of seizures?

Is it certain that publications and practice in the past did not contribute towards a positive image of people suffering from epilepsy?

Until the end of the last and the beginning of this century in various countries the horrible custom prevailed of drinking human blood as a cure for epilepsy. After the beheading of a criminal one had to drink the still streaming blood and then to run away as quickly as possible. Also there are publications from the last century which claim a relation between criminality and people with epilepsy.

Opinion polls from the last 15 years show that some parents object to their children playing with a child suffering from epilepsy. Moreover, some people are of the opinion that it should be made impossible for people with epilepsy to obtain a job.

In chapter II of this thesis a summary of attitudes towards epileptics in a number of countries is given.

Another important point under discussion is the age of onset of epileptic seizures and the question of whether different types of seizures occur preferentially at a particular age.

It might be expected that in children epilepsy would have an influence on the personality development.

However, it appears that - usually - the influence of the epilepsy in itself is not that great but it is often the overprotection from the environment which inhibits the emotional development of the child. The child is often isolated leading towards a decrease of self-confidence and consequent of his learning difficulties.

Prevention of seizures by way of medicaments often decreases the degree of overprotection and concern.

In view of this the results of drug therapy are discussed.

In about 60% of epileptics free from seizures for 2 years a 'recovery' can be achieved. This means that the patient remains seizure free even after gradually diminishing and eventually terminating the drugs.

The occurrence of epilepsy in employed people is also discussed. What is the usual procedure followed when applying and what is the cause of problems at work. It is striking that in keeping or losing a job the seizure frequency is not the most important factor.

The number of accidents occurring to people suffering from epilepsy does not differ from that of their colleagues doing the same work.

The last points to be discussed circumstantially are the influence of physical exercise on epilepsy and the relation between epilepsy and driving a car.

Attention is given to the terms for obtaining a drivers licence, the occurrence of road accidents as a result of epilepsy and the seriousness of those accidents.

In chapter III attention is paid to the pharmacokinetics and assay of alcohol.

Further an inventory is made of the information available about the influence of alcohol on drug metabolism, especially that of antiepileptic drugs.

However, data concerning interactions between so called 'social use' of alcohol and antiepileptic drugs are very scarce. More information is

available about the influence of alcohol abuse on the metabolism of those drugs.

There are many publications in which electroencephalographic changes due to alcohol are described. Most of these studies refer to changes of physiological rhythms. Publications regarding the influence of alcohol intake on epileptiform EEG-activity could not be found.

The last point to be discussed is the problem how to advise people with epilepsy about the use of alcohol and the data known about the relation of use or abuse of alcohol and occurrence of seizures.

In the current literature again, the main stress is on the relation between alcohol abuse and consequent provocation of epileptic seizures. In chapter IV the aim of the study is discussed and the methods used in selecting the patients.

Next the work of the ethical committee supervising the experiment is described and the way they obtained their information.

Finally the design of this double blind experiment is discussed.

Included is too a comprehensive view of the chemical analysis of the blood, and the determination of serum drug levels and alcohol concentration.

Chapter V describes the composition of the group of persons investigated, specifying both in the 'alcohol group' and in the control group the distribution of age, sex, type of epilepsy, degree of brain damage and a review of drugs used.

Both groups, 'alcohol group' and control group were chosen in such way that they did not differ statistically.

Chapter VI gives the results of the experiment with particular reference to:

- the influence of alcohol intake on seizure frequency on serum levels of antiepileptic drugs and on the epileptiform activity in the EEG;
- possible changes in physiological EEG-rhythms due to use of alcohol;
- the quantity of drink consumed by each of the groups and the alcohol concentration in the blood of persons from the 'alcohol group'.

Results of the poll, held in 25 different countries are discussed in chapter VII.

The reason for this part of the study was the possibility that, due to the lack of scientific data, great variations in advice about the use of alcohol, given to epileptic patients might be found when the results of

the different countries were compared.

In chapter VIII the results of the clinical experiment and the poll are discussed.

CHAPTER II: SOCIAL ASPECTS OF EPILEPSY

1 Introduction

Prejudices against people suffering from epilepsy still exist in our society. This bias is often based on inadequate knowledge. Some investigations into the public opinion regarding people with epilepsy are described in this chapter and a number of possible causes of this negative image are discussed.

A summary is given showing the age-dependence of various types of seizures.

For those epilepsies making their debut in an early age the possible consequences for personality development and educational attainment are examined together with the possible underlying mechanisms.

As drugs are used to prevent the occurrence of seizures a summary is given of the results of drug therapy reported by different authors.

It is very important for the epileptic patient to reach a state in which no seizures occur for then many restrictions can be abandoned. Besides, there is a possibility for a certain number of patients, if the fits have not been occurring for a couple of years, to withdraw the drugs altogether.

Also given is a summary of the factors influencing employment.

What is the occurrence of epilepsy amongst those people who are employed. How is the application procedure handled and which factors are responsible for the problems in the work situation.

Further the number of accidents involving people suffering from epilepsy is compared with that of a control group.

Finally attention is given to the influence of physical exercise on epilepsy and the relation between epilepsy and driving. When is a person with epilepsy allowed to drive a car. What percentage of epileptics has a drivers licence illegally and what are the consequences for traffic safety.

2 Implications of epilepsy for employment and rehabilitation

a Introduction

To understand the problems confronting an epileptic patient for his

rehabilitation and for finding and retaining a job one should first appreciate the relevant factors.

1 The attitudes of society towards the patient suffering from epilepsy. This largely determines whether or not the epileptic patient is accepted.

2 The age of onset of epilepsy.

After completion of vocational education retraining may be necessary whereas children may require special education.

3 The influence of the onset of epilepsy on the education of the child, plans for the future and academic attainments.

4 The prognosis with treatment? Where there is good seizure control, epilepsy may scarcely represent any disability.

5 The selection procedure of employers when engaging personnel? Which factors particularly impair employment prospects?

b Public attitudes

At 5 years intervals during the past 30 years the American Institute of Public Opinion (the Gallup Poll) has obtained answers to questions about epilepsy from representative members of the adult population throughout the United States (TROCH 1945; CAVENESS 1949, 1954, 1959, 1964, 1969, 1974, 1980).

In 1967 an investigation was also carried out by the EMNID institute at Bielefeld, as to the public opinion of the West-German population with regard to the epileptic patient (HAUCK 1968). It was repeated in 1973 (DIEHL). The same questions were asked as by the Gallup Polls in the United States.

Some of the questions were:

1 Have you ever heard or read about the disease called 'epilepsy' or convulsive seizures (fits)?

Never heard from it:

		United States 1949:	8%
		United States 1959:	7%
Germany 1967:	15%	United States 1969:	6%
Germany 1973:	11%	United States 1974:	6%

2 Would you object to having any of your children in school or at play associate with persons who sometimes have seizures (fits)?

There were objections in:

		United States 1949:	24%
		United States 1959:	18%
Germany 1967:	37%	United States 1969:	9%
Germany 1973:	27%	United States 1974:	5%

3 Do you think epilepsy is a form of insanity or not?

This was answered affirmatively in:

		United States 1949:	13%
		United States 1959:	4%
Germany 1967:	27%	United States 1969:	4%
Germany 1973:	31%	United States 1974:	2%

4 Do you think that epileptics should be employed in jobs like other people?

Objection was made in:

		United States 1949:	35%
		United States 1959:	11%
Germany 1967:	31%	United States 1969:	12%
Germany 1973:	21%	United States 1974:	8%

These findings suggest that there still exist considerable prejudices with respect to an epileptic patient.

The population of West-Germany more often had a rejecting attitude than that of the United States, also knowledge of the disease was much poorer in West-Germany.

HAUCK thinks this difference may in part be explained by the more authoritative value system in West-Germany.

On the other hand he thinks that public education concerning epilepsy has been achieved more rapidly in the United States, is more wide spread and therefore has had more influence than in West-Germany. He therefore considers the solution should be found in extensive dissemination of information.

EDWARDS (1974) thinks that especially myths about epilepsy, as they circulated in the past centuries, were responsible for this negative attitude. It was told that epilepsy was an infectious disease. Sexual perversion, criminal behaviour and insanity were, and still are, associated with epilepsy. These prejudices are reflected in the grotesque therapies employed.

WINTERS (1723) and GERBERS (1921) described the horrible custom of drinking the blood of human beings to recover from epilepsy. A remarkable detail was the requirement to run away as fast as one could after drinking from the blood. Especially in Germany and in the Scandinavian countries this custom persisted until the end of the last century.

Bromide was the first medicine that was to any significant degree effective in controlling epileptic seizures. It was introduced by Sir CHARLES LOCOCK, a gynaecologist, in 1857 on the basis of the hypothesis that epilepsy was caused by masturbation and should be treated with an anafrodisiac as bromide.

At the annual meeting of the British Medical Association at Cambridge in 1880 Dr. BACON and Dr. HACK TUKE exchanged views on the usefulness of castration of patients with epilepsy, this to prevent masturbation. MORCEAU DE TOURS (1854) recieved a prize of the French Academy for Medical Science for a study in which he observed no less than 42.637 epileptic seizures in 108 epileptic patients during 5 years and in which he was able convincingly to prove that there was no connection between the attacks and the position of the moon.

It frequently happens that epilepsy and criminality coexist. The belief in a caused relationship can be traced back to CESARE LOMBROSO who in 1873 related epilepsy and criminality to each other in his book 'l'Homme Delinquente'. This popular belief has a persistent life despite all investigatory results - ALSTROM 1950; HILL and POND 1952; JUUL-JENSEN 1964; GUNN and FENTON 1971; KLOEK 1971; WITTER 1972; GROSS a.o. 1975 - which have since proved that people with epilepsy are no less responsible than others, and do not have a greater tendency to criminal behaviour. It is to be regretted that this belief is also encouraged by newspaper articles in which a relation is suggested between epilepsy and criminality.

Some examples:

'Utrechts Nieuwsblad', September 20, 1979: on the front page the title 'Emotions in lawsuit against Dirk de Winne', in which it is mentioned that the boy was completely irresponsible at the time of the murders, since he found himself in a condition of loss of consciousness often occurring with epileptic patients.

'De Telegraaf', December 15, 1979: "Even after the devilish deed Paolo was still joyful", mentioned that the illness (epilepsy) of Paolo was the cause of the crime. In the same article a clergyman is quoted who warned against the many demons who are threatening us and who will strike at a certain moment. Sometimes those powers get hold of the souls of young people (Paolo).

'De Gooi en Eemlander', December 21, 1979: published a letter to the editor which was most offensive with respect to people suffering from epilepsy. The author is of the opinion that epileptic patients should be castrated and sterilized and also their brothers and sisters to prevent 'mental and physical murderers' originating from the family. In general it is suggested that epileptic patients are insane, that this is hereditary and among other things this is aggravated by excessive use of alcohol.

Unjustifiably connections are sought between circumstances which are unrelated. It is considered unremarkable if a murderer has diabetes mellitus but if a murder is committed by a patient with epilepsy a connection will be made.

The legal profession has much to answer for.

If an accused person suffers from epilepsy this is almost invariably used as the basis of a plea of diminished responsibility.

Indeed often the evidence of epilepsy is highly questionable.

In British jurisprudence a nadir was reached in the case of Regina V. de Costa (1968).

A man accused of murder and who had never had an epileptic seizure was acquitted on the evidence of an expert witness (who was not a trained clinical neurophysiologist) that the EEG showed a subclinical form of epilepsy. Since that historic case every conscientious British defending counsel in a murder trial demands an EEG in the hope of finding some abnormality suggestive of epilepsy.

c Summary

There still are many prejudices over epilepsy, some of which take their origin in the many stories about the disease that have been circulating for centuries.

Even today epilepsy, though wrongly, is still widely regarded as a mental disease. At a public opinion poll in 1973 in West-Germany 31% of the people asked thought so.

The false relation between epilepsy and criminality that was made in the last century seems very difficult to discredit.

d The age of onset of epilepsy

Epilepsy often makes its debut at an early age and can thus have a decisive influence on the individual and career.

According to FENTON (1976) 25% of patients has their first seizure before the age of 5 years. In several studies more than half of the patients develop epilepsy before the age of 20 years (see table II¹).

Table II¹: Age of onset of seizures

Authors		No. of patients	Age of onset (year)	%
Gowers	(1885)	1.450	0-19	75
Spratling	(1904)	1.320	0-19	83,7
Turner	(1907)	1.000	0-20	78
Natrass	(1943)	602	0-30	75
Sal y Rosas	(1948)	1.221	0-19	65,5
Bicard et al.	(1955)	1.000	0-20	67
Lennox and Lennox	(1960)	4.000	0-19	77
Juul-Jensen	(1964)	1.008	0-19	50,1
Gastaut	(1975)	4.591	0-15	47

GASTAUT et al. (1975) made a detailed study of the correlation between age and prevalence of partial or generalized epilepsy, making use of the International Classification of the Epilepsies (GASTAUT 1970;

MERLIS 1970; GASTAUT 1973).

A classification was possible in 4.591 (76,5%) patients out of 6.000 (GASTAUT 1975) (Distribution table II²).

Generalized epilepsy: which was seen in more than one-third of epileptics of all ages (37,7%), accounted for barely one quarter of the epilepsies seen in adults (22,3%) and for more than half of those seen in children (55%).

Partial epilepsy: seen in 62,3% of subjects of all ages was far more frequent in adults than in children, accounting for two-third of the epilepsies in the older age group (77,7%) and less than half (45%) of those in the younger age group.

e Summary

In general epilepsy makes its debut at an early age, in more than 50% before 20 years.

In children generalized epilepsy is most common, 55% against 23,3% at an age older than 15.

Conversely in the older age group partial epilepsy occurs more often, 77,7% against 45% in the younger age group.

f The influence of the onset of epilepsy on the education of the child, plans for the future, academic attainment

When seizures occur repercussions are to be expected both in the family relations and in the amount of social participation and schooling. It is therefore necessary to have both medical help and adequate social support.

A Family relations

On account of the seizures the parents are subject to psychological pressures especially where the seizures occur during the night or early morning or when it is feared that seizures outside the home may lead to accidents.

There also is the continuous anxiety that the child will forget to take his drugs, that he will not heed the restrictions placed upon him, that he will overstress himself in sport, play, work and so on and provoke a seizure at a moment when the parents are not at hand

Table II²: Distribution of 4,591 epileptics as a function of age, based on the classification of the International League Against Epilepsy

Classification	All ages	Above age 15	Below age 15
Generalized epilepsy	37,7%*	22,3%*	55,0%*
Primary generalized epilepsy	28,4%*	20,4%*	37,5%*
grand mal seizures	11,3%*	12,0%*	10,4%*
petit mal absences	9,9%*	2,8%*	17,8%*
myoclonus	4,1%*	4,4%*	3,7%*
other (clonic seizures, unilateral clonic seizures, etc.)	3,2%*	1,2%*	5,6%*
Secondary generalized epilepsy	9,3%*	1,9%*	17,5%*
Lennox-Gastaut syndrome	5,1%*	0,6%*	10,2%*
West's syndrome	1,3%*	0%*	2,8%*
other	2,8%*	1,3%*	4,5%*
Partial epilepsy, with	62,3%*	77,7%*	45,0%*
elementary symptomatology	10,0%*	12,3%*	7,4%*
complex symptomatology (+ equivalent to temporal lobe epilepsy)	39,7%*	55,9%*	21,4%*
secondarily generalized seizures	12,6%*	9,4%*	16,2%*

*Percentage of classifiable cases

GASTAUT, H. (1975) *Epilepsia* 16, 457-461

(MULDER 1977).

The parents also seem to think they have to devote more time to the 'sick child'.

The restrictions with regard to bedtime, watching T.V., going out all alone, reduce his esteem with his younger brothers and sisters. WARD and BOWER (1978) too, note in their study in 81 children that the occurrence of attacks can have a severe influence on the mutual family relation. Over-protection can cause a decrease of self-respect and self-confidence and the normal interaction with children of the same age group is also hampered (FENTON 1976; MULDER 1977; WARD 1978).

B Social consequences outside the family

Since the patient may not experience the attacks himself, he may treat them as of little importance and cannot understand the way others react so strongly (RABENDING 1976). This diminishes his self-respect and self-confidence. He is also rather often shunned by his class mates (MULDER 1977). Often the child avoids contact with others of his own age and compensates by associating with younger children. This creates an isolation with respect to children of the same age, often fortified by dependence on the parents, especially in case of over-protection by the mother.

In this way the child is discouraged from becoming independent. LUTZKI and MULLER (1976) note that an improved social integration of parents leads to a social maturation, showing itself in an improvement of manners, increased social contacts and developing hobbies.

C School achievement

SUURMEIJER (1978, 1980) studied the relation between epilepsy and school achievements. He selected children with epilepsy only, excluding significant brain damage or other chronic affections. From this study it appeared that the longer the child had the attacks the more pessimistic the plans for the future of the parents became with regard to their child, at the same time the relation between parents and child became less adequate in pedagogic and social respects (due to over-protection) and consequently the school achievements of the child with epilepsy were inferior.

PLESS and ROGHMANN (1971) assume that the process of 'school under-achievement' starts with a change of the self-concept of the child. ROSS (1978) also concludes that children with epilepsy function below their mental capacity.

SILLANPÄÄ (1977) made an epidemiological and prognostic study of 132 children with epilepsy in South Western Finland. Three percent (3%) had no education at all, due to extreme mental retardation. A special school had been attended or completed by 21% and junior school by 60%.

The numbers attending middle school and higher education were respectively 1/4 and 1/7 of those in the general population (table II³).

Table II³: Educational qualifications in epileptics compared to general population 14-29 years of age

Educational qualifications	Patients	General population
No education	4 (3%)	
Special school	28 (21%)	
Junior school	79 (60%)	191.264 (31%)
Middle school	20 (15%)	375.799 (62%)
High school, university research work	1 (1%)	45.010 (3%)

SILLANPÄÄ, M., *Int.J.Rehab Research*, 1 (0,1977) 27-33

The early onset of epilepsy does not necessarily imply a bad prognosis for frequency of seizures but is related to a poorer prognosis for intellectual development (RODIN 1968).

D Summary

The onset of attacks causes uncertainty and fear with the parents with regard to the education of their child. This can be demonstrated in their approach to the child, characterized by a great deal of attention and over-protection.

The imposition of restrictions will influence their normal

functioning and limit them in their possibilities to make social contacts, while at home they are diminished in the estimation of their brothers and sisters. Also impaired interactions can arise with people of their own age or their self-confidence. In this way a vicious circle is created. This decreased functioning has its repercussion on school achievements, which are not then in accordance with the potential mental capacity. The school level that is reached, is too low, implying less possibilities for further education and diminished chances to find a suitable job.

g Prognosis with medical therapy

The first publication on the prognosis of epilepsy is of HABERMAAS (1901) and is of historical importance only since bromide (from 1853 to 1912) was the only antiepileptic drug then available. The publication deals with a total of 937 patients. In 110 patients (11,7%) the epilepsy seemed to be 'curable'. However, in 57 patients the attacks relapsed after a short time. Thus in only 53 patients (5,6%) one could speak of a longer cure. 83% Of those 53 patients were cured for more than 5 years and 50% of those 53 patients for more than 20 years.

KIRSTEIN (1942) made a follow-up study with 174 patients who were treated from 1931 to 1938. The minimum follow-up period was 3 years. After 3 years 21,8% of this group was still free from seizures. Prognosis in epileptic patients with regard to seizure control is difficult to evaluate from the literature.

Various studies defined 'control' in different ways: e.g. 6 months to 5½ years (YAHR 1952), 1 year (STROBOS 1959), 4 years (KIØRBOE 1961), 2 years (JUUL-JENSEN 1964). Similarly, rates of control varied from 33% to 85%.

RODIN (1968) gives an extensive and critical review of the literature. He summarizes those findings on which the majority of authors agrees:

- 1 Approximately 34% of all epileptic patients is likely to achieve a sustained remission of at least two years.
- 2 The percentage rises to between 50 and 60 if one considers only those patients who have grand mal seizures without associated minor attacks.

- 3 It drops to approximately 20 to 30% if one deals with patients who have psychomotor seizures.
- 4 The percentage of patients who are considered to be in permanent remission is inversely related to the length of the follow-up.
- 5 The longer the illness has lasted, the less likely is control to be achieved.
- 6 The more seizures the patient has experienced prior to his first visit to the physician, the less likely will be complete control.
- 7 The more different seizure types a given patient has experienced, the less likely control.
- 8 The more abnormal the neurological examination, mental status examination and the lower the IQ, the more difficult it will be to control the patient.
- 9 The younger the patient at the time of onset of the illness, the less probably will complete control be achieved; but there are some authors who feel that age at onset is not a good prognostic indicator.
- 10 The initial EEG is of limited value for prognosis, but a persistently abnormal EEG during treatment tends to be associated with poor seizure control.

Also in the early seventies estimates of the proportion of patients in whom a complete remission can be achieved largely agree with the conclusion of RODIN (1968).

CURRIE et al. (1971) published the results of the treatment of 666 patients suffering from partial epilepsy with complex symptomatology. 9% Of them had a temporal lobectomy, the others had only a medical treatment. 40% Of those 666 patients was in remission, during a follow-up period of 1-25 years. The results in the operative group were the same.

EDWARDS (1974) reported his findings with 160 patients, 67 with primary generalized epilepsy and 93 with partial epilepsy. In 40% a remission was achieved, lasting for more than 2 years.

Several authors investigated what percentage of patients remitted with medical treatment. The minimum duration of full remission ranged from 1 to 4 years in the various studies. There was full agreement between several authors in the period 1958-1974, concerning the probability of

remission (table II⁴)

Table II⁴: Prognosis for fits

	Minimum duration of remission (years)	Percentage of patients remitted	No. of patients examined
Kiørboe et al. (1958)	4	32	130
Strobos (1959)	1	38	228
Trolle (1961)	2	37	799
Juul-Jensen (1964)	2	32	969
Lorgé (1964)	2	34	177
Rodin (1968)	2	32	90
Currie et al. (1971)	1	40	606
Edwards (1974)	2	40	160

Apart from complete seizure control a decrease of seizure frequency can often be achieved with the help of medicaments.

In a publication of the Epilepsy Foundation of America (1975) a review is given on this subject, showing a decrease or complete seizure control in circa 85% (see table II⁵).

Table II⁵: Percentage control of seizures with antiepileptic medication (from Epilepsy Foundation of America 1975)

Source	Complete control (%)	Partial control (%)	No control (%)
National Epilepsy League (1955)	50	35	15
Justis (1962)	48	37	15
Thomas (1962)	50	30	20
Lundervold and Jabbour (1962)	— 83 —		17
Fukuyama et al. (1963)	53	36	12
Bratanov and Kerekovski (1970)	70	14	16
NINDS Research Profiles (1972)	60	— 40 —	

This agrees with the 85% of those with epilepsy who can achieve enough seizure control to lead essentially normal lives (RODIN 1972).

In the late seventies publications appeared in which the percentage of patients reaching a complete seizure control of 2 years or more is higher than previously (table II⁶).

Table II⁶: Prognosis for fits

Author	Minimum duration remission (years)	Percentages of patients remitted	No. of patients examined
Janz et al. (1976)	2	71	396
Ohthara et al. (1977)	3	76	431
Annegers et al. (1978)	5	71	618

JANZ and SOMMER-BUCKHART (1976) mention that they reached a seizure control for a minimum of 2 years in 71% of 396 treated epileptic patients.

ANNEGERS et al. (1978) made a study of 618 patients treated in a period between 1935-1974. The criterion of remission was freedom for seizures 5 years or more at the time of the last follow-up.

10 Years after the diagnosis was made 56% was seizure free for at least 5 years. Of the patients followed for 20 years, 71% had been seizure free for at least 5 years at the time of the last follow-up.

OTHARA et al. (1977) made an investigation in 431 children. Their findings were: In 75,9% (327 children) seizures had been completely controlled for 3 years or more (for 6 months or more in the cases of minor seizures). In 64,5% (211 children) seizures were inhibited within a year after the initiation of treatment.

When considered by clinical seizure patterns, seizures were observed to have disappeared in 85,2% of grand mal for 3 years or more and in 70,5% cases of partial seizures. On the other hand, seizures disappeared in 40,6% of cases of Lennox syndrome and in 69,4% of cases of West syndrome.

As to the presumed etiology prognosis was good in many hereditary and idiopathic cases while intractable cases were often caused by peri-

natal or postnatal factors.

Prognosis was evidently poor in the cases accompanied by cerebral palsy or mental deficiency. As to the age of onset of epilepsy intractable cases were frequent when the seizures started at the age of less than 1 year.

h Summary

With medical treatment of epilepsy remission or control is reached in about 85% of the patients, sufficient to make it possible to function almost normally.

The final aim of both physician and patient is to reach a complete seizure control (remission).

There is some confusion in the older literature about the percentage of patients reaching a complete remission. This was caused by the variety of definitions for seizure control used by several authors. In a review of the literature, taking as the conclusion of remission a minimum of 1 year without seizures, many authors, in the period 1958-1974, agree on the results that are obtained. Those vary between 32 and 40%.

In the late seventies publications appeared in which the percentage of patients reaching a complete seizure control of 2 years or more, varied between 71 and 75%. This is significantly higher than previously. This improved prognosis is caused by the following factors:

- 1 Increased knowledge into the effect of various antiepileptic drugs.
- 2 Intensive monitoring of plasma levels. In this way a better effect can be reached especially in patients who are difficult to treat (PENRY 1977; MORSELLI et al. 1978).
- 3 Increased use of the medicaments carbamazepine and valproic acid, both of which were hardly used in the sixties.

i Factors influencing employment

A Prevalence of epilepsy in employees

Few facts are known about employment of people suffering from epilepsy. The difficulty in obtaining accurate data was noted by the

World Health Organization in 1957.

Accurate statistics are notoriously difficult to obtain especially in a disorder such as epilepsy that is so often concealed and that may only appear for a short time in a person's life.

One can also conclude from prevalence investigations in places of work that employees often do not reveal that they suffer from epilepsy.

McINTYRE (1976) assumes in his study that the number of persons in Great Britain suffering from epilepsy is about 300.000. If those over 65 years of age, those in hospital or longterm sick, children and housewives are excluded it seems reasonable to assume that there are at least 100.000 people with epilepsy in the workforce.

If there are about 25 million people in the British workforce then the number with epilepsy should represent about 0,4% of those at work. Of 150.000 employees only 177 were known as suffering from epilepsy, giving a prevalence of 0,12% (table II⁷).

Table II⁷: Prevalence of epilepsy

Source	Employees	Prevalence %
Beasly (1974)	42.000	0,09
McIntyre (1976)	150.000	0,12
Philips (Bakker 1978)	37.000	0,19
Estel Hoogovens (Bakker 1978)	24.000	0,31

Starting from the principle that there should be 0,4% employees suffering from epilepsy this means that there still are 100-150 employed people suffering from epilepsy who are unknown.

FENTON (1976) states in his study 'Rehabilitation problems in people with epilepsy' that from the estimates of the prevalence of epilepsy it can be assumed that there are probably some 90-100.000 people with epilepsy among the working population of England and Wales although only 19-20.000 are registered as disabled for employment purposes.

BEASLY (1974) collected figures from 14 works doctors, covering ap-

proximately 42.000 employees. He found a prevalence of 0,09%, ASTON (1974) has found a prevalence of 0,26% in the automobile industry. BAKKER (1979) found in an investigation at two Dutch industrial settlements a prevalence of respectively 0,19% and 0,31%.

To draw any conclusions from estimates of the prevalence of epilepsy in the workforce, it is necessary first to determine the incidence in the general population. The figures usually quoted in the range 0,5-1% are probably totally misleading.

Recent studies using marked research techniques in widely differing communities (Washington country, the Bronx New York and Bogota Columbia) suggested the true incidence to be substantially greater, of the order of 2,5-3% (ROSE et al. 1973; BAUMAN et al. 1977; GOMEZ et al. 1978).

Conclusion: There is reluctance on the part of people with epilepsy to disclose their disability because of the consequence this may have on their employment prospects.

B Application

In the study of McINTYRE (1976) only 44 epileptic patients out of 177 were known to suffer from epilepsy before they obtained employment.

In other instances the complaint either appeared for the first time after employment or it had been concealed because the employee thought it might hamper his chance of getting a job.

According to ASTON (1974) only 2 out of 27 men, suffering from epilepsy prior to employment, admitted this before they started work. JONES (1965) mentioned that in 10 out of 39 cases the diagnosis epilepsy was known before the work was started.

BAKKER (1979) found in her study in a publishing company in Holland with 500 employees that none of the applicants had mentioned epilepsy on the application form in the past 15 years.

In an other industrial concern also with 500 workers, had been no applicant who admitted to epilepsy in the past 5 years.

In a study by EDWARDS (1974) of 76 patients, 29 (38%) mentioned that a job had been refused after they had told the employer that they suffered from epilepsy. In the period 1966-1976, at 29 works in England, 24 employees were refused because they had epilepsy (Mc-

INTYRE 1976).

Conclusion: During the application often the epilepsy was concealed because the employee thought it might hamper his chance of getting a job.

C Factors for problems with jobs

RODIN asserts that seizure type has no direct relevance for the life performance of the individuals. In 1972 he showed that especially in regard to employment, seizure frequency was not the most important variable in relation to obtaining and holding a job but rather intellectual level, presence or absence of undesirable personality characteristics and motivation for work.

369 Patients with epilepsy had been seen for comprehensive evaluation at an Epilepsy Centre during a 5 year period by RODIN et al. (1977). They divided these patients into 2 basic groups:

- those with seizures only (23%) and
- others who had other associated handicaps (77%).

The patients with other handicaps were divided into the categories:

- epilepsy associated with intellectual disturbances or organic mental syndrome (48%)
- epilepsy associated with other neurological handicap e.g. hemiparesis etc. (10%)
- epilepsy associated with behavioural problems (54%)

The percentage totals over 100 because categories are not mutually exclusive and some patients had two or more handicaps in addition to epilepsy.

They made a detailed statistical comparison on selected variables between patients with epilepsy only and those who have additional other handicaps. The selected variables could be classified as average grades in school, degree of work impairment, usual occupation, present social isolation and IQ. Statistical tests on this wide variety of variables showed that patients in the 'epilepsy only' group were very little handicapped by their illness and functioned well at work. It was the larger group (77%) with associated handicaps who had impaired functioning in society or employment.

By blaming seizures for their failure in life rather than their as-

sociated problems, these patients tend to perpetuate the stigma against the illness.

Conclusion: In this study and others (RODIN 1968, 1972; FENTON 1976) it seemed that seizure frequency was not the most important variable in relation to obtaining and holding a job, but much rather intellectual level, presence or absence of undesirable personality characteristics and motivation for work.

D Job changes

In the study of McINTYRE (1976) out of 177 employees known to have epilepsy, 158 claimed to have no difficulty with their employment. This means that 89% was able to function without difficulty, although about 1/3 of these, 65 persons had required job change or modification.

In the period between 1966 and 1976 13 persons were dismissed on account of their affection: in those cases there were problems with regard to interpersonal relations or absence of suitable alternative work.

LIONE (1961) reported that out of 1.105 persons with epilepsy 73% was satisfactorily employed although 66% had some sort of restriction placed upon them.

JONES (1965) found that out of 39 epileptic applicants for jobs at a Welsh steel works, 33 were employed and satisfactorily settled but over half of them had to change their jobs within the steel works for safety reasons or in order to prevent possible disruption of production.

Similarly in a motor works study out of 51 epileptic employees 1/3 was advised at some time by the works doctor to change their jobs within the factory, mostly on safety grounds, while another third of those 51 had job changes within the factory at the request of the management or of the individuals themselves.

Conclusion: From many studies it seemed that more than 3/4 part of the employees with epilepsy was able to function without difficulty.

E Unemployment and accidents

SILLANPÄÄ (1977) examined in a follow-up study the influence of

childhood epilepsy on (adult) employability. The number of un-employed epileptics in this study was 41%. This percentage was in agreement with figures presented elsewhere in the literature (GOODGLASS et al. 1963; JUUL-JENSEN 1964; LORGE 1964; RODIN 1968). A survey covering almost 150.000 people employed in heavy industry in the north-west of England showed that 177 of them were people with epilepsy and were working in this industry. This group was doing a wide range of jobs and had an average accident frequency rate of 0,06% which compares favourably with healthy industrial workers (McINTYRE 1976).

Compared with an investigation to the accident frequency rate of people without epilepsy in the chemical industry (National Association of Mental Health 1972) in 29 companies, this seemed to vary between 0,09 and 4,64 with an average of 1,92.

One cannot conclude that the way to reduce accidents is to employ only people with epilepsy but certainly it is abundantly clear that those with epilepsy do not play any significant part in accident causation.

F Absenteeism due to illness

At the investigation of BAKKER (1979) in a steel company and an electronic industry it seemed that the frequency of absenteeism was as follows (table II⁸).

Table II⁸: Frequency of absenteeism

	<u>Steel company</u>	<u>Electronic industry</u>
Frequency of absenteeism	average 2,12 epilepsy 2,98	average 1,90 epilepsy 1,91
Duration of absenteeism	average 17,2 epilepsy 34,3	average 18,6 epilepsy 21,8
Percentage of absenteeism	average 10,0% epilepsy 28,0%	average 9,7% epilepsy 11,1%

The absenteeism of people with epilepsy employed in the steel industry is higher than that of people employed in the electronic industry. A consideration that might explain the increased duration of absenteeism at the steel company is the character of the work, heavy work, noise and such like.

It also seems that half the employees with epilepsy in the steel industry works in a shift system, in the electronic industry none.

There is insufficient information to draw any conclusions concerning absenteeism due to epilepsy.

G Summary

It is difficult to obtain an insight into the prevalence of epilepsy among employed persons.

In England where, from the number of people that suffers from epilepsy, one might expect that 0,4% of them takes part in the labour process, it appears from investigations that this percentage is much lower and varies between 0,09 and 0,26.

At an investigation with 2 Dutch works, this percentage is in the range of 0,31 to 0,19.

It seems the diagnosis of epilepsy is often concealed at the application since people expect to be refused a job in advance.

Consequently 'first attacks' often occur only after someone has been employed at a works for some time.

It is also striking that seizure frequency is not the most important variable in relation to obtaining and holding a job, but much rather intellectual level, presence or absence of undesirable personality characteristics and motivation for work. In case of dismissal it also appears that there usually are problems with regard to social relations.

Job changes within the same company are often reported, the initiative for which is taken by the works doctor or the management.

Those changes happen often for safety reasons.

Perhaps people are over-concerned with regard to this, given the relatively low accident rate of people with epilepsy.

Insufficient data are available concerning sick leave due to epilepsy.

3 Epilepsy and exercise

a Advice

When one takes part in various forms of sport physical exercise is almost a necessary condition. Participation in one or more sports can be of great importance for good social integration. We have therefore focussed our attention on the literature concerning the relation between epilepsy and exercise.

There appear to be few objective findings presented, concerning the effects of exercise on epilepsy. LENNOX (1960) states that "epileptic attacks mostly occur when the patient is not alert, when he is resting or relaxing". In the USA the 'American Medical Association Committee on the Medical Aspects of Sports' and the 'Committee on Exercise and Physical Fitness' published a Joint Statement in 1968 in which they argued that people with epilepsy should be encouraged to take part in sport and other forms of physical activity, providing that their attacks are under reasonable control.

This point of view is shared by many other authors (BOWER 1969; LIVINGSTON 1971; BOURCHELAT et al. 1973; LIVINGSTON and BERMAN 1973; ROHMANN et al. 1973).

Strict restrictions on sporting activities would be experienced as a social handicap and in children especially it might create difficulties with personality development (LENNOX 1960; BOURCHELAT et al. 1973).

Others find these psychological problems less important than the dangers which participating in sport may bring to people with epilepsy. They are of the opinion that a sufferer from epilepsy must learn to live with a handicap which implies many restrictions (McLAURIN 1973). Even if the psychological disadvantages of limitation of activity are considered to be important, one cannot avoid the fact that some precautions must be taken.

Some restrictions, mentioned in literature, seem to be reasonable such as avoiding diving, horse-riding, parachute-jumping and mountaineering. Usually swimming is only allowed under strict supervision (BOWER 1969), while some prefer to forbid it altogether (ROHMANN et al. 1973).

Although the advice to be given must vary from case to case, the above mentioned sport activities are probably unsuitable for people with epilepsy and involve great risks. Time and again restrictions are ad-

vised because of the fact that the chance of injury for people with epilepsy is assumed to be greater than in non-epileptics. It is questionable whether this is a good basis for advice on participation in sport in general by patients with epilepsy.

AIENSON (1948) compared a group of epileptic children with a normal control series. Both groups took part in the same rather heavy program of sport and athletics. The accident frequency rate was the same in both series, namely 2,8% and 2,9%. These findings do not give support to the assumptions mentioned above.

The Joint Statement (1968) indicated that it may be feared that even a light to moderate trauma might cause a renewal of attacks or an increased frequency of attacks. However, LIVINGSTON and BERMAN (1973) reported that, neither from the literature nor in their own experience, there were grounds for supposing that repeated brain traumata might give rise to renewed or more frequent epileptic seizure. GOTZE et al. (1967) mentioned some observations about the relation between epilepsy and sport, derived from an unpublished investigation concerning the therapeutic effect of swimming on people with epilepsy at an 'Air Force Rehabilitation Centre'.

No seizures occurred during physical activity. The authors themselves knew of several sufferers from epilepsy who took part in football matches, rowing and bicycle races without having had a seizure during these sports.

KUYER (1978) noted, when observing people with epilepsy taking part in sport, that few attacks occur during the exercise itself but that there is an increase in attacks in the period following the exercise. Furthermore it appeared that the increase after intermittent exercise i.e. a form of exercise with periods of work alternated with periods of relative rest, is less than after continuous exercise.

b Investigations into the influence of physical exercise on epileptic activity in EEG

The alterations in the frequency of seizure discharge as well as in the basic activity were telemetrically recorded in healthy persons and epileptic patients during a sequence of hyperventilation, physical stress and a subsequent hyperventilation period (GOTZE et al. 1967); KRAUSE et al. 1970). They found that both in people with epilepsy and

in healthy subjects there was an increased frequency and decreased voltage of the background activity during exercise. It was also noted that under physical stress a significant decrease in seizure discharge occurred as compared to the EEG recorded under standard conditions. Moreover, significantly less seizure discharges were recorded during hyperventilation after exercise compared to hyperventilation before exercise. In the group of healthy people fewer slow components occurred during the second hyperventilation period.

The authors give as a possible explanation for the decrease of the epileptic activity in the EEG during physical exercise, the induction of an acidosis.

GOTZE et al. (1967) suggest that acidosis might give an increase in the gamma amino butyric acid (GABA) concentration which would result in an increased inhibitory influence on the electrical activity of the nervous system.

In her study KUYER (1978) especially focussed attention on the period following the exertion. Investigated were: the incidence of epileptic activity in the EEG before and after the exercise, biochemical changes regarding the acid base equilibrium of the blood, the relationship between the EEG-findings and the biochemical changes, the type of epilepsy and the antiepileptic medication that was used.

Her most important conclusions were:

- there is a tendency towards an increase of epileptic activity in the EEG during the recovering phase after exercise, the degree of increase being different for various persons,
- the degree of increase is independent of the type of epilepsy and the type of medication used,
- the lower the value of the pH and base excess after the exercise and during the recovery phase, the greater the increase of epileptic activity. The gradual increase of pH and base excess in the recovery phase lags behind in those persons who show a strong increase of epileptic activity.

c Summary

With regard to advice on participation in sporting activities most authors are of the opinion that one should be very careful in imposing restrictions on an epileptic patient. A child can experience these

restrictions as discriminating and they can influence his social function. However, some sports are not advisable for patients with uncontrolled attacks, due to their character, e.g.: diving, mountaineering, parachute-jumping etc.

GOTZE et al. (1967), KRAUSE (1970) signalize a decrease of epileptic activity in the EEG during exertion. A possible explanation for this is the induction of an acidosis. However, in the recovery phase after exertion there is an increase of epileptic activity in the EEG of the patient, related to the changes in pH and base excess and due to exertion. The lower these values the stronger the increase of the epileptic activity on the EEG (KUYER 1978).

4 Epilepsy and driving

a Of what value and importance is a driving licence for an epileptic patient

Nowadays it is taken for granted that one has to have a driving licence. Refusing a driving licence or denying someone the qualification to drive is by most people considered to be a sensitive encroachment on their personal freedom. It is also experienced as a severe loss of social prestige. The car no longer is a luxury for some but is essential for many in order to follow their occupation. Since about 60% of the epileptic patients is completely integrated in society and also provides for their own livelihood (SILLANPÄÄ 1977; RODIN 1968), it seems as a matter of course that they require the same treatment as other people since for more than half of them seizure control can be achieved with medical therapy.

JUUL-JENSEN (1963) proved that at least 18% of the epileptics, not living in institutions, had an important reason for needing a driving licence, but had difficulties in obtaining one. Nowadays the number of epileptics, who need a car within the plan of their professional rehabilitation, will undoubtedly be considerably bigger (LUND 1974). To the patient, the possession of a driving licence can also be a symbol of his cure. After this he can give up the role of the sick or handicapped person and fulfil a normal position in society. The driving licence can therefore be the certificate of normality (GIETEMA and MULDER 1970).

b Conditions for issuing a driving licence to epileptic patients

For many years conditions for issuing a driving licence to epileptic patients have been under discussion in various countries. Due to the development of effective antiepileptics and the thereby improved therapeutic results a slow liberalisation of those conditions has taken place.

However, the governmental agencies are faced with the difficult choice between rehabilitation of people with epilepsy and considerations of road safety. On the one hand of course such a choice has to be based upon prognosis- and road statistical investigations, on the other hand it also has to be based upon an evaluation of the risk that recurrence of attacks may cause a serious road accident.

Casual investigations can easily lead to an emotional decision. One should start from the principle that it is unreasonable to attempt to prevent road accidents at any price, because then one should logically also have to introduce other and more serious restrictions with regard to the general traffic accident prevention.

The criteria used for issuing driving licences differ from country to country.

An important consideration is that the candidate has been free from seizures for a period of $\frac{1}{2}$ to 3 years (table II⁹).

Table II⁹: The criteria used for issuing driving licences

Country	Seizure free period
Australia	2 years
Denmark	2 years
France	2 years
Germany (West)	2 years
Great Britain	2 years
Israel	2 years
The Netherlands	2 years
Norway	3 years
Sweden	3 years
Switzerland	2 years
USA - Colorado	1 year
- Montana	2 years
- Ohio	$\frac{1}{2}$ year
- Wisconsin	$\frac{1}{2}$ year

A committee of experts that was founded by the Scandinavian association of neurologists pleads for further liberalization of the criteria for permitting driving licences.

Supported by expert opinion, it should be possible to issue a driving licence after a shorter period during which one has been free from seizures (of at least 3 months).

Such a decision should be based upon a medical testimonial with the essential neurological facts. When remission exists for less than 2 years a driving licence should be granted for only 1 year. During the last year it has also been noticed in Holland that whenever a driving licence has to be issued or renewed one does not keep strictly to a seizure free period of 2 years. The latest development in Holland is the issue of a driving licence with a validity of 1, 3 or 5 years.

c Road accidents due to epilepsy

Statistical data

A Accidents caused by epilepsy

According to several comparable statistics, 1 out of 3.000 to 1 out of 10.000 i.e. 0,1-0,3⁰/00 of all road accidents are caused by epileptic attacks (table II¹⁰) (EGLI 1977; GRATTAN 1968; HERNER 1966; VAN DER LUGT 1975).

Table II¹⁰: Accidents due to epilepsy

Author	Number of road accidents	Frequency of accidents due to epilepsy
Egli a.o. (1977)	26.000	1 out of 3.700 accident
Grattan and Jeffcoate (1968)	9.390	1 out of 3.130 accident
Herner a.o. (1966)	44.255	1 out of 3.700 accident
v.d. Lugt (1975)	179.000	1 out of 10.000 accident

With the accident frequency due to 'sudden illness' several authors mention in their studies frequencies varying from 1 out of 1.000 to

1,5 out of 10.000 accidents (table II¹¹) (GRATTAN 1968; HERNER 1966; NORMAN 1966; McFARLAND 1964).

Table II¹¹: Accidents due to chronic conditions/sudden illness

Source	Accident rates
Grattan and Jeffcoate (1968)	1 out of 1.000 accidents due to sudden illness
Herner a.o. (1966)	1 out of 1.000 accidents due to sudden illness
Norman (1966)	1,5 out of 10.000 accidents due to sudden illness
McFarland (1964)	1 out of 1.000 accidents due to sudden illness

Sudden illness refers to an unexpected episode of unconsciousness attributable to a chronic illness such as epilepsy, cardiac conditions, diabetes, alcoholism, drug use or mental illness. The percentage of epilepsy occurring in the group of sudden illness varies between authors from 18 to 29 (table II¹²).

Table II¹²: Accidents due to sudden illness/epilepsy

Author	No. of accidents sudden illness	No. of accidents epilepsy	Ratio epilepsy/sudden illness
Grattan 1968	41	12	29%
Herner 1966	15	3	20%
Norman 1966	46	8	18%

B Psyche epileptic road offenders

RITTER (1976) studied the psyche of the epileptic road offenders in Germany. During 2 years he followed a group of 130 epileptic patients. From 130 drivers with chronic epilepsy only a small group of 19 patients was responsible for all offences. The dangerous drivers with epilepsy can be characterized as people with

irregular therapy, psycho-organic defects, recurrent alcoholism and social isolation.

C Accident frequency of epileptic patients in comparison with a control group

The various studies differ on this subject. HORMIA (1961) mentioned that epileptic drivers had a 31% higher accident frequency than match controlled persons in Finland.

However, in that country there were no restrictions on the issue of driving licences to epileptics.

WALLER (1965) started from the principle of accidents per driven kilometer. Epileptics caused twice as many accidents as the control persons. However, there were several illegal drivers in this study, who probably increased the number of accidents out of all proportion.

KEYS (1961) found in a group of 888 patients studied over 11 years 3 road traffic accidents resulting from epilepsy and 74 accidents arising from other causes. The incidence of accidents in epileptics legally entitled to drive (who had been seizure free for 2 years) was thus 8,4%, while the comparable frequency amongst all healthy drivers in that area during the same period was 47%.

LAKS and KORCZYN (1977) in Israel also concluded in their investigation that epileptic patients had a lower accident rate in comparison with a control group.

RUEGG (1974) followed 308 legally driving epileptic patients and came to the conclusion that there was no difference in accident frequency compared with a control group. RITTER (1972) came in his investigation to the same conclusion.

D Accidents due to causes other than epilepsy

Only in 0,1-0,3⁰/00 of the accidents epilepsy can be implicated as the cause. The majority of the accidents, 80-90%, is due to human errors. In 1973 the traffic in 15 of the major European countries claimed 74.000 dead and 2.000.000 injured people. About 25% of accidents is caused by speeding and 15% by not giving way to others. In 6-9% of the road accidents alcoholism is the cause (EGLI 1977). In 1974 MILLINGEN (1976) investigated the cause of fatal road

accidents in Tasmania. It was proved that 50% of the 121 killed people has an excessive blood alcohol level. Most of the victims, 80%, were younger than 25 years.

d Illegal possession of a driving licence

In most countries people have to reveal their epilepsy when applying for a driving licence. From investigations of many authors however, it appears that the majority does not do so. In several studies the percentage varies from 70 to 96 (table II¹³) (EDWARDS 1974; LAKS 1977; VAN DER LUGT 1977; MAXWELL 1971; PHEMISTER 1961).

Table II¹³: Possession of driving licence and registration of epilepsy

Author	Driving licence held		% Not registered
	not registered	registered	
Edwards (1974)	21	5	80
Laks (1977)	16	7	70
v.d. Lugt (1977)	634	65	90
Maxwell (1971)	220	9	96
Phemister (1961)	25	3	82

e Seriousness and location of accidents caused by epilepsy

As for answering the question on the seriousness of accidents caused by epilepsy and where they happen most frequently, the study of VAN DER LUGT (1972) is of importance. In the period between January 1, 1959 and December 31, 1968 he selected 155 persons with an indisputable epilepsy in which there was a clear connection between the epileptic attack and the road accident. The 155 accidents were then compared with the 'average traffic accident', constructed from statistical data on traffic accidents in the Netherlands in 1963 when all traffic accidents were registered centrally. There were as many fatal accidents in the group of epileptics as in the control group. However, in the control group 4½ times as many serious accidents (severe personal injury) happened as in the group of epileptics. On the other hand there were

4 times as many collisions with only slight injury in the group involving patients. As for the frequency of material damage only there were no differences between the groups (table II¹⁴).

Table II¹⁴: Seriousness of 155 traffic accidents due to epileptic seizures

Seriousness	Epilepsy		Control	
	No.	%	No.	%
Fatal	1	0,6	1.000	0,5
Serious physical injury	3	1,9	14.000	7,8
Slight physical injury	30	19,0	7.000	3,9
Material damage only	<u>121</u>	<u>78,0</u>	<u>157.000</u>	<u>88,0</u>
Total	155	100,0	179.000	100,0

The difference in serious injuries between the two groups is highly significant ($\chi^2 = 24,47$, 3 df, $p < 0,001$) (VAN DER LUGT 1975).

One might conclude that epileptics cause considerably less road accidents with personal injury than healthy drivers. However, the types of accidents were different.

Collisions between a moving vehicle and fixed objects happened 7 times as often in the group of epileptics as in the control group. On the other hand the collisions with another vehicle are 4 times as frequent in the control group; accidents without personal or material damage to others happened 8 times less often in the control group than with epileptics. Of 155 road accidents due to epilepsy it appeared that 56,8% happened inside and 42,6% outside the built-up area. When comparing those figures with the average traffic accidents in 1963, it seemed that 82,1% of those accidents happened inside the built-up area and 17,9% outside of it. Thus accidents due to epilepsy happen comparatively more outside the built-up area, where usually the traffic intensity is lower, than in the built-up area. In a situation with heavy traffic less accidents happen, probably because then a higher degree of alertness is demanded, which has an inhibiting effect on the attacks (VIDART and GEIER 1967).

SULG (1965) also published some preliminary results showing that driving under stress seemed to suppress the paroxysmal EEG-activity.

f Relation between the type of attacks and road accident

When driving a car of course not every attack leads to an accident. HAFSTROM (1963) mentions that at the most 75% of the epileptic attacks leads to an accident.

In case of accidents preceded by an aura, it will sometimes be possible to stop the vehicle (LUND 1974).

There is no loss of consciousness in cases of partial epilepsy with elementary symptomatology. It will not be possible for an individual practitioner or a rule made by the government to prevent a road accident caused by the first attack. In studies of VAN DER LUGT (1975) and MILLIGEN (1977) it appeared that in 12 to 19% of cases an accident was caused by such a first attack.

The type of attack that most results in accidents seems to be the psychomotor attack. In the study of VAN DER LUGT (1975) one could speak of psychomotor attacks in 76% of the 155 patients.

In the study of GASTAUT (1975) who tested 4.591 epileptic patients to gain more insight into the correlation between age and prevention of partial or generalized epilepsy, such a type of attack occurred in only 56%.

The time of the attacks is also important. For years some patients only have their attacks at night, when sleeping. The chance that they occur in the daytime is small but it cannot be completely excluded (EGLI 1977).

g Summary

Driving a car or having the possibility of doing so by possession of a driving licence probably gives a feeling of freedom and power (VAN DER LUGT 1972). These are withheld from patients to whom a driving licence is refused.

Epileptic attacks seldom cause an accident, in 0,1-0,3 ⁰/00 only.

In 6-9% alcoholic leads to accidents while in 80-90% human failure is responsible.

From several studies one may draw the conclusion that legally driving

epileptics certainly have no higher accident frequency than other people.

In principle one should follow the principal that it is not the aim to prevent accidents caused by attacks at any price, otherwise one should also introduce other and more serious limitations to prevent road accidents in general.

Although in several countries there are legal regulations for obtaining a driving licence (being free from seizures during $\frac{1}{2}$ to 3 years) it appears that 70-96% of epileptic drivers give incorrect information concerning their condition to the responsible authorities and so are illegally in the possession of a driving licence.

Usually epileptic patients cause more accidents outside the built-up area because there is less intense traffic, their alertness decreases and because of that there is more chance of an attack.

The seriousness of accidents with epileptics especially show the differences between the control group in those cases where it concerns accidents with slight personal injury and accidents with considerable personal injury.

The last ones mostly occur with people who are suffering from epilepsy and in 12 to 19% of the accidents it appears that a first attack is responsible for it.

CHAPTER III: REVIEW OF THE LITERATURE ON ALCOHOL AND EPILEPSY

1 Introduction

When studying the relation between alcohol use and epilepsy it is also important to have an insight into the pharmacokinetics and assay of alcohol.

A review is given of the influence of alcohol on various organic systems, brain, alimentary system etc. as well as the influence on circulation and respiration.

The course of the blood alcohol level is described and a review is given of the factors that might influence this course.

Also various methods for the determination of the blood alcohol concentration are compared to one another and the disadvantages of some methods are mentioned.

An inventory is also made in this chapter of the information that is available concerning the influence of alcohol on medicine metabolism with special attention to the antiepileptic drugs.

However, most studies are related to the influence of *alcohol abuse* on the metabolism of antiepileptic drugs.

In many studies also the changes in the EEG due to alcohol use are described in detail.

Also a review is given of the existing information on the neuro-physiological effects of alcohol.

Finally information is given on the advice with regard to alcohol use in epileptic patients and an inventory is made of the data available concerning the relation between alcohol use/abuse and seizures.

In the literature most studies concern again the relations between attacks and alcohol abuse.

The percentage of patients in whom withdrawal seizures occur shows great differences between the several authors.

2 Pharmacokinetics and assay of alcohol

a Pharmacology of alcohol

The effects produced by alcohol on the brain when given in increasing doses may be summarized as follows (WILSON 1961):

Stage 1: Euphoria and minor disorders of conduct

The subject may appear to be uninfluenced by the drug, but adequate tests will show that the speed and accuracy of all reflexes are impaired. The power of restraining emotions is impaired; the sociable individual becomes more talkative and the reserved individual often becomes morose. Behaviour in this stage partly depends on the nature of the individual and partly on his surroundings.

Stage 2: Obvious symptoms of impaired function

Speech becomes careless, the gait slightly unsteady and movements are performed less accurately. Self-control is greatly impaired, but, as in the first stage, the effects observed depend on the nature of the individual and the character of his surroundings.

Stage 3: Deep sleep passing into coma

The stage of 'dead-drunk'. Blood alcohol about 3 ⁰/100. Still larger quantities of alcohol produce impairment of the medullary centres, and may lead to death from respiratory failure. Blood alcohol about 4-5 ⁰/100. Besides the effects of alcohol on higher functions we can also distinguish:

Action on body temperature

Alcohol acts as an antipyretic by depressing the activity of the heat regulation centre: the temperature of a person under the influence of alcohol can be depressed more easily than with a normal person.

Probably as a consequence of this action, the alcohol causes a dilatation of the skin vessels thus producing an increase in the rate of heat loss and a subjective feeling of warmth. Therefore, it is unwise to take alcohol before or during exposure to severe cold, for although it produces a temporary feeling of comfort, it diminishes the power of the body to conserve its heat.

Action on circulation and respiration

Doses of alcohol which produce excitement cause a rise of the blood pressure, but alcohol has no direct stimulating action on the vasomotor centre and produces no rise of blood pressure by any direct action on the vasomotor system. Concentrated solutions of alcohol such as brandy

stimulate the sensory nerve endings in the mouth and stomach and this reflexy causes an acceleration of the pulse and respiration.

Action on the alimentary system

When taking in dilute solution alcohol can aid digestion in two ways. In the first place it stimulates the taste buds in the mouth and causes a flow of saliva and it also stimulates the secretion of gastric juice. Alcoholic drinks contain numerous flavouring agents which intensify these actions; e.g. the bitters in beer and the ethereal esters in wines. Secondly by acting as mild hypnotic it inhibits the disturbing influences of emotions upon digestion. Concentrated alcoholic solutions produce gastric irritation, they cause at first a secretion of gastric juice, but this is followed by an inhibition of gastric secretion, which may last for days.

The mechanism of the stimulation of gastric juice secretion by alcohol is only partially known. For a long time it was thought that histamine played a part in this, but one has never been able to show an increase of the histamine level.

However, the gastrin level does increase both after oral and intravenous administration of alcohol. A direct influence of alcohol on the acid producing cells of the gastric mucous membrane or a stimulating effect through the n. vagus on these cells was supposed but has never been proved.

b Course of blood alcohol level

When we analyse the course of the blood alcohol level we can distinguish 3 stages: absorptive stage, maximum, post-absorptive stage (figure III¹).

A Absorptive stage

It is not necessary to convert alcohol for its resorption. The usual way to absorb alcohol is through the gastro-intestinal tract, in which case alcohol comes into the blood stream by diffusion.

In this way hardly any alcohol is resorbed through the cavity of the mouth (NEMSER 1907; ELBEL 1956).

HANZLIK et al. (1913) experimented with ligated intestinal loops of

Figure III¹: The blood alcohol level as function of the time

anaesthetized cats and dogs. They investigated the course of the alcohol absorption in several intestine areas. After 30 minutes the following amounts of alcohol were absorbed: from the stomach 59,2%, from duodenum 52%, from jejunum 70,7%, from ileum 51,4% and from colon 76,3%. The extent of the absorbing area does not markedly influence the intestinal absorption. The absorption of alcohol from the intestine of cats and dogs is practically completed at the end of half an hour after injection.

NEMSER (1907) proved by oral administration of alcohol to dogs that 20,8% is resorbed in the stomach, 8,7% in duodenum, 52,7% in jejunum and 17,8% in ileum. In the colon no alcohol remained. In the human being too only 10-20% of the alcohol is absorbed from the stomach (FROENTJES 1968; QUE 1975).

The greater part of the alcohol absorption takes place from the intestine. Alcohol is carried in the blood to all organs of the body and is distributed about equally to the water content of the tissues.

The metabolism of alcohol, wherein the enzyme alcohol dehydrogenase (ADH) plays the most important part, happens for the main part in the liver.

The alcohol is oxidized to acetaldehyde which again is broken down to carbonic acid and water. About 5% of the alcohol absorbed by the body is secreted unchanged in the urine, the sweat and through respiration (QUE 1975). Since initially the amount of alcohol, that is absorbed per unit of time from the gastro-intestinal tract is much greater than the amount that is eliminated (burned or excreted) per unit of time we see a more or less fast rise of the alcoholic content in the blood in the absorptive stage.

This lasts until most alcohol from the digestive tract is absorbed and the elimination starts to predominate.

B Maximum

The maximum in the curve has been reached when the elimination of the alcohol has become equal to the absorption; after that the elimination starts to dominate and the alcoholic content in the body declines. The position of the maximum, its height and time in which it is reached, determine the first part of the curve. The height of the maximum is of course directly connected to the amount of alcohol that is consumed. The time that passes between the alcohol consumption and the maximum depends in the first place on the rapidity with which the alcohol diffuses through the wall of the digestive tract and is absorbed in the blood. This again is influenced by such factors as temperature of the alcoholic beverage, whether it contains carbonic acid, the alcohol concentration of the drink and the stomach contents. Usually the maximum is reached within an hour after drinking has ceased (KRAULAND 1964; PONSOLD 1967).

C Post-absorptive stage

This stage starts directly after the maximum. The elimination is now greater than the absorption.

The breakdown occurs chiefly in the liver with the help of the enzyme alcohol dehydrogenase. This metabolism eliminates about 95% of the total amount that has been absorbed, while through kidneys, lungs and

skin the last remaining few percents leave the body.

The elimination of alcohol is linear, which means that a constant absolute amount of alcohol is broken down per unit of time (FROENTJES 1968; DE JONGH 1964).

Only the first part of this stage, directly after the maximum, and also the very last part are not linear. Usually the elimination rate is indicated with the symbol β_{60} , by which the decreasing blood alcoholic content per hour is meant and this is expressed in mg alcohol per gram of blood.

c Influence of external factors on course of blood alcohol level

A Consumption pattern

The consumption of alcohol can vary in respect of quantity, rate and strength of the alcoholic beverage.

The influence of these three factors on the course of the blood alcohol time curve manifests itself exceedingly clearly in the first part of the curve. The higher the alcohol concentration of the drink, the more rapid the absorption.

Thus gin or brandy give a steeper absorption and an earlier maximum than a same quantity of alcohol as beer (figure III²).

The maximum that is reached with beer will also be lower than with gin, because the maximum is reached later during which period more alcohol has been metabolised.

Alcohol is absorbed much faster under the influence of carbonic acid (e.g. in champagne). The temperature of the alcoholic beverage is also important, warm drinks are absorbed faster than cold ones (PONSOLD 1967).

B Food intake

It is well known that taking food just before or during the use of alcohol decreases the effect of alcohol on behaviour. In the alcohol blood level we see that the effect of taking food manifests itself in a later appearance of the maximum, while the maximum is also significantly lower than when alcohol is taken on an empty stomach (figure III³).

Figure III²: The effect of the alcohol concentration of the consumed drink on the course of the blood alcohol level

Figure III³: The influence of food intake on the course of the blood alcohol level

The differences can be large and in case of use of equal quantities of alcohol with or without food the maximum can be 40% lower and appear 1 to 2 hours later (ELBEL 1956; HERBICH 1963; KRAULAND 1964; FROENTJES 1968).

As soon as the alcohol has been absorbed into the blood, it seems that the elimination and the post-absorptive stage is not further influenced by the food intake.

C Vomiting

In the post-absorptive stage some alcohol absorption from the digestive tract continues. Since this absorption is very small in proportion to the quantity that is eliminated, the blood alcohol curve will hardly be influenced at this stage. With a strong increase of intestinal motility this absorption also increases strongly. Vomiting in the post-absorptive stage can cause a rise in the blood alcohol level of 0,1-0,2 ‰ (RAUSCHKE 1954; DITT 1964).

Vomiting for a second time causes an increase of the blood alcohol level that is significantly smaller than the first time.

Drugs increasing the intestine motility, e.g. doryl, also cause such a rise of the blood alcohol level (ELBEL 1956).

D Loss of blood

In humans loss of blood has no influence on the blood alcohol level. With animals we see a rise of the blood alcohol concentration of 0,3 ‰ when taking blood from the heart by direct puncture.

However, if a human being lost an equivalent amount of blood through arterial bleeding he would not survive (RAUSCHKE 1954; PONSOLD 1967).

d Influence of physiological factors on course of blood alcohol level

A Weight and physique

Factors like weight and physique influence the alcohol concentration so far that in order to reach the same alcohol concentration tall and heavy people have to drink relatively more than small and light persons. However, to reach the same content it is not the case that someone weighing 50 kg should drink half of the amount required by

a person weighing 100 kg. It is not only a matter of weight, but also of physique, since alcohol does not dissolve in fat.

In 2 groups of people of the same weight of which 1 group has a considerably higher fat content of the body than the other, one finds that if the 2 groups take an identical quantity of alcohol, those with a higher fat content attain a higher blood alcohol concentration.

B Individual and dispositional differences in absorption velocity

These are connected to varying physiological conditions in the alimentary canal. JUNGMICHEL (1933) was the first to prove that the degree of filling of the stomach has an important influence on the alcohol absorption. Differences in acidity of stomach- and small intestine contents play a part and also the time during which the alcohol stays in the stomach and intestine (HANEBOG 1921; ELBEL 1956).

A high degree of acidity accelerates the alcohol absorption, as does a fast passage of the alcoholic beverage through the stomach, and rapid entry to the small intestine, while on the contrary circumstances causing a longer stay of the alcohol in the stomach, result in a slow absorption, i.e. consequent to complete or partial obstruction of the gastric exit.

C Rapidity of elimination of alcohol

The elimination of alcohol from the organism, shows large differences in individuals and in the same person.

The rate of metabolism is in the first place determined by enzyme activity and this is liable to large variations. Therefore the alcohol curve will differ from time to time in the same individual under apparently identical conditions.

When different persons with a same weight drink alcohol in identical conditions big differences occur in the course of the blood alcohol level.

FROENTJES (1968) examined 136 alcohol curves in 12 people. The limits in the elimination velocity per hour (β 60) varied from 0,07 to 0,24 ‰/00. The average of all β 60 in those 136 cases was 0,16 ‰/00,

which is in conformity with the averages mentioned in literature (ELBEL 1956; ROBLJEK 1958; PONSOLD 1967).

It is difficult to influence the elimination from without.

Only 2 methods are known causing an acceleration of the alcohol metabolism namely the administration of insulin and fructose.

However, to be effective both substances have to be administered in high doses.

During sleep the elimination goes on normally and heavy labour has little effect.

e Comments regarding the relation of alcohol consumption to blood alcohol level

As already mentioned the alcohol metabolism is different for each individual but usually it is possible to make an estimation of the height of the alcohol concentration after use of some glasses of alcohol.

One can roughly estimate the contribution to the rise in blood alcohol level at 0,20 to 0,25 ‰ per normal glass of wine or spirits, and at 0,15 to 0,20 ‰ per glass of beer.

Whenever there is food in the stomach during the drinking the contribution is 20-40% lower.

In 90% of the people studied by FROENTJES (1968) the β 60 varies between 0,10 ‰ and 0,20 ‰. The rapidity with which the alcohol disappears can be estimated at an average of 0,15 ‰ per hour, counting from the time on which the drinking started.

Whenever the alcohol concentration has to be estimated at judicial inquiry in Holland one starts from the principle of a β 60 of 0,20 ‰.

So when for example somebody had 8 glasses of beer after a meal then the blood alcohol level 3 hours later will vary between approximately $8 \times 0,1 - 3 \times 0,1 = 0,5$ ‰ and $8 \times 0,1 - 3 \times 0,2 = 0,2$ ‰.

f Alcohol determination in the blood

In principle a blood sample test is necessary to determine the blood alcohol content since estimates based on analyses of exhaled air or urine are inaccurate.

It is also important to know if the blood that is obtained is of

arterial, venous or capillary origin, because of the differences between samples from different sources can be more than 50%.

Those differences are the greatest during and shortly after alcohol use and become smaller with the passage of time. Only after approximately one hour, is a certain balance established the alcohol being distributed equally throughout the organism.

The alcohol content of capillary blood is near to arterial level and alcohol determination from venous blood will give low values, at least in the period shortly after alcohol use (ELBEL 1956).

There are 3 methods that can be used in order to determine the alcoholic content of blood:

- 1 Chemical analysis method of Widmark (WIDMARK 1932).
- 2 Enzymatic method with the help of the enzyme alcohol dehydrogenase ADH (BUCHER 1951; LEITHOFF 1964; GRUNER 1967).
- 3 Physical method by gaschromatography (PONSOLD 1967).

A Method of Widmark

The principle is based upon oxidation of ethanol by potassium-bichromate. In practice a blood sample is rarely unsuitable to be analysed by this method (10 out of 50.000 blood samples) (FROENTJES 1968).

The determination is disturbed by other substances in the blood which have an oxidizing activity such as acetone and ether.

MULLER (1950) wrote that with diabetics suffering from an acetonemia, disturbances may occur increasing the estimated alcohol concentration by 85 ‰. There are also analytical problems when the blood is decomposing such as with deceased persons found some days after death.

Due to bacterial processes in the organism after death oxidizing products can arise disturbing the Widmark analysis and giving a result that is much too high. Another problem can be the post-mortal alcohol formation by bacterial processes, through which the alcoholic content can increase with 1 ‰ or more.

B Enzymatic method

The principle is based upon the oxidation of ethanol into acetaldehyde, in which case the alcohol dehydrogenase serves as a catalyst.

When this method is used no substances other than alcohol will be measured.

Whenever there is a suspicion on post-mortem alcohol formation this method cannot be applied. In that case one is dependent on gas-chromatographical investigation. The analysis is not disturbed by acetone and ether and it can be used to check whether or not the Widmark analysis is disturbed by oxidants.

C Gaschromatographical method

Gaschromatography is a technique for the division of gas mixtures into their components. This gas mixture is sent by an inert carrier gas through a column filled with carrier material.

The division of the gas mixture comes about through a different affinity of the components for the carrier material. By using this method it is possible to determine besides ethanol also acetone, ether, acetaldehyde, methanol and chloroform, just as other, higher alcohols.

This is especially important to check on possible post-mortem alcohol formation.

g Analysis and value of alcoholic content in urine

For a long time it was thought that there was a constant ratio between the alcoholic content of urine and blood.

FROENTJES (1966) made an extensive study of the relation. It seemed that allowance had to be made for a large variability in the ratio factor which in 95% was between 0,5 and 2,5. During the initial stage of alcohol use the concentration in the blood will be higher than in the urine. After the maximum concentration in the blood has been reached the differences between both values will become smaller, until the concentration in the urine will exceed the concentration in the blood. So by comparing the alcoholic content in urine and blood one can get an impression whether the blood alcohol value is still increasing or already in the decreasing stage.

h Breath alcohol analysis

Physiologically the breath method is based upon the principle that

whenever our blood contains alcohol, this alcohol will partly be released into the air content in the lungs.

It is assumed that the air that is in the alveoli contains an amount of alcohol that is in a constant ratio to the alcohol concentration of the blood in the lungs whenever a condition of balance between air and blood has been established.

However, the expired air is never pure alveolar air but always and usually in changing amount, mixed with the air from the upper bronchial tubes, which contains hardly any alcohol. The temperature of the atmospheric air is also a very important factor in the ratio factor air-blood-alcohol. Consequently there is no permanent correlation between the alcoholic content of the expired air and the blood.

Table III¹: Alcohol concentration in various beverages

Drink	Alcohol concentration by temp. 20° C		
Light beer	2,79	gram alc/100 ml	
Strong beer	3,94	"	
Special strong beer	5,14	"	
Natural wines	9,48-11,00	"	
Sherry	14,21	"	
Port	15,80	"	
Egg flip	11,05	"	
Gin	23,71-27,63	"	
Brandy	23,71	"	

Too high a value is obtained if one does not wait for at least 20-30 minutes after the last alcoholic drink due to mouth alcohol and also due to alcohol vapours released from the stomach by eructation.

In order to obtain a good respiratory sample it is necessary to carry out single expiration. Too low a value is obtained whenever one does not expire in one time, but inhales the air again in between or when one blows too slowly. The expiration should not last longer than 20 seconds.

The alcohol respiratory test is a rough screening test. With an alcohol

concentration of 0,3 $\frac{0}{00}$ there is no discolouration of the yellow tubes which turn green at the blowing end. The length of the green zone seems to be a good measure for the amount of alcohol that is blown through the tube.

Usually the discolouring appears at a concentration above 0,3 $\frac{0}{00}$, while at 0,8 $\frac{0}{00}$ the maximum effect is reached.

i Composition of alcoholic beverages

Ethanol is the main organic constituent of alcoholic beverages, but these contain in addition various constituents which determine their flavour. Beer contains 2,79 to 5,1 gram alc/100 ml together with a large amount of solids which are mainly starch derivatives. Natural wines contain 9,48-11,00 gram alc/100 ml but fortified wines such as port contain 15,80 gram alc/100 ml (see table III¹).

All wines contain organic acids, e.g. tartaric, succinic and acetic acid and red wines also contain considerable quantities of tannic acid derived from the grapeskins. The flavour of wines is due to the presence of minute quantities of complex esters.

The size of the glasses is different for various alcoholic contents, however, different drinks are commonly drunk from glasses which give a similar alcohol content. Thus a 'single' of spirits has an equivalent alcohol content to a glass of wine or a small (250 ml) glass of beer.

j Summary

To determine the alcohol contents in the blood one can use blood-, breath- or urine samples.

Determination with the help of blood samples is to be preferred since analysis of the alcohol contents with the help of expired air is dependent on the co-operation of the patient and is influenced by the temperature, moreover there is a fluctuating correlation between the alcoholic content of the expired air and the blood.

Whenever an analysis is made with the help of an urine sample it is a problem that there is no fixed relation between the blood alcohol concentration and the urine concentration, but that this relation is dependent on the stage of the blood alcohol curve namely the absorptive or post-absorptive stage.

When alcohol is taken there will be, dependent on the quantity, various influences on the brain, body temperature, circulation, respiration and the alimentary system.

This may even lead to death when very excessive amounts are used. The various alcoholic drinks contain varying alcohol concentrations but the size of the glass per specific drink usually is such that per glass of beer, wine or gin a same amount of alcohol is taken.

After ingestion of alcohol the greater part is absorbed from the small intestine. Then the enzyme alcohol dehydrogenase (ADH) plays an important part in the metabolism of alcohol. The alcohol is oxidized into acetaldehyde which again is broken down to carbonic acid and water.

When using alcoholic drinks with a high alcohol concentration there is a more rapid increase of the blood alcohol in the absorptive stage while the maximum that is attained is much higher compared with the consumption of the same amount of alcohol as beer.

Taking food just before or during alcohol consumption causes the maximum concentration to be as much as 40% lower and attained later than when one drinks on an empty stomach. Thus the effect on behaviour is reduced.

Vomiting after use of alcohol causes a rise in the blood alcohol concentration.

When comparing two persons with the same weight and both using an identical amount of alcohol the blood alcohol concentration will be higher in the person with a greater fat content.

The elimination of alcohol is linear, which means that an equal absolute amount of alcohol is broken down per unit time.

The elimination of alcohol from the organism shows big differences in individuals and in the same person. The rate of elimination cannot readily be influenced.

3 Influence of alcohol on drugs

a Effects of alcohol on drug metabolism

The effects of alcohol ingestion on drug metabolism appear paradoxical. Chronic alcoholics, when not under the direct influence of alcohol are unusually resistant to the action of drugs such as sedatives and barbiturates (ISBELL 1955).

In contrast to chronic ingestion acute alcohol intoxication leads to increased sensitivity to the effects of barbiturates and tranquillizers (KOPMANN 1959).

A Acute alcohol intoxication

Studies on the metabolism of pentobarbital and meprobamate in acutely inebriated rats and human volunteers (RUBIN a.o. 1970) showed that there was a significant slowing in the disappearance of these drugs from the blood of both men and rats. The plasma half-life of pentobarbital in alcohol treated rats was 150 minutes, compared to 70 minutes in glucose treated control animals.

In human volunteers the plasma half-life of pentobarbital was approximately twice the control value whereas the plasma half-life of meprobamate was augmented 2 to 5 fold. That the slowing was due to a direct effect of alcohol on hepatic drug metabolism was indicated by the observed in vitro inhibition of meprobamate metabolism in the rat liver slices. Measurements of specific enzyme activities in rat liver microsomes have shown that ethanol inhibits the activities of drug metabolism systems e.g. pentobarbital hydroxylase, ethylmorphine dimethylase and cytochrome P450 reductase. The inhibition by alcohol of these hepatic microsomal drug-metabolizing enzymes is probably due to its competitive binding to liver microsomes and its oxidation at the binding site. This sub-cellular mechanism is reflected in a reduced rate of drug bio-transformation in liver slices.

Summarizing: Thus, enzyme inhibition rather than drug synergism or summation of drug effects on the brain emerges as the basic mechanism of drug sensitivity in acute alcoholism.

B Chronic alcohol administration

The oxidation of alcohol is catalyzed by liver alcohol dehydrogenase and a nicotinamide adenine dinucleotide phosphate (NADPH) dependent microsomal enzyme system (LIEBER 1968).

Administration of alcohol to rats has been shown to enhance the rate of alcohol disappearance from the blood and the activity of the

microsomal enzyme system, but not that of alcohol dehydrogenase (LIEBER 1970; TOBON 1971).

MISRA et al. (1971) studied the effects of chronic alcohol consumption on alcohol and drug metabolism in alcoholic- and non-alcoholic subjects who were given alcohol for 1 month in a metabolic ward. The rate of disappearance from the blood of alcohol, meprobamate and pentobarbital was significantly accelerated in the alcoholics and this acceleration lasted for a period of several weeks after the experiment had been stopped.

To clarify the mechanism of the increased clearance of drugs in chronic alcoholics, these investigations studied the metabolism of meprobamate in rats, fed for 28 days with adequate diets providing 36% of calories either in the form of alcohol or in the form of carbohydrates.

The half-life of the drugs was almost twice as long in the control- as in the alcohol fed animals. Liver slices and microsomal preparations of the latter showed significant increases in rates of meprobamate metabolism, probably a result of the stimulation of a hepatic NADPH dependent drug metabolizing system. Previous experiments (RUBIN 1968) have also demonstrated that alcohol increases the activity of liver microsomal pentobarbital hydroxylase.

Indeed, the fact that the alcohol can be oxidized by a microsomal system which shares many properties with other microsomal drug-detoxifying enzymes strongly suggests that alcohol is an enzyme inducer, comparable to an enzyme inducing drug like phenobarbital, which interacts with hepatic microsomes.

Summarizing: The accelerated drug clearance by chronic alcohol ingestion helps to explain the tolerance to drugs which is known to develop in alcoholics.

b Interaction alcohol with antiepileptics

A Phenobarbital

Phenobarbital appears to enhance the disappearance of alcohol from the blood resulting in somewhat decreased blood alcohol concentrations (FISCHER 1961; LIEBER 1972; MOULD 1972; MEZY 1974).

MEZY (1974) determined the effects of phenobarbital administration on rates of alcohol disappearance from the blood and on the hepatic activities of the alcohol oxidizing enzymes in 4 male chronic alcohol patients without significant clinical evidence of liver disease. Phenobarbital administration resulted in a significant increase in the rate of alcohol disappearance from the blood. No changes were observed in the activities of either alcohol dehydrogenase or of the NADPH (nicotinamide adenine dinucleotide phosphate) dependent alcohol oxidizing system. On the other hand the urinary excretion of D-glucaric acid, an index of hepatic enzyme induction, was increased. The mechanism for this enhancement remains uncertain. CURRY and SCALES (1973) have studied the phenobarbital alcohol interaction in mice. When phenobarbital was given with alcohol the peak phenobarbital concentration was attained earlier than when it was given alone, but the area under the plasma level curve was not altered, this means that the same amount of phenobarbital was absorbed.

B Phenytoin

Alcohol, when administered chronically, has been demonstrated in man and animals to increase its own metabolism, presumably by stimulation of a microsome system (LIEBER 1968; RUBIN 1968).

Heavy practicing alcoholics were compared with non-drinking or infrequently drinking control subjects with respect to the removal rate of 3 microsomally metabolized drugs from the body (KATER 1969). The drugs employed were intravenous tolbutamide, oral warfarin and phenytoin. The half-life of the drugs in the blood of the alcoholic test subjects was significantly shorter than in the controls of all 3 drugs.

Phenytoin was administered 3 times daily in 100 mg dosages for 3 days and then stopped to determine the disappearance rate. Samples were taken 12, 24, 48, 96 and 120 hours after administration. The mean half-life of 76 control subjects was 23,5 hours and of the 15 alcoholics 16,3 hours, a significant difference.

Theoretically, prolonged excessive alcohol ingestion could result in seizures in an epileptic controlled by a given dose of phenytoin. SCHMIDT (1975) studied the effect of alcohol intake on phenytoin me-

tabolism in volunteers.

Ingestion of alcohol, 1 gram/kg did not influence the phenytoin half-life in 5 volunteers after single intravenous administration of 3 mg/kg phenytoin.

DE LEACY et al. (1979) studied the effect of alcohol use on steady state plasma phenytoin levels in 210 epileptic patients. The results of the study showed alcohol intake not to have a significant effect on plasma phenytoin level.

C Valproic acid

VREE and VAN DER KLEIJN (1977) studied the interaction between valproic acid and alcohol. In dogs and monkeys no interaction was observed unless a certain level of valproic acid was reached.

Above a dose of 90 mg/kg in the dog and 45 mg/kg in the rhesus monkey, the elimination of both compounds was mutually inhibited. Information on this interaction in man is lacking.

As experiments with epileptic patients easily raise ethical and medical objections, a single dose experiment was performed in a volunteer (SCHOBEN 1979). The elimination of valproic acid was monitored on 2 occasions after intake of 600 mg valproic acid. The second time an alcohol blood level was maintained above 0,5 ‰ from 2 to 12 hours after drug intake. Plasma half-lives did not differ nor did the area under the plasma concentration curve. The urinary excretion of valproic acid itself and its glucuronide were also unchanged.

The elimination of alcohol appeared also not to be significantly impaired. A previous single dose of alcohol followed by frequent blood sampling had revealed a maximal metabolic rate of 8 gram per hour for this volunteer. After intake of valproic acid, intake of 10 gram ethanol per hour caused a stable alcohol blood level for about 7 hours.

From these results it was concluded that combination of the usual doses of valproic acid and alcohol is not likely to cause serious interference with elimination in man.

D Carbamazepine

An account was given of the effect of alcohol on changes in visual perception caused by carbamazepine (SCHWEITZER 1970). At blood alcohol concentrations of 1,3 ⁰/00 the visual field was reduced. The decrease in visual field caused by alcohol was almost entirely compensated by taking 200 mg carbamazepine 24 hours previously. Visual activity was not significantly altered by carbamazepine nor by alcohol.

ETZLER et al. (1969) studied the interaction between alcohol and carbamazepine, methaqualon and nitrazepam in animals.

In combination of alcohol with methaqualon or nitrazepam the alcohol effect was stronger, in the combination with carbamazepine it was weaker.

No studies are known on the human being or animals concerning the influence of ethanol on the pharmacokinetics of carbamazepine.

E Diazepam

McLEOD et al. (1977) found that diazepam administered with alcohol produced higher plasma diazepam levels between 7,5 minutes and 8 hours after ingestion than did diazepam administered with water. In that study, however, alcohol was given as the pure compound, thus leading to local intragastric concentrations of alcohol that are much higher than those usually encountered during 'social' ethanol ingestion. These high intragastric concentrations of alcohol may disrupt the 'barrier' function of the gastric mucosa (GORDON et al. 1974; MURRAY et al. 1974) possibly facilitating permeability to drugs.

HAYES et al. (1977) also observed higher diazepam levels between 30 minutes and 4 hours after dosing when diazepam was given with alcohol as opposed to water. Again rather high concentrations of alcohol (50% by volume) were used in this study.

Furthermore, the investigators suspended and/or dissolved powdered diazepam tablets in the alcohol solution before administration, a manoeuvre not relevant to usual clinical circumstances.

LINNOILA et al. (1974) reported no significant difference in diazepam plasma concentration between 30 minutes and 4 hours after dosage when

the drug was taken with water or with pure alcohol.

GREENBLATT et al. (1978) utilized an alcohol cocktail containing low alcohol concentrations (about 10% by volume) typical of those used during social alcohol ingestion. Plasma diazepam concentrations were measured at multiple points in time between 15 minutes and 24 hours after dosage, thus allowing an estimate of the rate and completeness of diazepam absorption.

The absorption tended to be slowed by co-administration of the alcohol cocktail. Peak diazepam concentrations were lower and were reached after the dose. The completeness of diazepam absorption, judged by the area under the 24 hour plasma concentration curve was nearly identical for the 2 conditions.

Alcohol and diazepam are likely to have additive central nervous system depressant activity. Simulated driving investigations in normal volunteers indicate that diazepam and alcohol in combination may have additive or synergistic detrimental effects on driving skills (LINNOILA and HÄKKINEN 1974).

Changes in plasma drug binding may be important since decreases in the degree of drug binding may increase the pharmacologic effect. Further, modified unbound ('free') drug concentration will affect distribution equilibria while drug clearance may be altered (MEHAR et al. 1974).

THIESSEN et al. (1976) studied the plasma protein binding of diazepam in chronic alcoholics; the binding of the diazepam to the plasma proteins was significantly less in the alcoholics.

The resultant increase of free drug in the plasma of alcoholics compared to normal subjects was 46,7%. The increased incidence of drowsiness in chronic alcoholic patients who use diazepam may be due to changes in plasma protein binding.

c Summary

- In case of acute alcohol intoxication there is an inhibition of hepatic microsomal drug metabolizing enzymes. This is reflected in a reduced rate of drug biotransformation which is the basic mechanism of drug sensitivity in acute alcoholism.
- Chronic alcohol ingestion results in accelerated drug clearance from the blood caused, at least partly, by enhanced hepatic microsomal

drug metabolism. This helps to explain the tolerance to alcohol and other drugs which is known to develop in alcoholics.

- Phenobarbital appears to enhance the disappearance of alcohol from the blood. In experiments with animals alcohol absorption was slowed in the presence of phenobarbital whereas alcohol accelerates the phenobarbital absorption.
- Alcoholics have been shown to metabolize phenytoin more rapidly than control subjects. Social alcohol intake does not have a significant effect on plasma phenytoin level.
- In dogs and monkeys the elimination of valproic acid and alcohol above a certain dose was mutually inhibited. From the results in man in a single dose experiment, it was concluded that combination of valproic acid and alcohol is likely to cause serious interference with elimination in man.
- Carbamazepine seems to lower the action of alcohol in some experiments. No studies are known on the influence of alcohol on the pharmacokinetics of carbamazepine.
- Diazepam administered with alcohol produced higher diazepam plasma levels than did diazepam administered with water. In other studies there was no significant difference in diazepam plasma concentration when the drug was taken with water or alcohol whereas in other studies alcohol slowed the diazepam absorption. Alcohol and diazepam are likely to have additive central nervous system depressant activity.

4 Influence of alcohol on the EEG-registration

a Electroencephalographic changes due to use of alcohol

BERGER (1929) demonstrated the feasibility of registering electrical potentials originating in the brain through the intact human skull in various neurologic and pharmacologic conditions, and made records of them.

Electroencephalographic changes during acute alcohol intoxication have been observed by several investigators.

8 Years after BERGER wrote his article on electroencephalographic techniques, GIBBS et al. (1937) made an extensive investigation of the influence of alcohol on the EEG. He and his co-workers found that a

patient in alcoholic coma had high voltage slow delta waves similar to the EEG-pattern of coma from other causes. On recovery the record returned to normal.

During the following years many authors (ENGEL and ROSENBAUM 1945; HADJI-DIMO et al. 1968; PERSON and GUNN 1974) described the EEG-changes following alcohol intoxication.

The opinions on this matter are unanimous.

In lower dosages it has a general stimulating effect expressing itself in a desynchronisation of the EEG leading to an increase of beta activity. In higher dosages it has a depressant action which leads to a slowing of the cerebral activity - decrease of the frequency - and an increase of the amplitude.

b Correlation EEG-changes - blood alcohol concentration

DAVIS et al. (1941), HEDENSTROM and SCHMIDT (1950), HOLMBERG and MARTENS (1955) tried to correlate electroencephalographic changes and the blood alcohol concentrations.

DAVIS et al. (1941) investigated the EEGs of 6 men aged 22 to 25, following the ingestion of alcohol. The blood alcohol was measured and psychometric tests given. Definite clinical intoxication occurred. Blood alcohol levels reached 125-140 $\text{mg}/100$ and at this time the psychometric test results gave the lowest scores. At a relatively low blood alcohol concentration, not above 0,35 $\text{mg}/100$ a decreased amount of 10-13 c/c rhythm was seen. At higher concentrations an increase of 4-8 c/s activity occurred and was associated with decreased muscle tone and impaired co-ordination.

HEDENSTROM (1950) noticed that after a possible activation of the alpha rhythm, expressing itself in an increase of amplitude and quantity of occurrence, slower waves occurred. These low frequency waves could be found with blood alcohol concentrations of 0,90 $\text{mg}/100$, but were definitely there with blood alcohol concentrations of 1,5 $\text{mg}/100$. There was a correlation between blood alcohol concentration and the occurrence of low frequency waves in the absorption phase. This correlation was missing in the post-absorptive phase.

HOLMBERG (1955) administered a standard dose of ethanol to a group of 10 male hospital attendants and to a group of 10 hospitalized male patients diagnosed as alcoholics. During the experiments the alcohol

curves were largely the same in both attendants and patients. The maximums ranged between 1,08 ⁰/00 and 1,96 ⁰/00. EEG-frequencies shifted toward slower ranges in a range of 0,7 and 3,0 cps (average 1,4-1,5 cps) and the amplitudes increased at the same time by about 50 to 100%. There was no statistically significant difference between the two groups. In the alcoholic patients the maximum EEG-changes coincided with maximum blood alcohol concentrations whereas in the attendants the EEG-changes remained on the average 45 minutes after the maximum blood alcohol concentration. This was probably due to drowsiness that followed intoxication in the attendants.

c EEG-changes in the post-alcohol state

NAGY et al. (1973) investigated the EEG-changes occurring under influence of alcohol both in the absorptive and in the post-absorptive phase.

During the period of EEG-examination, hyperventilation and light stimuli of different frequencies were employed. It was established that in accordance with data from the literature a slowing of the cerebral electrical activity and an increase of amplitude ensued, which changed under the influence of hyperventilation and light stimuli according to the individual sensitivity.

Based on their investigatory results they especially warned against the heightened seizure risk reflected in increased EEG-abnormality in the post-alcohol state. They noted that any abnormal photic response not associated with clinical symptoms, disappeared under the influence of alcohol.

However, when several hours after the excretion of alcohol light stimulation was used a general spike-, wave- and poly-spike activity could be registered.

d Genetic control of alcohol action on the central nervous system

PROPPING (1977) made an investigation in order to clarify the genetic contribution to the interindividual variability of alcohol action on the central nervous system in man. 52 Healthy adult male twins, 26 identical and 26 fraternal twins were given 1,2 ml/kg alcohol under standardized conditions. Furthermore, 13 non-twin subjects were re-

peatedly subjected to the same procedure in order to test the intra-individual variability. The EEG was recorded before and 60, 120, 180 and 240 minutes after alcohol intake. The extent of the alcohol effect on the EEG varied considerably between individuals. The EEGs of identical twins proved to react identically to alcohol loading whereas the EEGs of fraternal twins became more dissimilar during the course of the experiment. The low voltage EEG is an EEG with low amplitudes as is commonly found in anxious subjects, is said to be resistant to alcohol. The identical reaction of the brain wave pattern in monozygotic twins cannot be attributed to more similar blood alcohol concentrations; instead this finding is a genetic phenomenon of the central nervous system.

The author proposes the hypothesis that differences in the extent of the alcohol effect on the EEG between individuals might reflect differences in the sensitivity of the ascending reticular activating system (ARAS). This is a region within the reticular formation which normally has a desynchronizing effect on the cortex.

CASPERS (1957-1958) has shown that alcohol diminishes the spontaneous activity of the ARAS in rats.

So with alcohol the degree of synchronization of the EEG will increase which again will lead to an increase of the beta activity in the EEG.

e Influence of alcohol on the evoked response

GROSS (1966) showed that a moderate dose of alcohol reduced substantially the amplitude of the human auditory evoked response. A similar finding in cats has also been reported (NAKAI 1964; DI PERRI et al. 1968). LEWIS et al. (1970) examined the effects of varying doses of alcohol on human visual and somato-sensory evoked response. 9 Subjects, all moderate drinkers, imbibed various amounts of alcohol or a placebo. The alcohol doses were 0,41 gram/kg and 1,23 gram/kg body weight, equivalent to 1 and 3 ounces, respectively for a 160 pound man. After ingestion of 3 ounces of alcohol the amplitude of a number of late waves of both visual and somato-sensory evoked responses recorded from central areas was attenuated significantly. Evoked responses recorded from the occipital area showed no such changes. With some subjects, a hemispheric asymmetry of amplitude, generally noted with recordings from central areas, disappeared after alcohol

ingestion.

In his study TANIELI (1971) came to the same conclusion. He examined the effects of alcohol on the visual, auditory and somato-sensory cortical evoked responses in 14 young people. Here too the amplitude of the evoked responses was reduced after ingestion of alcohol. This effect was marked more at the vertex and in the central regions than in the occipital region. The late components of the evoked responses, which is the main target of the action of alcohol, seem to originate from non-specific thalamo-cortical diffuse pathways (LINDSLEY 1961; TOWE 1965). It is in line with the findings that alcohol has stronger effects upon subcortical than upon cortical structures (DI PERRI 1968).

f Changes in EEG and evoked responses during the alcohol withdrawal period

The occurrence of withdrawal signs and symptoms upon cessation of alcohol ingestion by alcoholics is evidence of physiological dependence.

Excellent descriptions of the alcohol withdrawal syndrome have been reported by ISBELL et al. (1955), VICTOR and ADAMS (1953) and MENDELSON (1964). The various clinical findings fall on a continuum of increasing severity, from the mildest case of tremulousness, sleeplessness and irritability, increasing through hallucinatory states and seizures to the severest type, delirium tremens. It is important to realize that all of these states are characterized by various degrees of hyperexcitability and hyperactivity of the central nervous system. Recovery functions of somato-sensory evoked potentials have been used to measure central nervous system excitability (SHAGASS 1972). This method was that pairs of somato-sensory stimuli were delivered and the effect of varying the time interval between the 2 stimuli was examined. The size of the second response relative to the first response is indicative of the extent to which responsiveness has recovered after a particular time interval has elapsed.

BEGLEITER et al. (1974) studied the changes in brain excitability in human alcoholics during intoxication and withdrawal, using the recovery cycle of somato-sensory evoked potentials as an indicator (method of Shagass 1972).

A recovery function was always determined in the morning, during the 3 days of baseline, 4 days of alcoholization and the 4 days subsequent to withdrawal from alcohol. They observed an increase in central nervous system excitability 10 hours subsequent to the last drink when the blood alcohol level was still elevated. A similar observation has been reported by GOLDSTEIN (1972).

The excitability reached a peak approximately 34 hours after the last drink and does not return to baseline levels until 58 hours subsequent to withdrawal from alcohol.

SALAMY et al. (1980) investigated changes in the amplitude of auditory average evoked responses (AER) in chronic alcohol abusers. The subjects were 11 normal controls and 11 alcoholic in-patients following a period of abstinence.

AERs elicited by speech sounds and tones were obtained from frontal and parietal leads over both hemispheres. Subjects were tested on 2 occasions separated by about 20 days. On the first run the mean amplitude of the alcoholics' AER was smaller than that of the controls, whereas the frontal AERs remained significantly smaller than those of the control subjects. This improvement in the alcoholics AERs suggests the hypothesis that the evoked responses reflect a process of cerebral recuperation from the damaging consequences of alcohol abuse. Such an hypothesis is consistent with recent data from CARLEN et al. (1978) indicating that both cortical shrinkage and functional impairment associated with chronic alcoholism are partially reversible. They measured the cerebral shrinkage reversibility with the help of computerized tomography scans.

The lack of recovery of the alcoholics' frontal responses is in accordance with the hypothesis of TARTER (1975) that alcohol abuse especially leads to frontal damage.

Whenever there is a reduction of the amplitude of the AER due to use of medicines we notice the occurrence of a recovery of the amplitudes both frontal and parietal after withdrawal of the medicaments. In this way it is possible to make a distinction between chronic drug intoxication and atrophy.

From many EEG-studies with alcoholics, made in the fifties, it had already become evident that often a distinctive phenomenon could be noted, in periods of alcohol abstinence. With so called intermittent

photic stimulation - stroboscopy - usually made as a routine matter with an EEG-registration, a very strong reaction was seen, consisting of muscle contractions of neck and body and at the same time the registration of scalp EMG-activity in the EEG-curves (GIOVE 1965). This reaction, known as the photomyoclonic response, is obtainable with an adequate stimulus in 50% of normal subjects during voluntary tensing of facial and scalp muscles. Its occurrence under the conditions of a routine clinical EEG recording generally reflects increased muscle tone which is probably the explanation in the present context (BICKFORD et al. 1952).

VICTOR (1967) found in a detailed study that this photomyoclonic response was most strongly shown during the first and second day after withdrawal of the alcohol and after that it disappeared completely. NAGY et al. (1973) also mentioned the strong sensitiveness for light stimuli in the post-absorptive stage.

For the rest the EEG-registration in the withdrawal period does not show any abnormal activity (KLINGER 1975).

g Summary

In low dosage alcohol has a general stimulating effect which leads to desynchronizing of the EEG causing an increase of the beta activity. In higher dosages it depresses the frequency and increases the amplitude.

In the absorptive stage this slowing of the activity can be signalized whenever the blood alcohol concentration is higher than 0,90 ‰. In the post-absorptive stage the correlation between blood alcohol concentration and EEG-changes is much smaller. The extent of the alcohol effect on the EEG varies enormously between individuals. PROPPING (1977) showed that the EEG-reaction on use of alcohol hardly varied with identical twins, while with fraternal twins there were large individual differences. This indicates a genetic influence on the action of alcohol on the central nervous system.

The amplitudes of the evoked responses, especially of the late components, are reduced under influence of alcohol. This effect is more marked at the vertex and in the central regions than in the occipital region.

In the withdrawal period there is an excitability of the brain that

can be registered both in the evoked responses and on the EEG. In case of photic stimulation there is often a very strong photomyoclonic response. The decreased amplitude of auditory evoked responses in the stage of alcohol use will normalize again in the withdrawal period unless there is an irreversible atrophy. Profuse use of alcohol leads especially to an irreversible frontal cortical atrophy.

5 Relation alcohol use-/abuse and seizures

a Development of drinking habits in the 20th century

Between 1936 and 1940 LENNOX (1941) held an inquiry amongst 1.254 epileptic patients who were 15 years or older to get an insight into their extent of the use of alcohol. For the purpose of securing control data, similar question blanks were filled out by 693 persons, viz. 394 male medical students, 150 female student nurses and a mixed group of 112 male and 92 female non-epileptic hospital patients.

In comparison with the patients the control group did not contain enough women and the general economic status was probably too high. Of the epileptic patients 864 or 69% said they never used alcohol, 330 or 26% stated they used it sometimes and 60 patients or 5% used it frequently. Of the control group 53% was drinker in comparison with 31% of the patients (see table III²).

Table III²: Use of alcohol by patients and controls

Frequency of use	Patients		Control group	
	No.	%	No.	%
Abstainer	864	69	329	47
Infrequent	330	26	339	49
Frequent	60	5	25	4

By order of the Health and Social Department, SYLBING (1978) held an inquiry to get an insight into the drinking habits of the Dutch people from 12 up to 70 years old. The inquiry was not limited to the so called drinking age population (15 years and over) since the authori-

ties also wanted information on the drinking habits of the 12 to 14 year olds.

From this investigation it appeared that drinking in Holland is the norm in our present society. It appeared that 81% of the Dutch people aged between 12-70 years occasionally has a drink. When we limit ourselves to persons of 20 years and over we reach a percentage of 87,5. Of the adult men 93% sometimes has a drink and of the adult women 82% admits to having one now and then. Comparing this study of SYLBING (1978) with an investigation of GADOUREK (1963) the number of male drinkers is increased by 7% and the number of female drinkers by 3%. Drinking habits have especially changed with respect to the circumstances of alcohol use. Formerly the use of alcohol was mainly limited to holidays, but that has changed.

Male respondents of 19 to 29 years have the highest intake but the habit of having a daily drink is the strongest with men of 40 years and over. 53,6% Of the youth (12-19 years) drinks occasionally, the quantity and frequency is very moderate.

The Protestant Christian Faith seems to have a negative influence on the use of alcohol. Members of this church drink less than catholics and non-believers.

Attitudes with regard to the amount of drink have also changed during the recent years. Over 30% of the respondents thinks that male persons may reasonably take more than 6 alcoholic drinks at a party and 22% thinks this amount is admissible for females. GADOUREK obtained percentages of respectively 23 and 16.

In 1975 the average Dutch inhabitant had used the equivalent of 8,8 litre pure alcohol per year. He thus ranks 13 on the list of alcohol consuming countries (PHILIPSEN 1976).

Between 1966 and 1976 there was a rise in the use of alcohol, of 73% for spirits, 115% for beer and 224% for wine.

In Germany alcohol use has increased in the period of 1956 to 1977 from 5,57 litre per inhabitant to 12,25 litre, an increase of 120% (FEUERLEIN 1979).

In Denmark the consumption of alcohol is also continually increasing and in 1976 it had reached the proportion of approximately 10 litres of alcohol per inhabitant annually (PALUDAN 1976).

In 1976 the French had the greatest consumption of alcohol with 16,5

litres annually.

In the Epidemiologisch Preventief Onderzoek Zoetermeer (EPOZ) that was held in the period September 1977-May 1978, questions were asked concerning the alcohol use of respondents. It appeared that at the time of the investigation 91,7% of them used alcohol; of the 1.069 questioned people not suffering from epilepsy 96,1% used alcohol (VALKENBURG 1978).

b Summary

A survey of several literature studies ascertains that there has been a strong increase in the use of alcoholic beverages during the last decade. In the study of LENNOX (1941) 53% of the non-epileptics used alcohol whereas in the study of SYLBING (1978) 87,5% of the Dutch inhabitants over 20 used alcohol.

c Survey of opinions before 1950 concerning interactions between alcohol use and epilepsy

In the 2.000 years during which convulsive seizures have been discussed a confusing variety of opinions about their cause and treatment has been advanced.

Unanimity of opinion, however, has prevailed on one point: namely the harmful effect of alcohol. Even the Romans considered drinking of great quantities of wine as one of the causes of epilepsy and one of the names for epilepsy in Roman days was morbus comitialis (LENNOX 1941; TEMKIN 1971). The Romans attributed the name to the fact that an epileptic attack used to spoil the day of the comitia, the assembly of people.

QUINTUS SEREMUS ref. by ECHEVERRIA (1881) found a high incidence of alcoholic epilepsy and later that century, BRATZ (1899) in a series of 51 alcoholic epileptics noted that 13 of his cases had been seizure free prior to the onset of alcoholism.

In the 19th and early part of the 20th century considerable discussions occurred concerning the effects of the abuse of alcohol as a cause of fits, not only in the alcoholic himself, but in his progeny.

Several authors stated that the intoxication of the parents might injure germ cells of the fetus in a manner that would favour the develop-

ment of seizures in the child. KUFFNER (1927) refers to a study of MARTIN (1910) from which appeared that 1/3 of the children of alcoholic parents suffered from epilepsy.

In his own study KRAEPELIN (1916) comes to percentages of 18-21.

Also the suggestion has been advanced that epilepsy and alcoholism are related genetically. Weight has been given to the finding of frequent alcoholism or epilepsy in the family tree of epileptic or alcoholic patients (MOELI 1885; HARE 1890; LENNOX 1941). KUFFNER (1927) is of the opinion that we may take it as certain that many epileptic patients are liable to abundant use of alcohol.

This relation is denied in a study of LENNOX (1941). Out of 1,254 epileptic patients who were 15 years or over, 26% used alcohol moderately and 5% used it to excess, figures that are no higher than those of a control group.

BOWMAN and JELLINEK (1951) however, come to the conclusion that, at variance with LENNOX's findings, abnormal drinking is found to be greater amongst epileptics than in the general population. In families with a 'psychopathic heredity' there is a high concomitance of alcohol addicts and epileptics. There is an increase of convulsive seizures through use of alcohol and there is some indication that alcohol may precipitate latent epilepsy.

KRAEPELIN (1916) already gave a description of the increased sensitivity to alcohol in case of epilepsy.

GEDDES (1950) reported the results of a questionnaire of 25 patients with epilepsy and concludes that in most cases moderate drinking did not interfere with fairly effective control of seizures by medication.

KUFFNER (1927) and LENNOX (1941) also found that the increased sensitivity to alcohol as is supposed to be the case with most epileptics, occurs only in some people.

KALINOWSKY (1942) discusses the fits which occur on withdrawal of various hypnotic drugs, including alcohol. He described 2 chronic alcoholics, one of them experienced seizures between 15 and 20 hours after cessation of drinking, then 2 more fits in the next 24 hours after which he developed delirium tremens.

In the beginning of this century the term alcohol epilepsy was introduced. It was the idea that generalized attacks occurred under influence of the toxic action of alcohol. Those attacks appeared with

alcohol abuse and thus were especially noted in alcoholics.

d Summary

Throughout the ages alcohol has had the name to have a detrimental influence on epilepsy. By the end of the 19th century and at the beginning of the 20th century many authors advanced the hypothesis that alcohol has an injurious influence on the germ cells or the development of the fetus.

There has never been any well documented study to prove the reliability of this hypothesis. There are conflicting opinions concerning the association of alcoholism with epilepsy.

Several authors did come to the conclusion that with most epileptics limited use of alcohol does not mean an increase of the seizures.

'Alcohol epilepsy' indicates the appearance of attacks due to alcohol abuse.

e Relation alcohol abuse - seizures

A The role of abstinence in the genesis of alcoholic epilepsy

The idea that withdrawal of alcohol in some way is responsible for seizures is hardly new. Statements on this effect date back to many years (BRATZ 1899; MULLER 1910) but have also been made by authorities on epilepsy in the past years (McNAUGHTON 1954; GIOVE and GASTAUT 1965; VICTOR 1967; MEYER 1976).

KALINOWSKY (1942) described 2 alcoholic patients who had an onset of seizures after they had stopped drinking.

VICTOR and ADAMS (1953) described 68 cases of convulsions in which there was a relation between seizures and withdrawal from alcohol, rumfits.

In 54 cases a period of complete abstinence and in 7 other cases a period of partial abstinence had preceeded the onset of seizures. The experimental study of ISBELL et al. (1955) demonstrated more precisely than any previous one the role of withdrawal of alcohol in the precipitation of seizures. 2 Volunteer subjects who drank between 400 and 500 ml of 95% alcohol for periods of 48 and 78 days respectively, developed seizures after the abrupt discontinuance of

the drug. One patient had a generalized convulsion 41 hours after cessation; the other had a series of 7 grand mal convulsions between 12 and 34 hours after withdrawal, after which he developed delirium tremens.

This concept has received strong support from the animal experimental studies of McQUARRIE and FINGL (1958). These authors showed that in mice single doses of alcohol temporarily raised the seizure threshold. Administration of alcohol in high doses for a prolonged period produced a more marked and prolonged drop in the seizure threshold after alcohol was withdrawn.

FREUND (1969) described a withdrawal syndrome in mice following after a severe intoxication during 4 to 5 days.

This syndrome was characterized by over-activity, increased startle and seizures.

VICTOR and BRAUSCH (1967) investigated the temporal relationship between the onset of seizures and cessation of drinking in 162 alcoholic patients (see table III³). It seemed that in almost 50% of the cases the onset of seizures occurred between 13 and 24 hours after the cessation of drinking.

The majority of convulsive attacks (83,3%) occurred between 7 and 36 hours after cessation and over 90% between 7 and 48 hours.

Table III³: Relation of onset of seizures to cessating of drinking

Time of onset of seizures (hours after last drink) (VICTOR and BRAUSCH 1967)

B Metabolic changes

Biochemical changes were found in both blood and liquor after cessation of alcohol. WOLFE and VICTOR (1969) pointed out that there was a relation between hypomagnesemia and rumfits. This hypomagnesemia becomes evident within a few hours after cessation of drinking, is transient in nature and occupies mainly the early stage (8-60 hours) of the withdrawal period.

They found that the extent to which a patient becomes hypomagnesemic during alcohol withdrawal correlates closely with a propensity to spontaneous seizures and sensitivity to photic stimulation and that both are decreased or abolished by the intravenous administration of magnesium sulfate. At the same time alteration in pH represented a respiratory alkalosis, probably based on hyperventilation.

SUTER (1955) also proved in his study that a decreased magnesium level can easily lead to the onset of epileptic seizures, both with animal experiments and in clinical practice.

MEYER et al. (1977) investigated the electrolyte changes after alcohol withdrawal with 70 chronic alcoholics, 45 with convulsions and 25 controls without convulsive seizures.

Investigations were made into the changes of electrolytes and acid base balance in serum or blood and cerebrospinal fluid (CSF).

It was of special interest to note that there was a partial interdependence between magnesium levels in serum and CSF. Thus the serum level only has a limited reliability whenever magnesium depletion is suggested to be responsible for seizure precipitation.

In the seizure group a slightly but significantly lower magnesium potassium and calcium in serum was revealed. In the non-seizure controls there was a similar decrease of serum magnesium, CSF potassium and chloride in serum and CSF, while serum potassium and calcium still remained in the low normal range. In both groups there was a prominent respiratory alkalosis. The authors concluded that not only a deficiency of magnesium is responsible for the precipitation of seizures but a complex of several factors.

C Various kinds of attacks with alcoholism

The attacks occurring in case of alcoholism can be divided as follows

(VICTOR 1967; LINDEBOOM 1978):

- 1 Rumfits or withdrawal seizures in a narrow sense. These comprise about 80% of all epileptic seizures in alcoholics.
- 2 Late abstinence seizures on the 5th or 6th day of a withdrawal period. These seizures occur very seldom.
- 3 Seizures on those alcoholics who already suffered from epilepsy before there was any question of alcohol abuse. This is a very small amount (about 5%) of the total group of seizures.
- 4 Attacks occurring in alcoholics who have suffered from brain damage or where a cerebral process exists (bleeding, tumour etc.).
In fact one can speak of post-traumatic or symptomatic attacks.
This group accounts for 10-15% of the cases.

The seizures from group 1 and 2 are limited to a period of alcohol abstinence. This is not necessarily so in group 3 and 4.

Ad 1: Rumfits or withdrawal seizures

These seizures usually occur in severe alcoholics having a case history of alcohol abuse (mostly periodic) that goes back for years. They occur after a comparative or absolute abstinence and some authors see them as being a part of an acute abstinence syndrome (KALINOWSKY 1958; VICTOR 1970; FEUERLEIN 1972; ADAMS 1977). In those cases in which the syndrome ends in delirium tremens it is always preceded by attacks (whenever they occur). The convulsive episode either of a single seizure or somewhat more often, of a short burst of seizures: 2-4 seizures, as a rule occurring over a period of 6 hours or less. The seizures rarely take the form of status epilepticus.

- In 80-90% of the cases seizures take place between 10 and 36 hours after cessation of alcohol (GIOVE 1965; VICTOR 1967).
- The kind of attack in the group of abstinence seizures is practically always a generalized seizure. A focal attack leads to a strong suspicion that one has to do with a seizure of the type mentioned in group 4.
- Usually the EEG is normal, also when it is made several hours after the attack has taken place. However, on the first and second day of alcohol withdrawal the EEG shows an oversensitiveness for photic stimulation and a photomyoclonic response

that disappears again completely.

- In the first 48 hours after withdrawal of alcohol, biochemical changes consist amongst others of a decreased magnesium level in the blood and liquor and an increased pH, with at the same time a decrease of the carbonic acid level in the blood.

Ad 2: *Late abstinence seizures*

Sometimes one is confronted with a seizure occurring late in the abstinence period for instance the 5th or 6th day.

Usually those patients did not have a delirium and there also were no epileptic seizures in the initial stage of the abstinence period. LINDEBOOM (1978) mentioned from his own clinical experience that the cause of these seizures can also be found in a biochemical disorder, namely an extreme decrease of sodium level in the blood. EARNEST (1976) also mentions hyponatremia as being one of the causes of seizures in alcoholic patients.

Ad 3: *Seizures on those alcoholics who already suffered from epilepsy before they became alcoholic*

With the rumfits it has already been mentioned that biochemical- and EEG-changes take place, through which seizures might be provoked.

In addition alcohol abuse is often accompanied with an insufficient night's rest. So it is understandable that patients who suffer from epilepsy and are alcoholics will easily have a seizure under the influence of the combination of insufficient night's rest, biochemical changes and EEG-sensitivity in the withdrawal period. These seizures also distinguish themselves from rumfits by appearing in an earlier stage of the withdrawal period and the EEG also shows often an irregular build-up. This in sharp contrast to EEG-findings after an abstinence seizure, which is usually normal.

Ad 4: *Post-traumatic or symptomatic seizures in alcoholics*

Seizures caused by brain damage as for instance a tumour or

vascular disease may occur in alcoholics in the same proportion as in the average population.

Chronic alcoholics however, have a relatively greater chance of traumatic brain damage and therefore are a risk group for so called post-traumatic seizures (WESSELY 1973; GIOVE 1965; EARNEST 1976).

The provoking factors, which as explained before, exist during the first abstinence days may therefore also provoke post-traumatic or symptomatic seizures.

In contradistinction to the already mentioned groups (especially 1 and 2) it is conspicuous that the insults of this group often manifest themselves as focal seizures.

It is important to distinguish and if possible to recognize this group of insults while a closer neurologic examination with this group of patients is indicated in order to exclude a cerebral affection. Usually a computerized tomography and an EEG-registration are useful measures to make this distinction, because with these patients there will often be found local abnormalities.

D Frequency of seizures in case of delirium tremens

In the literature there are several studies which investigated the frequency of occurrence of seizures in case of delirium tremens. The percentages in those studies show large differences (table III⁴). With 3.349 patients suffering from delirium tremens we find an average seizure frequency of 20,8%.

Especially in recent studies (MEYER 1976; KOUFEN 1980) high frequencies are mentioned: 51,2% and 60%.

PHILIPP (1976) however, quotes a percentage of occurrence of 9. An explanation of this discrepancy cannot be given.

E Summary

After a period of alcohol abuse, cessation can lead to abstinence symptoms amongst others seizures and delirium tremens.

ISELL (1955) made a very rigorous study to prove this relation.

Most abstinence insults occur between 10 and 36 hours after cessa-

tion of alcohol use.

The frequency of occurrence varies strongly with an average of 20%. In the withdrawal period there is an over-sensitiveness for photic stimulation on the EEG while at the same time metabolic changes occur consisting of hypomagnesemia and respiratory alkalosis.

MEYER et al. (1977) still found other biochemical changes in both liquor and blood, pointing to a complex of biochemical changes that could be responsible for the precipitation of seizures. Seizures occurring in the withdrawal period are generalized.

Whenever they have a focal aspect it is necessary to consider whether it is just a co-incidence or that the seizures are due to brain damage.

Table III^b: Frequency of seizures with delirium tremens

(N = number of patients with delirium)

Author	N	Number of seizures	Frequency of occurrence
Auersperg (1953)	76	7	9,2%
Bischof (1969)	209	23	11,0%
Boeger (1963)	60	16	26,7%
Bonhoeffer (1901)	250	58	23,2%
Bouman (1911)	67	15	22,4%
Bourchalat (1969)	112	22	19,6%
Feuerlein (1972)	112	11	9,8%
Helbig (1962)	244	54	26,2%
Kallwellis (1972)	83	17	20,5%
Kat (1940)	172	59	34,2%
Koufen (1980)	201	103	51,2%
Kryspin-Exner (1966)	200	26	13,0%
Meyer (1976)	92	55	60,0%
Müller (1965)	100	36	36,0%
Philipp (1976)	220	20	9,0%
Pohlisch (1927)	162	25	15,5%
Rosenbaum (1941)	305	29	9,5%
Scheid (1958)	182	19	10,4%
Wassermeyer (1908)	284	70	24,6%
Wessely (1973)	218	30	13,8%
Total	3.349	695	20,8%

f Relation alcohol use - seizures in epileptic patients

On the basis of observations made by KUFFNER (1927) he concludes that the general opinion of alcohol having epileptogenic characteristics, has no scientific support.

LENNOX (1941) thought that whenever seizures occurred with epileptic patients due to alcohol use, they usually were a cause of alcohol abuse and occurred in the abstinence period. So he is inclined to ascribe the seizures to the circumstances that attend or are a cause of alcohol use rather than to alcohol use itself.

From a literature study BERRY (1952) comes to the conclusion that alcohol is a narcotic and thus it should have an anticonvulsive action. He finds neither pharmacological nor experimental evidence of a convulsive action of alcohol and therefore concludes that it still has not been proved that moderate or excessive use of alcohol might provoke epilepsy.

RODIN (1961) administered large quantities of alcohol to 25 epileptic patients. They all showed clinical symptoms of intoxication.

The blood alcohol levels 1 hour after alcohol ingestion came to an average of 1,25 ⁰/100. There was no appreciable influence of alcohol intake on the patients seizures. It could not be demonstrated that alcohol predictably produces seizures in the epileptic patient when he is kept on anticonvulsant medication. On the principle of this study he comes to the conclusion that instead of categorically forbidding all epileptics to use moderate amounts of alcohol it would be advisable to discuss alcohol intake with each patient.

The epileptic patient who drinks alcohol occasionally may continue to do so on a trial basis provided that he does not omit his anti-convulsant medication as a result of drinking.

LUND (1974) thinks that whenever alcohol is used in small quantities it cannot be seen as seizure provoking; prohibition of alcohol is regarded as an unacceptable intervention in personal freedom.

PALUDAN (1976) thinks that epileptic patients who take large quantities of alcohol usually suffer from attacks the day after the night they used alcohol. It may not be that alcohol itself caused the attacks; an additional explanation may be that intoxication causes them to forget the daily dose of medicine so the serum level decreases thus provoking the attacks. There is nothing to prevent people with epilepsy enjoying

a beer with a meal or a few drinks on festive occasions, i.e. 2 or 3 glasses of wine at dinner or a corresponding quantity of beer at lunch.

g Summary

In the literature several opinions are expressed concerning the influence of alcohol on seizure frequency in epileptics. However, there is only one investigation that studied this relation (RODIN 1961) and from this study it became evident that there was no influence of acute alcohol intoxication on epileptic seizures.

6 Advice in textbooks concerning the use of alcohol

It is striking that many textbooks offer dogmatic advice concerning the use of alcohol by people with epilepsy, seemingly without any scientific foundation and with a total disregard for the available published evidence. RODIN (1961) in his study on the effects of acute alcohol intoxication in epilepsy comments that 8 textbooks which he consulted (on neurology, psychiatry and internal medicine) recommended that the use of alcohol should be discouraged or prohibited. Review of 14 further texts showed a lack of consistency but in general the same negative advice (table III⁵).

Table III⁵: Advice with regard to use of alcohol - in textbooks

Author	Professional speciality	Year of publication	Advice	±
Berg v.d.	psychiatry	1966	no alcohol	-
Bergh v.d. a.o.	neurology	1972	no alcohol	-
Biamond	neurology	1972	no alcohol	-
Brain a.o.	neurology	1969	no alcohol	-
Davidson	int. medicine	1965	unclear	±
Epen van	psychiatry	1974	no alcohol	-
Gibbs	neurology	1958	moderate alcohol	+
Kraus	psychiatry	1964	no alcohol	-
Laidlaw a.o.	epileptology	1976	unclear	±
Livingston	neurology	1972	moderate alcohol	+
Mumenthaler	neurology	1977	no alcohol	-
Scheid	neurology	1966	no alcohol	-
Schulte	neurology	1964	no alcohol	-
Scott	psychiatry	1973	no alcohol	-

+ = positive advice - = negative advice ± = unclear advice

The amount of consideration given by the various authors to this question varies considerably.

VAN DE BERGH and FOLKERTS (1972) mention in their chapter on therapy (author LORENTZ DE HAAS) that epilepsy is a disease with several aspects and so no uniform therapy can be given.

During the treatment special attention should be paid to possible factors that may provoke seizures. These might consist of psychological tensions, lightflash stimulation, sleeplessness and alcohol use. They are of the opinion that sometimes abolishing such provocative factors is sufficient to prevent the onset of seizures.

BIEMOND (1972) discusses the relation of alcohol and epilepsy in both the chapter on etiology and therapy. It is claimed that alcohol, though very seldom, may sometimes be the only etiological factor.

It is stated that alcohol can have a provocative action in all forms of epilepsy. Alcohol might also cause genetic damage, through which epilepsy occurs more frequently with children of alcoholics than in normal families. In the chapter on therapy the advice is somewhat confusing, since it is mentioned that drinks with a high percentage of alcohol should be especially avoided.

BRAIN (1969) however, thinks that even small amounts of alcohol have to be avoided in connection with seizure provocation.

DAVIDSON (1965) is more specific in his advice. Beside alcohol use full account should also be taken of shortage of food and lack of sleep, which can also be provocative factors. Excessive alcohol use has to be avoided; however, no definite opinion is given by him with regard to alcohol use with epileptics.

VAN EPEN (1974) especially points to the fact that alcohol decreases the convulsive threshold in epileptics.

During the fifties GIBBS (1958) is the only author saying that alcohol and tobacco when taken in small quantities are not provocative of seizures and do not complicate therapy.

KRAUS (1964) thinks radical alcohol prohibition is necessary because of seizure provocation as well as the possibility of the occurrence of a 'pathological intoxication'. By this is meant an abnormal situation after relatively low alcohol use which would not normally cause intoxication. The patient enters a twilight state lasting for some minutes to some hours. Terror and aggression are conspicuous features leading to

aggressive acts as murder and arson.

SCHULTE (1964) also warns against the occurrence of pathological intoxication and mentions the 'typical New Year seizures' occurring as a result of a combination of lack of sleep and alcohol use.

LAIDLAW and RICHENS (1976) indicate that alcohol might affect the metabolism of anticonvulsants.

It is also difficult to control adequately a patient's anticonvulsants if they are liable to be influenced by excessive and erratic alcohol intake. Furthermore, patients who drink excessively may be unreliable in taking prescribed drugs. There is no reliable evidence that strictly moderate drinking needs to be forbidden to the epileptic patient. Already subject to many restrictions it might be wiser to advise 'a gin and tonic' rather than 'several pints of bitter' in view of the effects of hydration.

VAN DEN BERG (1966), MUMENTHALER (1977), SCHEID (1966) and SCOTT (1973) also prohibit alcohol intake without giving clear reasons.

LIVINGSTON (1972) is the only author who bases his advice upon a practical experience of years. Use of alcoholic beverages is rarely a cause of seizures. His experience is that alcohol related attacks almost always occur in combination with excessive alcohol intake and that they occur during the acute stage of alcohol intake or afterwards.

He has not encountered evidence that epileptic patients are more prone to alcohol convulsions than other people. Attention is directed to the fact that this experience is based upon a large number of treated teenagers, and at least 5.000 grown up patients. Consequently he states that taking small quantities of alcohol does not adversely affect an epileptic disorder.

a Summary

Most textbooks forbid the use of alcohol with epileptic patients without, however, any reference to the literature on which they base their pronouncements. Also the reasons cited for prohibiting alcohol are very varied. The advice of LIVINGSTON (1972) is the only one that is based upon a practical experience of years. His experience is based upon a large number of treated teenagers, and at least 5.000 grown up patients. He states that taking small quantities of alcohol does not adversely affect an epileptic disorder.

1 Introduction

In this chapter the aims of the research are formulated. Also the admission and exclusion criteria are discussed as well as the reason why a clinical setting was required.

The ethical committee supervised the entire investigation in an advisory role. The composition of this committee is described as well as the working procedure and how they were informed on the results of the investigation.

The research was carried out double blind and in this chapter it is explained how this was done. The plan of the investigation and the examinations during the various periods are mentioned in detail.

Finally several methods are described of chemical blood examination, blood level and alcohol concentration determination and EEG-investigation.

2 Reason of the study

Before a decision can be made what advice to give it is necessary to determine the consequences of the social use of alcohol in epilepsy. From personal experience of out-patient treatment of people with epilepsy it seemed that abolishing the absolute prohibition of use of alcohol did not influence the frequency of the seizures.

However, in most handbooks alcohol intake is prohibited without giving data from literature.

Therefore the present research was undertaken.

3 Questions which the study addressed

1 Does social alcohol intake, twice a week, of 1 to 3 glasses of alcohol within a time of 2 hours influence seizure incidence?

The period during which social alcohol intake took place was 16 weeks.

2 What is the effect of alcohol intake on the bloodlevels of anti-epileptics?

3 When clinically there is no change in seizure frequency, are there any indications that a change in the amount of epileptic EEG-activity is caused by social use of alcohol?

- 4 What is in general the attitude of Dutch neurologists with regard to alcohol intake by epileptics?
- 5 What is the attitude of the attending specialists in various other countries with regard to alcohol intake by epileptics?

4 Conditions for participation in the study

The persons taking part in the research had to fulfil the following criteria:

a They were all in-patients of the epilepsy centre Kempenhaeghe in Heeze. The clinical setting was necessary to ensure that:

- The quota of alcohol would not be exceeded.
- The number of seizures would be registered correctly.
- The intake of the medication was reliable.

A polyclinic setting would also give practical difficulties whenever blood samples had to be taken for chemical blood tests, alcohol concentrations and determinations of serum levels of antiepileptic drugs.

b The diagnosis of epilepsy had to be certain.

The diagnosis confirmed during the stay in the hospital was supported by:

- Careful observation of the seizures by experienced observers.
During the seizures attention was paid to whether or not the attacks had a symmetrical start, the level of consciousness, the pupil- and cornea reflex, change of complexion etc., meanwhile attention was also paid to the course of the post-ictal condition.
- The EEG: Epileptic activity had to have been registered in one or more EEGs, either spontaneous or occurring after provocation.
- Seizures based on cardiovascular causes were excluded, also seizures based on a disturbance in carbohydrate metabolism.

c After explanation of the purpose and the plan of the investigation, the patients participated of their own free will and had to give written consent. During the information of the plan one of the members of an ethical committee was present as an observer to convince himself that the patient understood what the research implied. Parents and

relatives were also asked for their permission to let the experimental person take part in the investigation.

d Whenever there existed a functional disorder of the liver or the kidneys this would be a contra-indication for participation in the research. It did not seem justified and ethical to give alcohol to a patient with a functional disorder of the liver, while with a functional disorder of the kidney the course of excretion was unpredictable.

e Age between 17 and 50 years. This choice of age limit was rather arbitrary.

From practical considerations younger people were not chosen, since they were in childrens wards where ages varied from 10 till 17 years. Persons of 15 years and younger would absolutely have to be excluded from the investigation.

Selecting volunteers from these wards would have meant that from each ward some persons could take part in the investigation while others had to be excluded considering their age. This might have led to disagreements in the ward which again could have its influence on the frequency of the epileptic seizures.

Older patients often are hospitalized for years already, which does not promote the flexibility in acting and thinking.

For many years already they had been subject to the existing rule of alcohol prohibition for epileptic patients so that it was to be expected that there would be few volunteers in the age category above 50 years.

f There should have been no or very incidental use of alcohol in the past, since otherwise the effect of alcohol is difficult to measure.

g According to other members of the supporting team, namely: psychologist, social worker and observers, there should be no contra-indications for participation in the investigation.

5 Advisory and ethical committee

A commission was formed comprising both a number of experts, who were not connected to our centre, and a number of staff assistants of our institute. The last group was better informed on the internal structures and could, by working in the field, signalize possible occurring problems faster.

On an average of once per 2 months the investigator reported to this committee on his findings and results. He discussed various problems with them, like e.g. the plan of the investigation, who had to be informed of the research etc. For more detailed description see later in this chapter.

The interchange of ideas during the meeting was recorded on a tape-recorder, of which afterwards a report was typed.

In this committee 5 non-resident members took part. The chairman of the committee was a neurologist. Other members were:

a psychiatrist,

a family doctor,

a psychologist,

the chairman of the parents association of Kempenhaeghe who was also a physician.

The resident members were:

a neurophysiologist,

a psychologist,

a social worker,

2 attendants, head of respectively an intake- and a rehabilitation ward.

The following subjects were discussed during the meeting of the ethical committee:

a To what extent can initiating the use of alcohol give risk to addiction. Of course no specific predictions can be made on this matter and theoretically the risk can be present that after the investigation 1 or 2 test subjects might start to use alcohol more than is normal. The last is never to be excluded with a 100% certainty.

One of the factors why alcohol can be addictive, is that people feel themselves more comfortable when using alcohol.

b Is it possible to predict, during the investigation, to what extent persons who start using alcohol will behave differently than persons

who do not use alcohol?

Probably not. The adolescent who has started with his first alcoholic drink showed often a somewhat extrovert behaviour that is induced more by the atmosphere of the party than due to alcohol use.

- c The psychologist underlined once more that it is of great importance, whenever this seems to be admissible for medical reasons, to reduce the stigma of 'being different' (not using alcohol).

6 Deliberations on the plan of investigation with outsiders

- a Inspection Medical Health department:

The provincial inspector was informed on the plan of the investigation. People who would take part in the investigation, should be able to appreciate the consequences of their decision and so of course several mentally retarded people were excluded.

In his opinion it was necessary that there was an ethical committee that looked through the plan of investigation very thoroughly.

- b Contact Scientific Committee Koninklijke Nederlandse Maatschappij voor Geneeskunde - district Eindhoven:

With the secretary of this committee there was a detailed exchange of views on the plan of investigation. It appeared to him as being very sensible. He once more mentioned, that whenever the patients wanted to co-operate to the investigation they also would have to confirm this in writing.

- c Contact with the Control Institute General Health Insurance:

The medical practitioner of the Control Institute was informed of the plan.

7 Deliberations on and judgment of the investigation

- a At first it was considered to administer beer versus non-alcoholic beer. However, there is no such thing as non-alcoholic beer. The so called non-alcoholic beer contains 0,5% alcohol.

- b Social use of alcohol.

This term cannot be correlated with higher or lower dosages. This is the appreciation the outside world gives to the use of a certain amount of alcohol.

Supposing that alcohol addiction develops in 4 stadia, during the

first 2 stadia, with a possible duration of 15 years, the outside world does not notice anything of the antisocial behaviour.

The antisocial aspects are not merely determined by the amount, but especially by the preoccupation with the alcoholic drinks e.g. drinking at times others do not, creating secret hiding places, drinking secretly etc.

After ample discussion it was finally decided to define the use of alcohol in this investigation as the use of 1 to 3 glasses a day drinking in 2 hours in the evening.

c It is useful to carry out a dose response experiment.

At the preliminary stage this idea had our full attention.

It would have to be an experiment; some people would get alcohol in an increasing dose, limited to a certain maximum and in the course of which EEG registration would be made periodically during the alcohol period and in the withdrawal period. This to verify the hypothesis that alcohol causes more seizures in an unknown dosage.

The opinions on this subject were rather divided also because of the ethical aspects.

By contacts with Dr. MOUSSALLI, neurophysiologist in Créteil, France, we were informed on the publication of RODIN (1961) (see chapter III) so the plan of this investigation was no longer necessary.

RODIN administered large amounts of alcohol to 25 epileptic patients. All patients showed clinical symptoms of intoxication. However, no significant influence of the use of alcohol on the attacks could be shown.

d Before the patients took part in the investigation detailed information on several aspects of their illness was given to the members of the committee. They also got an impression of the character and seriousness of the epilepsy, mental functioning, seriousness of the brain damage, medication etc.

e Information on observation during the investigation.

2 Experienced observers were on duty on the evenings that drinks, with or without alcohol, were used. They registered accurately how many glasses were taken.

A note was also made whenever behaviour was altered. In some patients 'intoxicated behaviour' was noticed in a period in which no alcohol was used.

Figure IV¹: Plan of investigation

Periods of investigation	Time weeks	Medication	EEG	Investigations				Seizure registration	Beverage use a week with alc. without alc.
				Blood levels a.e. drugs 8.00-22.00	Liver function 8.00-22.00	Kidney function 8.00-22.00	Alcohol 0/00		
Basic period PI	22								
Preliminary stage PII	6		EEG	Blood levels Blood levels Blood levels	Liver function Liver function Liver function	Kidney function Kidney function Kidney function
Alcohol stage PIII	16		EEG	Blood levels Blood levels Blood levels Blood levels Blood levels	Liver function Liver function Liver function Liver function Liver function	Kidney function Kidney function Kidney function Kidney function Kidney function	0/00 0/00 0/00 0/00 0/00
Final stage PIV	5		EEG	Blood levels	Liver function	Kidney function

The observers were not informed when during the investigation the switch from non-alcoholic drinks to alcoholic drinks was made (see plan, figure IV¹).

f Information on the interim results of the investigation.

To the members of the committee surveys were given on findings in the several stages, such as:

- 1 The course of the seizure frequency.
- 2 Information on findings during the neurophysiological investigation.
- 3 Results of laboratory examination, alcohol level determinations, blood level findings, as well as the results of chemical blood tests.
- 4 Information on the amount of alcohol used.
- 5 Remarks on the reported changes in behaviour.

The interim findings were studied thoroughly and if necessary discussed.

This review does not cover all subjects discussed.

However, it does give some insight in the way the committee carried out its task. For that reason one might see it besides being a committee for judgment of ethical aspects also as a brain trust with whom the investigator exchanged ideas on the scientific plan of the investigation.

8 Plan of investigation

a General information

The investigation was carried out double blind and it was arranged that the group that used alcohol was completely comparable with the group that did not use alcohol.

Attention was paid to the items: age, sex, type of epilepsy, IQ, medication and the seriousness of the brain damage (see chapter V). During the investigation alcoholic drinks were provided in the evening between 20.00 and 22.00 o'clock, twice a week.

For this purpose a combination of orangeade with or without vodka was used. This was a result of an investigation whereby the combination coca-cola, tonic, orange juice and orangeade with and without alcohol was given to 10 healthy volunteers. In 80-90% the recognition of vodka in coca-cola, tonic or orange juice did not seem to present any

difficulty. However, the combinations of orangeade with or without vodka were indistinguishable. The volunteers were nevertheless asked to make an attempt to indicate which glass did or did not contain alcohol. In 40% the score was correct, in 60% incorrect. Vodka was also chosen because it does not have a smell which could be recognized by the observers.

At the beginning of the experiment the head of the catering department decided which patients were to use orangeade bottles with seven-up stoppers and which ones orangeade bottles with cola stoppers. Once a patient was assigned e.g. a bottle with seven-up stopper, this was maintained throughout the whole experiment. These stoppers were the code by means of which the head of the catering department knew which ones were the vodka containing bottles (in fact those with cola stoppers).

As the alcohol could not be tasted nor smelled, neither by participants nor nursing staff, it was undetectable.

During the first 6 weeks of beverage intake none of the bottles contained alcohol. This period served to eliminate imaginary side-effects and to allow the participants to become used to their code. The fact that this period was free of alcohol was not known to participants or nursing staff. Thus it sometimes happened that in this first period some participants thought they had to show a change in behaviour due to the alcohol they supposed themselves to be taking. Some patients vomitted, some walked unsteadily.

Later on, the switch from the preliminary stage (PII) to the alcohol stage (PIII) went smoothly.

A system of some bottles with seven-up stoppers and some bottles with cola stoppers with alcohol as well was not used because of a greater risk of mistakes, especially as the locations of patients changed rather often during the experiment.

Not until the experiment was finished was the code broken.

The maximum number of glasses that was allowed to use in the evening was 3.

The amount of vodka in the glass was comparable with the alcohol content of a glass of beer, 9,85 gram alcohol.

During the investigation it was not permissible to change medication.

When this was necessary for clinical reasons, the patient was excluded from further participation.

The investigation was to be divided into 4 stages (figure IV¹):

- A Basic period - 22 weeks PI
- B Preliminary stage - 6 weeks PII
- C Alcohol stage - 16 weeks PIII
- D Final stage - 5 weeks PIV

A The basic period of 22 weeks

- This was the stage of about 5 months preliminary to participation in the investigation, in which medication was held constant.
- In this way an insight could be obtained in the course of the seizure frequency under unchanged medical conditions.
- The seizure frequency in this period was compared with that in the alcohol stage.

B The preliminary stage of 6 weeks

- Twice a week drinks (without vodka) were given to the participants. The observers and participants were not informed how long this stage would last.
- The patient had his own bottle code with seven-up or cola stopper which he retained during the rest of the investigation.
- The following investigations were performed:
 - Comprehensive determination of liver- and kidney functions.
 - Determination of blood levels of antiepileptics, urea concentration and enzyme functions of the liver, at 22.00 p.m. and 0.800 a.m., *3 times in this stage.*
 - Routine EEG-registration, once.
 - Observation of behaviour and notes on possible altered behaviour.
 - Seizure frequency registration, medication unchanged.

C The alcohol stage of 16 weeks

- Twice a week drinks with or without vodka were given to the participants.
- Determination blood levels antiepileptic drugs, urea concentra-

tion and enzyme functions of the liver at 22.00 p.m. and 08.00 a.m. *5 times in this stage.*

- Determination alcohol concentration at 22.00 p.m., 5 times.
- 2 Times EEG-registration the morning after the use of alcohol.
- Observation of behaviour and annotation of behavioural changes.
- Seizure frequency registration, medication unchanged.

D The final stage of 5 weeks

- Twice a week drinks without alcohol.
- Determination of blood levels of antiepileptic drugs, urea concentration and liver enzyme function at 22.00 p.m. and 08.00 a.m., once in this stage.
- 1 EEG-registration in the morning after the use of beverage.
- Observation of behaviour and recording of different behaviour.
- Seizure frequency registration, medication unchanged.

9 Techniques of blood level examination

The quantitative determination of phenobarbital, phenytoin, carbamazepine and primidone was performed according to CRAMERS et al. (1976) and DRIESSEN et al. (1974) by gas liquid chromatography.

Prior to the gaschromatography determination extraction of the serum sample was performed.

100 μ l Of the sample was mixed with 10 μ l ethylacetate containing 1 μ g cyheptamide (internal standard). Subsequently 3 mg digitonine powder and 25 μ l saturated ammonium sulphate solution in water was added.

The mixture was heated at 50° C for 5 minutes. The mixture was extracted 3 times with 1,5 ml diethyl ether. The combined ether fractions were evaporated to dryness and redissolved in 100 μ l ethylacetate containing 2 μ g tetracosanoic acid methyl ester. Finally 1 μ l of this mixture was transferred to the injection system (solid injection).

Gaschromatography was partly performed on SCOT columns and partly on micro packed columns. The chromatography conditions are presented in the next table.

	<u>SCOT</u>	<u>Micro packed</u>
Column dimensions	15 m x 0,4 mm	1,50 m x 2 mm
Temperature:		
Injection	270° C	240° C
Columns	210° C	225° C
Detector	300° C	270° C
Stationary stage	5% OV 225	1,2% OV 225 - 1% OV 17
Packing material	Cab-O-Sill	Gaschrom. Q

The quantitative determination of valproic acid was performed by gas-chromatography according to the method of DIJKHUIS and VERVLOET (1974). 200 µl Of serum or aqueous standard solution was pipetted into a 2,5 ml glass tube, 50 ml of an internal standard (cyclohexane carbonic acid) was added to the mixture and stirred on a Vortex mixer.

500 µl Tetrachloromethane was added simultaneously with 50 µl of a 10% perchloric acid solution in water. The mixture was stirred for at least 20 seconds and centrifuged. The aqueous layer was discarded by suction and 5 µl of the organic layer was brought into the injection system. Gaschromatography was performed on a column system with a length of 50 cm and internal diameter of 1,1 mm. The column was filled with 5% FFAP Chromosorb WHP (80-100 mesh).

The process temperatures were: injection part 160° C, column 150° C, detection system 175° C.

10 Alcohol determination

Principle

Ethanol was determined according to the method of BUCHER and REDETZKI (1951). Ethanol is dehydrogenated enzymatically by alcohol dehydrogenase in the presence of the co-enzyme NAD (nicotinamide adenine dinucleotide). NAD is reduced to NADH, the increase of which is measured by spectrophotometry at 340 nm.

Materials and methods

All materials used are of pure analytical grade and are obtained from

Boehringer Mannheim. Reagents used are:

- 1 The buffer contains a mixture of pyrophosphate (75 mmol/l), semicarbazide (75 mmol) and glycine (21 mmol/l).
- 2 The NAD solution in water has an initial concentration of 24 mmol/l.
- 3 The enzyme solution of alcohol dehydrogenase (ADH) contains more than 8.000 U/ml ADH.
- 4 Perchloric acid with a concentration of 0,33 mmol/l.
- 5 Stock solution of ethanol 10 gram/l in water.

All reagents are prepared directly before use.

Apparatus: Spectrophotometry was performed in a Pye-Unicam model SP 1800

Procedure

The sample was obtained by venous puncture using a vacuum system.

500 μ l Of the whole blood sample is directly transferred to 4,0 ml ice cold perchloric acid in a glass tube. Adequate standards containing 20-50-100-200 mg/l are treated in the same way as the blood samples. The tubes are stoppered, mixed and centrifuged during 5 minutes at 3000 RPM.

The supernatant is transferred to another glass tube and can be stored for a maximum period of 24 hours at 4° C.

500 μ l Of the supernatant (blood samples as well as standard samples) is pipetted into 4,80 ml of the buffer solution.

To each tube 100 μ l of the NAD solution is added. All tubes are mixed thoroughly and are incubated in a waterbath of 37° C.

When temperature is constant within 0,05° C, 20 μ l of the ADH solution is added to each tube. After approximately 25 minutes the reaction is stopped and the extinction of the reaction mixture at 340 nm is determined. In order to be informed on the blank value the whole procedure is performed simultaneously with a reaction mixture not containing ethanol. Instead of this 500 μ l perchloric acid is used to obtain the same reaction volume.

11 Chemical blood examination

- Alanine aminotransferase (ALT, SGPT) was determined according to the method of the Dutch normalization institute (NEN 2419).

The reaction mechanism is:

The decrease of the NADH concentration results in a decrease of extinction at 340 nm and is a measure for the ALT activity in the serum.

- Aspartate aminotransferase (AST, SGOT) was determined with the NEN 2418 method of the Dutch normalization institute.

Reaction mechanism:

The decrease of extinction at 340 nm, due to a decrease of NADH is a measure of the AST activity in the serum.

γ -Glutamylferase (γ -GT) activity was measured according to the method of SZASZ (1969) with the modification of PERSIJN et al. (1976).

The method is based upon the hydrolysis of the substrate L- γ -glutamyl-3-carboxy-4-nitranilide producing the chromogen 3-carboxy-4-nitroaniline which can be measured at 405 nm.

- Alkaline phosphatase (ALP, orthophosphoric mono ester phosphohydrolase, alkaline optimum) was determined according to the method of the Dutch normalization institute (NEN 2409) using p-nitrophenylphosphate as substrate and aminopropanol buffer (pH = 10,6). The increase of extinction at 400 nm, due to the liberation of nitrophenol, is a measure for the phosphatase activity of the serum.
- Urea was determined using the method of the Dutch normalization institute (NEN 2410). With the aid of the enzyme urease urea is transformed into ammonium carbonate. Using disodiumpentacyanonitrosylferrate as a catalyst the NH^+ forms with phenol and

hypochlorite the blue coloured indophenol.

- Creatinine was determined with the Jaffé reaction after isolation of the creatinine with Fuller's earth.

The orange-yellow colour produced with alkaline picrate is a measure of the creatinine concentration of the serum.

12 EEG-examination

In order to control the effect of alcohol on the EEG 4 EEGs were made from a number of patients.

1 Was recorded during the preliminary period, 2 during the period of alcohol intake and 1 during the final period.

These EEGs were made both from patients using alcohol and from patients belonging to the control group. These recordings were made with a 16 channel apparatus and the routine procedure of the laboratory was used, 5 minutes hyperventilation and a period of stroboscopy were included. Each of the 4 EEGs was made on the same hour of the day in order to prevent as much as possible the occurrence of variations due to differences in physiological state during the day.

The EEGs were inspected visually by a skilled electroencephalographer. This part of the experiment also had a double blind set up: neither the technician nor the electroencephalographer knew whether or not the patient belonged to the alcohol group or to the control group.

Further: When reading and scoring the EEGs the electroencephalographer did not know the sequence of the EEGs.

From the EEGs the following items were scored and compared to each other according to a 4-point scale:

- a frequency of the alpha rhythm
- b frequency of the beta rhythm
- c frequency of the theta rhythm
- d the amount of alpha rhythm
- e the amount of beta rhythm
- f the amount of theta rhythm
- g the reaction on hyperventilation
- h the reaction on stroboscopy
- i the amount of epileptic activity

With respect to the items a, b and c the following procedure was followed:

When there happened to be a frequency band the average was scored.

In comparing the 4 EEGs the lowest value was scored as 0 and for the other 3 EEGs 1 point was added for each $\frac{1}{2}$ cycle/second.

For the other items a regular 4-point scale was used, 1 being the lowest value and 4 the highest.

When in an EEG there was no activity of a frequency band such as beta or delta rhythm it was not scored. When in the other 3 EEGs the frequency band was present the maximum reached score in such a person was then 3, 1 for the lowest amount, 2 for the amount that occurred and 3 for the highest amount.

Score example of the 4 EEGs in one patient concerning delta activity:

1 - 3 2 1 EEG without delta activity

When there was the same amount of activity in 2 EEGs they got the same score and the maximum reached score was also 3.

Score example of the 4 EEGs concerning epileptic activity:

1 3 2 1 2 EEGs with the same amount of epileptic activity

- 1 2 - 2 EEGs without epileptic activity

1 3 4 2 in 4 EEGs there is a different amount of epileptic activity

CHAPTER V: DESCRIPTION OF THE INVESTIGATED GROUP

1 Introduction

In this chapter the selection method is described. Also the several types of epilepsy are once more accurately defined.

After that the grounds on which one is assigned to the category of brain damage are mentioned.

A description is given of the composition of the investigated group and also how the control- and alcohol group are divided as for age, sex, type of epilepsy and if any seriousness of brain damage and medication. Finally a statistical comparison was made between the 2 groups concerning the above mentioned items.

2 Selection method

Concerning the selection of persons taking part in the experiments see the conditions for participation mentioned in chapter IV.

All the persons taking part in the experiments were suffering from epilepsy. The diagnosis epilepsy was based on the clinical picture as well as on EEG-findings.

The experiment covered a period of 2 years. In the first year 22 persons took part, divided in 2 groups of 11.

The head of the catering department was asked to allocate the patients to an alcohol using group and a control group and divulge this information only after this study was finished.

When afterwards the results of this experiment were studied no effects due to the use of alcohol could be found.

32 Patients took part in the second part of the experiment.

In the light of the results from the first year it was decided to choose 3 participants in a control group against 5 in an alcohol using group. The 32 persons were numbered and labelled according to age, sex, type of epilepsy, drug and degree of brain damage by an independent colleague not involved in this study.

Next the experiment leader chose, at random, 3 numbers for the control group and 5 numbers for the alcohol using group until all patients were allocated. The groups were tested to see if significant differences in the various items could be found. The system of coded bottles was the

same as described before. Because the patients lived in different wards it was not possible to find out which type of bottles was distributed most.

In each group there was, during the experiment, 1 drop-out due to transfer to a hospital elsewhere.

3 Classification type of epilepsy

The classification of the 'Proposal for an International Classification of the Epilepsy' was used (GASTAUT 1969):

1 Generalized epilepsies

a Primary generalized epilepsies

b Secondary generalized epilepsies

2 Partial epilepsies

Primary generalized epilepsies

Seizures are generalized from the start and can consist of tonic-clonic seizures, absences and massive bilateral epileptic myoclonus. The interictal EEG has a normal background activity, upon which brief paroxysms of generalized spike-and-wave complexes are superimposed. It is often easier to register these paroxysms with children and adolescents than it is with adults. There is a frequent onset in children and adolescents. At neurological examination no abnormalities are found and intelligence is usually normal. There is a good response to anticonvulsants.

Secondary generalized epilepsies

The seizures can be generalized from the start or secondarily generalized. When seizures are secondarily generalized the focal onset is not apparent.

In the EEG-registration bilateral and relatively synchronous and symmetric epileptic discharges occur: pseudo rhythmic spike-and-wave complexes (about 2 c/s), isolated slow spike-and-wave complexes and rhythmic polyspike-wave complexes.

The interictal EEG usually has a slow background rhythm upon which the slow spike-and-wave discharges are superimposed.

Very often the onset is in childhood, although GASTAUT (1979) also mentions onset in grown-ups. Often neurological disorders are found and the patient is usually retarded.

In this type of epilepsy the patient has usually diffuse brain damage. The response to anticonvulsants is poor.

Partial epilepsies

Partial seizures whose symptoms take on different forms according to the functions of the part of the brain where the discharges occur.

The interictal EEG usually has a normal background rhythm upon which interictal paroxysms of spikes and intermittent spike-and-wave complexes are superimposed, localized above the epileptic focus.

The onset can occur in all ages. Sometimes there are neurological disorders, related to the site of the epileptic focus.

There is a fairly good response to the antiepileptic drugs.

4 Degree of brain damage

All patients taking part in the experiments were long-stay patients of the epilepsy centre Kempenhaeghe. This gives a selection of seriousness and type of the epilepsy, for often these patients suffer from therapy resistant epilepsies since the more benign types of epilepsy are not treated in special centres.

Patients who suffer from a therapy resistant epilepsy frequently have focal or diffuse brain damage, of which the seriousness is not so easy to diagnose.

Yet a classification has been made in seriousness of brain damage, based on anamnestic facts, neurological- and EEG-findings.

If available, also PEG-findings or CT-scans were included.

The following classification was made:

Category I

History	: no evident lesions of the brain
Neurological examination:	no anomalies
EEG	: no hemispherical asymmetry, normal or slowed background rhythm
PEG/CT	: normal

Category II

History	: onset of seizures few days post-parturition
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onset of seizures just after meningitis or encephalitis

Neurological examination: no anomalies or reflex asymmetry.

EEG : slowed background rhythm, possibility of asymmetry of left and right hemispheres

PEG/CT : focal or diffuse dilated ventricular system

Category III

History : onset of epilepsy after an encephalitis

Neurological examination: hemiparesis

EEG : asymmetry of left and right hemispheres

PEG/CT : dilated ventricular system, focal or diffuse

5 Description of the alcohol group

This group consisted of 29 persons, 20 male of various ages from 17-45 years, average age 27,7 years, s.d. $\pm$ 7,2, and 9 female of various ages from 18-41 years, average age 29 years, s.d. $\pm$ 8,7.

For distribution of sex see table V¹ and for distribution of age see table V².

Table V¹: Distribution of sex in both groups

	Women	Men	Total
Alcohol group	9	20	29
Control group	10	13	23
Total group	19	33	52

Table V²: Age distribution of the population

	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	Total
Alcohol group	4 (14%)	7 (24%)	6 (21%)	7 (24%)	2 (7%)	2 (7%)	1 (3%)	29 (56%)
Control group	1 (4%)	3 (13%)	6 (26%)	5 (22%)	4 (17%)	3 (13%)	1 (4%)	23 (44%)
Total group	5 (10%)	10 (19%)	12 (23%)	12 (23%)	6 (12%)	5 (10%)	2 (4%)	52 (100%)

With these 29 persons the epilepsy was classified as follows (table V³):

- 1 Primary generalized epilepsy
- 14 Secondary generalized epilepsy
- 14 Partial epilepsy

Table V³: Type of epilepsy occurring in both groups

	Primary generalized epilepsy	Secondary generalized epilepsy	Partial epilepsy	Total
Alcohol group	1 (3%)	14 (48%)	14 (48%)	29 (56%)
Control group	1 (4%)	12 (52%)	10 (44%)	23 (44%)
Total group	2 (4%)	26 (50%)	24 (46%)	52 (100%)

The distribution of seriousness of brain damage (table V⁴):

- 11 Persons category I
- 16 Persons category II
- 2 Persons category III

Table V⁴: Distribution seriousness of brain damage

	Seriousness of brain damage			
	Category I	Category II	Category III	Total
Alcohol group	11 (38%)	16 (55%)	2 (7%)	29 (56%)
Control group	10 (43%)	10 (43%)	3 (13%)	23 (44%)
Total group	21 (40%)	26 (50%)	5 (10%)	52 (100%)

6 Description of the control group

This group consisted of 23 persons: 13 male of various ages from 18-41 years, average age 28,8 years, s.d. $\pm$ 6,4, and 10 female of various ages from 21-46 years, average age 35 years, s.d. $\pm$ 7,9.

(For the distribution of sex see table V¹ and for distribution of age see table V².)

With these 23 persons the epilepsy was classified as follows (table V³):

- 1 Primary generalized epilepsy
- 12 Secondary generalized epilepsy
- 10 Partial epilepsy

The distribution in seriousness of brain damage (table V⁴):

- 10 Persons category I
- 10 Persons category II
- 3 Persons category III

7 Medication

Control group: average use per patient: 2,74 medicaments.

Alcohol group: average use per patient: 2,79 medicaments.

Table V⁵ gives the distribution of medication in both groups.

Table V⁵: Distribution of medication in both groups

Generic name of the antiepileptic drug	Alcohol group n = 29 number %		Control group n = 23 number %	
Carbamazepine	21	72	18	78
Phenobarbital	20	69	17	74
Phenytoin	17	59	14	61
Valproic acid	10	34	8	35
Primidone	4	14	1	4
Clonazepam	3	10	1	4
Ethosuximide	5	17	3	13
Sulthiam	1	3	1	4

8 Comparisons between control group and alcohol group

The 2 groups were compared statistically with respect to age, sex, type of epilepsy, medication and seriousness of brain damage.

Table V⁶ shows that there are no significant differences between both groups.

Table V⁶: Deviations between control group and alcohol group

Age	chi-square = 3,47	
Sex	chi-square = 0,85	
Type of epilepsy	primary generalized	} chi-square = 0,14
	secondary generalized	
	partial	
Medication	phenobarbital/no phenobarbital	chi-square = 0,15
	phenytoin/no phenytoin	chi-square = 0,00
	carbamazepine/no carbamazepine	chi-square = 0,24
	valproic acid/no valproic acid	chi-square = 0,00
	primidone/no primidone	chi-square = 1,31
	clonazepam/no clonazepam	chi-square = 0,65
	ethosuximide/no ethosuximide	chi-square = 0,15
	sulthiam/no sulthiam	chi-square = 0,03
Seriousness of the brain damage	chi-square = 0,72	

With chi-square = 3,8415 - p = 0,05

Thus there are no significant differences between both groups.

CHAPTER VI: RESULTS OF THE CLINICAL STUDY

1 Introduction

In chapter IV the objectives of the research were stated.

This chapter presents the following results:

- 1 The amount of alcohol intake and the serum alcohol concentration reached.
- 2 The changes in the seizure frequency in the alcohol- and control group.
- 3 A summary of the results of investigations of blood level concentrations of antiepileptic drugs and the changes in chemical blood examination.
- 4 The changes in epileptic activity and various rhythms of the EEGs recorded the morning after alcohol use with respect to the findings in the pre-alcohol period (20 patients). These were compared with the changes in the corresponding records of the control group (17 patients).

2 Alcohol intake

In the evening the participants in the examination could determine their alcohol intake themselves, during a 2 hours period. The number of glasses per evening per participant was minimum one and maximum three. For each participant it was noted how many glasses of alcohol he used per evening. Five times both in control- and alcohol group venous blood was taken for determination of the alcohol concentration.

The participants were not told on which evening blood would be taken. Table VI¹ gives a review of the recorded intake during the evenings on which blood was taken for determination of blood concentration.

Those 5 evenings the participants in the control group took a total of 251 glasses, an average per person per evening of 2,18 glasses.

The participants of the alcohol group had a total of 317 glasses of beverage with alcohol, an average per person per evening of 2,19 glasses.

Beverage intake during the entire period of 16 weeks:

control group 1.589 glasses - 2,16 glasses per person, per evening;

alcohol group 1.982 glasses - 2,14 glasses per person, per evening.

Table VI¹: Beverage use in the alcohol- and control group in the evening of blood sampling

Alcohol group n = 29		Control group n = 23	
Patient No.	Alcohol beverage intake/ glasses per evening	Patient No.	Beverage intake/ glasses per evening
2	2-2-1-2-2	1	2-3-2-2-2
4	3-1-2-3-1	3	1-1-1-1-1
5	1-2-1-2-1	7	2-2-1-1-2
6	3-3-2-3-3	12	3-3-3-3-2
8	3-3-2-3-2	18	1-1-1-1-1
9	3-3-2-1-3	20	3-3-3-3-3
10	2-3-2-1-1	22	3-3-2-3-3
11	3-3-2-1-3	24	3-2-3-3-3
13	3-3-2-1-2	26	3-3-3-3-3
14	3-2-2-1-2	27	3-3-3-3-3
15	1-2-3-3-3	28	3-3-3-3-3
16	3-3-2-3-3	31	1-1-1-1-1
17	3-2-2-1-3	33	2-2-2-2-2
19	3-3-3-2-1	36	2-2-2-1-2
21	3-3-3-2-2	43	3-3-3-2-3
29	3-2-3-1-2	44	2-2-2-2-2
30	3-3-2-3-1	45	1-2-3-2-3
32	2-3-3-1-3	46	2-1-1-1-2
34	3-3-3-2-3	47	2-3-3-3-2
35	2-2-2-1-2	49	3-3-2-3-3
37	2-2-2-1-2	52	2-2-2-1-2
38	2-1-1-2-2	53	2-3-1-2-2
39	2-3-2-1-2	54	2-2-1-1-2
40	2-2-2-1-2		
41	2-3-2-3-3		
42	3-2-2-2-2		
48	3-3-2-1-3		
50	1-1-1-2-2		
51	2-3-2-2-2		

Serum alcohol concentration

In the alcohol group the measured maximum serum alcohol concentration varied between 0,05 and 0,33 ‰.

For a review of the maximum blood alcohol concentration per participant see table VI².

Table VI³ compares the average peak alcohol concentrations after consumption of 2 to 3 glasses. It is of interest that the serum concentrations attained all lower than the legal maximum in the Netherlands for driving a car (0,5 ‰).

Table VI²: Review maximum alcohol concentrations per participant

Patient No.	Alcohol permillage	Amount of alcohol taken
2	0,08	2 glasses
4	0,21	3 "
5	0,09	2 "
6	0,12	3 "
8	0,12	3 "
9	0,19	3 "
10	0,10	3 "
11	0,08	3 "
13	0,20	3 "
14	0,22	3 "
15	0,13	3 "
16	0,20	3 "
17	0,15	3 "
19	0,28	3 "
21	0,22	3 "
29	0,12	3 "
30	0,16	3 "
32	0,24	3 "
34	0,33	3 "
35	0,08	2 "
37	0,05	2 "
38	0,06	2 "
39	0,14	3 "
40	0,13	2 "
41	0,09	3 "
42	0,05	2 "
48	0,20	3 "
50	0,12	2 "
51	0,33	3 "

Table VI³: Peak alcohol concentrations

Amount of alcohol taken	N	M 0/00	SD
2 glasses	8	0,08	0,03
3 glasses	21	0,18	0,07

3 Seizure frequency

Seizures often occur at irregular intervals. Especially in cases of partial epilepsy attacks often occur in clusters. Spontaneous fluctuations in seizure frequency also occur when there are no changes of medication.

For all 52 people taking part in the examination the basic period, that is the period during which no changes of medication were made, was divided into 2 stages of 11 weeks each.

When comparing the total number of seizures per person in the 2 stages of period I it seemed that in 17 persons there were no changes in the occurrence of attacks, in 21 persons there was an increase and in 14 persons a decrease of the attacks. This illustrated the spontaneous fluctuations in seizure frequency in a steady state.

To check the influence of alcohol upon the seizure frequency the total attacks per person in the basic period, during 16 weeks previous to the examination, were compared with the total seizures during 16 weeks in the alcohol stage (see table VI⁴).

Table VI^a: Comparison seizure frequency basic period - alcohol stage

Alcohol group n = 29				Control group n = 23			
No.	Tot. number seizures in 16w period I basic period	Tot. number seizures in 16w period III alcohol stage	+ -	No.	Tot. number seizures in 16w period I basic period	Tot. number seizures in 16w period III alcohol stage	+ -
2	0	0	0	1	13	18	+
4	69	71	+	3	4	6	+
5	5	0	-	7	69	98	+
6	11	10	-	12	113	178	+
8	31	35	+	18	0	0	0
9	20	33	+	20	1	0	-
10	0	0	0	22	7	8	+
11	17	14	-	24	45	61	+
13	15	19	-	26	22	6	-
14	0	0	0	27	17	22	+
15	2	4	+	28	7	5	-
16	7	10	+	31	0	0	0
17	5	5	0	33	0	0	0
19	20	12	-	36	0	0	0
21	6	16	+	43	0	3	+
29	0	0	0	44	37	57	+
30	6	5	-	45	17	14	+
32	11	0	-	46	0	0	-
34	0	1	+	47	1	25	0
35	4	3	-	49	9	7	+
37	5	1	-	52	6	0	-
38	0	0	0	53	1	0	-
39	10	2	-	54	0	0	0
40	3	5	+				
41	0	0	0				
42	2	0	0				
48	8	8	0				
50	5	4	-				
51	25	26	+				

Summary of changes in seizure frequency between patients of the alcohol- and control groups during the basic period and alcohol stage.

Table VI⁵: Changes in seizure frequency: PI - PIII

Changes in number of seizures	No. of patients in alcohol group	No. of patients in control group	Total
Unchanged	8	6	14
Increased	10	10	20
Decreased	11	7	18
	29	23	52

chi-square = 0,48 df = 2

No significant difference between both groups.

It was also checked whether these findings were reproducible when the 16 weeks of the alcohol period were compared with another period of 16 weeks during which no alcohol was taken. This non-alcoholic period was composed of the last 5 weeks of the basic period, 6 weeks of the preliminary stage and 5 weeks of the final stage (see table VI⁶).

Summary of changes in seizure frequency between patients of the alcohol- and control group during both stages.

Table VI⁶: Changes in seizure frequency: 5w PI + PII + PIV - PIII

Changes in number of seizures	No. of patients in alcohol group	No. of patients in control group	Total
Unchanged	7	7	14
Increased	11	10	21
Decreased	11	6	17
	29	23	52

chi-square = 0,83 df = 2

No significant difference between both groups.

The rate of the number of attacks per week with respect to the total number of attacks in a certain period of 16 weeks were also investigated in both control- and alcohol group. On closer inspection of the cumulative increase of the proportional seizure frequency both control- and alcohol group showed a pattern that was practically identical and almost linear. So no cumulative effect through alcohol is demonstrable in the alcohol stage.

Although in both groups there is no demonstrable change in seizure frequency this does not exclude the occurrence of a possible significant change in the number of days with seizures. Therefore during 16 weeks of the basic period both in control- and alcohol group changes were examined in the number of days on which seizures occurred, which were compared with examinations during 16 weeks of the alcohol stage (see table VI⁷).

Table VI⁷: Comparison: Days with seizures: 16 weeks basic period -
16 weeks alcohol stage

Alcohol group n = 29				Control group n = 23			
No.	16w PI	16w PIII	±	No.	16w PI	16w PIII	±
2	0	0	0	1	9	12	+
4	39	55	+	3	4	4	0
5	4	0	-	7	36	37	+
6	10	9	-	12	56	80	+
8	18	20	+	18	0	0	0
9	20	24	+	20	1	0	-
10	0	0	0	22	7	8	+
11	14	12	-	24	31	43	+
13	15	14	-	26	16	5	-
14	0	0	0	27	15	22	+
15	2	4	+	28	7	3	-
16	7	8	+	31	0	0	0
17	5	4	-	33	0	0	0
19	20	10	-	36	0	0	0
21	5	13	+	43	0	1	+
29	20	10	-	44	26	25	-
30	5	13	+	45	14	13	-
32	0	0	0	46	0	0	0
34	0	1	+	47	1	13	+
35	5	3	-	49	3	7	+
37	5	1	-	52	6	0	-
38	0	0	0	53	1	0	-
39	10	2	-	54	0	0	-
40	3	4	+				
41	0	0	0				
42	2	0	-				
48	3	4	+				
50	5	4	-				
51	16	20	+				

Summary of changes in the number of days with seizures between patients of the alcohol- and control group during the basic period and the alcohol stage.

Table VI⁸: Changes in number of days with seizures

Changes in number of days with seizures	No. of patients in alcohol group	No. of patients in control group	Total
Unchanged	6	6	12
Increased	10	9	19
Decreased	13	8	21
	29	23	52

chi-square = 0,54 df = 2

No significant difference between both groups.

Tabel VI⁹ gives a review of the seizure frequency per week per patient in the basic period (PI), preliminary stage (PII), alcohol stage (PIII) and final stage (PIV).

In this review it is conspicuous that the seizure incidence of patient No. 12 strongly deviates from the other participants in the investigation in both control- and alcohol group. None of the other participants has an average seizure frequency higher than 6,17 seizures per week. In the above mentioned 4 stages, patient No. 12 has respectively 6,09, 7,83, 11,25 and 9,40 seizures per week.

By way of the Friedman test was checked if the average seizure frequency was distributed at random between the periods. In the alcohol group chi-square was 1,62 df 28 and in the control group chi-square was 1,42 df 22. There can be concluded that there was a distribution at random.

Table VI³: Seizure frequency per week in several stages of the research

Alcohol group					Control group				
No.	Period I	Period II	Period III	Period IV	No.	Period I	Period II	Period III	Period IV
2	0	0	0	0	1	0,73	0,83	1,13	0,80
4	4,27	4,50	4,50	4,40	3	0,18	0	0,37	0
5	0,50	0,33	0	0	7	3,45	4,00	6,12	4,00
6	0,73	0,33	0,62	1,00	12	6,09	7,83	11,25	9,40
8	2,00	1,16	2,18	0,60	18	0	0	0	0
9	1,04	0,80	2,12	2,80	20	0,41	0,33	0	0
10	0	0	0	0	22	0,55	0	0,50	0,60
11	0,95	0	0,87	0,60	24	2,45	2,66	3,87	3,40
13	0,77	0,33	1,18	0,60	26	1,00	0,83	0,44	0,40
14	0	0,17	0	0,40	27	1,04	1,66	1,37	2,40
15	0,01	0	0,25	0,20	28	0,54	0,66	0,31	0,60
16	0,41	0	0,62	1,00	31	0	0	0	0
17	0,36	0	0,31	0	33	0	0	0	0
19	1,01	0,33	0,75	1,00	36	0	0	0	0
21	0,36	0,83	1,00	0,60	43	0	0	0,19	0
29	0	0	0	0	44	1,73	6,17	3,56	2,20
30	0,38	0	0,38	1,00	45	1,05	0,17	0,88	0,60
32	0,81	0	0	0	46	0	0	0	0
34	0	0	0,06	0	47	0,05	0,17	1,56	1,00
35	0,23	0,50	0,19	0,20	49	0,59	0	0,44	1,60
37	0,23	0,17	0,06	0,40	52	0,45	0	0	0
38	0,05	0	0	0	53	0,05	0	0	0
39	0,50	0,50	0,31	0,20	54	0	0	0	0
40	0,27	0,50	0,31	0,60					
41	0	0	0	0					
42	0,14	0,33	0	0,20					
48	0,50	0,17	0,50	0					
50	0,27	0,33	0,25	0,20					
51	1,36	1,50	1,63	1,40					

Friedman test: chi-square = 1,62 df = 28

chi-square = 1,42 df = 22

A comparison of the averages per period in both control- and alcohol group shows how great the influence of this patient is on the average seizure frequency per period. See table VI¹⁰ with patient No. 12 and table VI¹¹ without patient No. 12. Also in these tables no alcohol effect is demonstrable.

Table VI¹⁰: Seizure frequency per week control group - alcohol group with patient No. 12

	PI Basic period	PII Preliminary stage	PIII Alcohol stage	PIV Final stage
Alcohol group	0,6	0,4	0,6	0,6
Control group	0,9	1,1	1,4	1,2

Table VI¹¹: Seizure frequency per week control group - alcohol group without patient No. 12

	PI Basic period	PII Preliminary stage	PIII Alcohol stage	PIV Final stage
Alcohol group	0,6	0,4	0,6	0,6
Control group	0,7	0,8	0,9	0,8

a Conclusion

A variety of statistical tests failed to demonstrate an effect of alcohol on seizure frequency.

4 Blood levels

In total 8 different antiepileptics were used by patients taking part in the examination: carbamazepine, phenobarbital, phenytoin, valproic acid, primidone, clonazepam, ethosuximide and sulthiam (see chapter V) The number of patients which used primidone was too small for

investigating the influence of alcohol on the primidone blood levels. It was not possible to determine the serum concentration of clonazepam and sulthiam. During the entire investigation 9 pairs of blood samples were taken (evening and the following morning) for estimating anti-epileptic drugs; 4 times in the period of the investigation without alcohol (PII + PIV) (3 times in the preliminary stage and once in the final stage) and 5 times in the alcohol stage (PIII).

a Carbamazepine blood levels

In 18 persons in the control group and 22 persons in the alcohol group the carbamazepine levels were determined. This was done in the morning and in the evening; 4 times in the stage without alcohol (PII + PIV) and 5 times in the stage during which alcohol was used (PIII) see table VI¹²). With the help of the t-test 2 tailed (DAVIES 1947) in the anti-epileptic drugs was tested, both in control- and in alcohol group, whether or not there were significant differences between the average determinations in the PII + PIV and PIII stage at 8 a.m. and at 10 p.m. In carbamazepine in none of the comparisons P was < 0,05.

b Conclusion

There is no significant influence of alcohol use on the carbamazepine levels.

Table VI¹²: Blood levels carbamazepine

		PII + PIV 08.00	PIII 08.00	
Alcohol group n = 22	m sem	4.3 (.3)	4.5 (.3)	ns (t = 1.80)
Control group n = 18	m sem	4.3 (.4)	4.5 (.4)	ns (t = 1.91)

		PII + PIV 22.00	PIII 22.00	
Alcohol group n = 22	m sem	6.3 (.4)	6.1 (.4)	ns (t = 1.07)
Control group n = 18	m sem	6.0 (.5)	6.1 (.5)	ns (t = 0.64)

c Ethosuximide blood levels

Only 4 patients in the control group and 5 in the alcohol group used ethosuximide. Table VI¹³ gives a summary of the mean ethosuximide blood levels at 8 a.m. and 10 p.m. in stage PII + PIV and PIII in both control- and alcohol group.

d Conclusion

The number of subjects taking ethosuximide was too small to permit any conclusion.

Table VI¹³: Blood levels ethosuximide

		PII + PIV 08.00	PIII 08.00
Alcohol group	m	54.7	53.9
n = 5	sem	(8.3)	(7.4)
Control group	m	26.3	24.7
n = 4	sem	(4.2)	(4.2)

		PII + PIV 22.00	PIII 22.00
Alcohol group	m	62.8	64.0
n = 5	sem	(9.1)	(8.4)
Control group	m	30.6	30.8
n = 4	sem	(4.2)	(4.9)

e Phenobarbital blood levels

With 18 persons in the control group and 22 persons in the alcohol group the phenobarbital levels were determined. Table VI¹⁴ shows a summary of the mean phenobarbital levels at 8 a.m. and 10 p.m. in stage PII + PIV and PIII both in control- and alcohol group. There was no influence of alcohol use on the blood levels. However, there was a marginally significant effect $P = 0.049$ as for the differences of the phenobarbital levels at 8 a.m. in the control group. The reason for this is not evident, but it should of course be appreciated that if statistical tests are repeatedly applied even to random data 5% may be expected to give a result significant at the 5% level.

f Conclusion

There was no significant influence of alcohol use on the phenobarbital levels.

Table VI¹⁴: Blood levels phenobarbital

			PII + PIV 08.00	PIII 08.00		
Alcohol group n = 22	m sem		29.9 (2.9)	29.4 (2.8)	ns	(t = 1.21)
Control group n = 18	m sem		24.9 (2.2)	24.0 (2.2)	P = 0.5	(t = 2.12)

			PII + PIV 22.00	PIII 22.00		
Alcohol group n = 22	m sem		30.8 (2.9)	30.2 (2.9)	ns	(t = 1.50)
Control group n = 18	m sem		25.0 (2.3)	24.4 (2.3)	ns	(t = 1.99)

g Phenytoin blood levels

Table VI¹⁵ gives a summary of the mean phenytoin blood levels at 8 a.m. and 10 p.m. in stage PII + PIV and PIII both in control- n = 13 and alcohol group n = 18. No significant difference could be shown between the mean determinations in stage PII + PIV and PIII.

h Conclusion

No alcohol effect on the phenytoin levels can be demonstrated.

Table VI¹⁵: Blood levels phenytoin

		PII + PIV 08.00	PIII 08.00	
Alcohol group	m	6.9	7.0	ns (t = 0.43)
n = 18	sem	(1.2)	(1.2)	
Control group	m	8.3	7.8	ns (t = 1.62)
n = 13	sem	(1.0)	(.9)	

		PII + PIV 22.00	PIII 22.00	
Alcohol group	m	7.4	7.4	ns (t = 0.074)
n = 18	sem	(1.1)	(1.2)	
Control group	m	8.4	8.4	ns (t = 0.00)
n = 13	sem	(.9)	(.9)	

i Primidone blood levels

Only 2 patients in the control group used this drug; in the alcohol group there were 3 patients. In view of the small number no opinion can be given upon the influence of alcohol on the levels.

j Valproic acid blood levels

Table VI¹⁶ gives a summary of the average valproic acid blood levels at 8 a.m. and 10 p.m. in stage PII + PIV and PIII in both control- n = 8 and alcohol group n = 10. It becomes evident that when testing there are significant differences in the alcohol group between the valproic acid blood levels at 8 a.m. $P = 0.022$ and at 10 p.m. $P = 0.0038$. There are also significant differences in the control group between the valproic acid blood levels at 8 a.m. $P = 0.0049$.

k Conclusion

In several stages significant differences have been found between the average valproic acid blood levels. In the discussion the possible sources of these differences in various stages will be given: an alcohol effect is not excluded.

Table VI¹⁶: Blood levels valproic acid

		PII + PIV 08.00	PIII 08.00	
Alcohol group n = 10	m sem	53.7 (3.8)	51.1 (3.8)	
Control group n = 8	m sem	42.3 (5.8)	44.3 (9.9)	P = 0.022 (t = 2.77) P = 0.0049 (t = 4.05)

		PII + PIV 22.00	PIII 22.00	
Alcohol group n = 10	m sem	59.2 (3.1)	53.7 (3.1)	
Control group n = 8	m sem	45.2 (4.8)	42.7 (4.8)	P = 0.038 (t = 3.87) ns (t = .67)

5 Chemical blood examination

Before admission and following the study each patient was screened for hepatic and renal function. The following blood concentrations were determined: urea, creatinine, transaminases, SGOT, SGPT, alkaline, phosphatase, bilirubine and gamma-GT. Disturbances in liver and/or kidney function were a contra-indication for participation in the examination. During the entire investigation when blood samples were taken to determine the concentration of the antiepileptic drugs blood estimations were also performed of urea, alkaline, phosphatase and gamma-GT. Vene puncture was performed 4 times in the morning and evening in the stage without alcohol and 5 times in the alcohol stage.

Results

During the entire investigation the concentrations of urea, gamma-GT and alkaline phosphatase remained within the norm. Due to use of alcohol there was a slight increase in the gamma-GT concentration at 10 p.m. (table VI¹⁷). The following morning this effect was no longer demonstrable.

Table VI¹⁷: Means of the measured gamma-GT

		PII + PIV 08.00	PIII 08.00		
Alcohol group	m	43.2	44.5	ns	(t = 1.72)
n = 28	sem	(4.4)	(4.7)		
Control group	m	36.5	37.0	ns	(t = .56)
n = 23	sem	(4.2)	(4.1)		

		PII + PIV 22.00	PIII 22.00		
Alcohol group	m	42.3	43.9	P = 0.5	(t = 2.05)
n = 28	sem	(4.4)	(4.7)		
Control group	m	36.0	37.0	ns	(t = 1.14)
n = 23	sem	(4.2)	(4.2)		

There was also an increase of the mean alkaline phosphatase concentration at 10 p.m. but this effect persisted to the following morning (table VI¹⁸). The alcohol had no influence on the urea concentration.

a Conclusion

In the alcohol group there is an influence of the alcohol use on the mean gamma-GT and alkaline phosphatase concentration in the evening, while the last was still elevated the following morning.

Table VI¹⁸: Means of the measured alkaline phosphatase

		PII + PIV 08.00	PIII 08.00		
Alcohol group	m	130.2	137.7	P = 0.0024	(t = 3.34)
n = 28	sem	(7.8)	(7.6)		
Control group	m	125.4	126.4	ns	(t = .43)
n = 23	sem	(7.3)	(7.2)		

		PII + PIV 22.00	PIII 22.00		
Alcohol group	m	130.5	138.7	P = 0.0012	(t = 3.60)
n = 28	sem	(7.5)	(7.5)		
Control group	m	125.1	128.5	ns	(t = 1.40)
n = 23	sem	(7.3)	(7.2)		

a Changes in frequency

Of 20 non selected patients in the alcohol group and 17 non selected patients in the control group, 4 EEG-registrations were made; 1 during the preliminary stage, 2 during the period of alcohol intake and 1 during the final stage. As already described in chapter IV (EEG-registration) this part of the examination was also carried out double blind. While judging the EEGs the average frequency was determined whenever there was question of a frequency band. The averages of the frequency bands of those 4 EEGs were compared one to another. The EEG with the lowest frequency in a particular frequency band was scored as 0. In the other 3 EEGs a score of 1 point was given for each $\frac{1}{2}$ cycle/second difference with the lowest average frequency.

Table VI¹⁹, VI²⁰ and VI²¹ give a review of these scores of respectively alpha, beta and theta rhythm both in alcohol- and control group. Statistical analysis with the sign test showed no clear alcohol effect.

Table VI¹⁹: Frequency changes alpha rhythm

Alcohol group n = 20				Control group n = 17			
Patient No.	Preliminary stage	Alcohol stage	Final stage	Patient No.	Preliminary stage	Alcohol stage	Final stage
2	1	1 2	0	1	1	1 0	1
5	0	3 0	3	18	2	2 3	0
10	0	1 2	1	20	2	2 1	0
11	0	1 1	0	24	2	0 1	0
15	0	- -	5	26	0	0 0	0
16	3	1 2	0	27	1	0 1	2
17	1	3 1	0	33	0	0 0	0
19	1	0 0	0	36	0	0 0	1
30	0	1 1	0	43	0	0 1	2
34	0	0 0	0	44	0	1 0	3
35	0	0 0	0	45	0	2 2	5
37	1	2 0	1	46	4	4 0	4
38	0	0 0	1	47	0	0 0	0
39	1	0 0	0	49	0	0 0	0
40	0	0 0	0	52	0	0 0	1
41	0	0 0	0	53	3	0 1	0
42	1	0 0	0	54	2	2 1	0
48	1	0 0	2				
50	0	1 1	1				
51	2	1 0	0				

0 = score lowest frequency

1 point is added to the score for each $\frac{1}{2}$ cycle/second

Table VI²⁰: Frequency changes beta rhythm

Alcohol group n = 20				Control group n = 17			
Patient No.	Preliminary stage	Alcohol stage	Final stage	Patient No.	Preliminary stage	Alcohol stage	Final stage
2	4	0 0	4	1	0	0 5	5
5	0	4 0	4	18	4	0 4	4
10	0	4 2	0	20	-	- -	-
11	6	0 4	4	24	5	3 0	1
15	0	0 0	0	26	5	0 5	0
16	4	0 0	0	27	4	4 8	0
17	7	7 5	0	33	8	6 8	0
19	0	0 0	0	36	3	0 5	3
30	0	4 8	4	43	5	0 4	5
34	1	0 0	1	44	0	0 6	11
35	0	2 2	2	45	0	6 -	0
37	4	8 0	2	46	8	14 0	8
38	0	0 0	0	47	4	0 4	4
39	3	0 9	5	49	0	0 5	5
40	5	- 7	0	52	1	1 0	1
41	9	0 6	5	53	6	0 11	9
42	0	9 7	7	54	0	0 9	0
48	-	4 0	4				
50	0	- -	-				
51	6	13 0	0				

0 = score lowest frequency

1 point is added to the score for each $\frac{1}{2}$ cycle/second

Table VI²¹: Frequency changes theta rhythm

Alcohol group n = 20				Control group n = 17			
Patient No.	Preliminary stage	Alcohol stage	Final stage	Patient No.	Preliminary stage	Alcohol stage	Final stage
2	0	0 0	2	1	0	0 2	0
5	0	0 0	0	18	1	1 0	2
10	-	- -	-	20	1	0 1	1
11	0	0 0	1	24	0	2 1	1
15	3	0 2	0	26	2	2 2	0
16	0	1 0	0	27	0	0 2	1
17	0	0 0	0	33	0	1 1	1
19	0	0 0	0	36	-	- -	-
30	0	0 0	0	43	0	0 1	1
34	-	- -	-	44	0	1 1	1
35	0	0 0	0	45	1	0 0	1
37	1	0 0	1	46	0	1 3	3
38	0	- 0	0	47	0	2 0	2
39	0	0 0	0	49	0	0 0	0
40	2	0 0	0	52	1	0 1	2
41	0	1 0	0	53	0	0 0	0
42	0	1 0	0	54	1	0 2	0
48	0	0 3	0				
50	1	1 1	0				
51	0	0 0	0				

0 = score lowest frequency

1 point is added to the score for each $\frac{1}{2}$ cycle/second

b Amount of occurrence of rhythms

Again use was made of a 4-point scale, whereby 1 is the score for the smallest amount present and the amount of increasing occurrence is classified with 2, 3 or 4 for the amount that occurs most.

Table VI²² gives the distribution of the amount of alpha and beta activity in the preliminary (PII), alcohol (PIII) and final stage (PIV) in control- and alcohol group. With the help of the t-test 2 tailed it was tested both in control- and in alcohol group whether or not there were significant differences between the mean amount of alpha or beta activity in the various stages with or without alcohol.

Table VI²²: Amount of alpha activity

Amount of beta activity

Alcohol group n = 20					Control group n = 17					Alcohol group n = 20					Control group n = 17				
Pat. No.	PII	PIII	PIII	PIV	Pat. No.	PII	PIII	PIII	PIV	Pat. No.	PII	PIII	PIII	PIV	Pat. No.	PII	PIII	PIII	PIV
2	1	2	3	1	1	3	4	2	1	2	3	1	1	4	1	1	3	2	2
5	1	4	2	3	18	1	4	3	1	5	1	1	1	1	18	1	3	1	2
10	1	3	1	2	20	1	1	1	1	10	1	3	2	1	20	-	-	-	-
11	1	2	3	2	24	3	1	2	2	11	3	2	2	1	24	1	1	1	1
15	1	1	1	1	26	1	1	1	1	15	3	2	2	2	26	1	1	1	1
16	1	1	1	1	27	4	2	1	3	16	2	2	3	2	27	4	1	3	2
17	2	1	2	2	33	1	1	1	1	17	3	1	1	3	33	1	2	2	1
19	2	1	2	2	36	1	1	1	1	19	2	2	3	2	36	3	2	1	3
30	3	3	2	1	43	1	1	1	1	30	1	2	2	3	43	1	2	3	2
34	1	1	1	1	44	1	1	1	1	34	3	3	1	2	44	1	1	1	1
35	1	1	1	1	45	2	2	1	1	35	2	3	1	2	45	3	2	1	2
37	1	1	1	1	46	1	1	1	1	37	1	2	3	2	46	2	4	1	3
38	1	1	1	1	47	1	1	1	1	38	1	1	1	1	47	2	1	2	2
39	2	1	3	2	49	1	1	1	1	39	3	3	2	4	49	1	1	1	1
40	1	2	3	4	52	1	1	1	1	40	1	1	1	1	52	1	2	3	3
41	2	1	1	2	53	1	1	1	1	41	1	1	1	1	53	1	1	1	1
42	1	1	1	1	54	1	1	1	1	42	1	1	3	3	54	4	1	3	2
48	2	3	1	2		1	1	1	1	48	1	2	1	1					
50	1	1	1	1						50	2	1	1	3					
51	1	1	1	1						51	1	1	1	1					

PII = preliminary stage

PIII = alcohol stage

PIV = final stage

Summary

<u>Alpha activity</u>	<u>Alcohol group</u>		<u>Control group</u>	
Average PII + PIV - PIII	3.0	3.25	2.71	2.71
SD	1.1	1.07	1.36	1.45

Alcohol group alpha activity PII + PIV - PIII ns (t = 1, df = 19)

Control group alpha activity PII + PIV - PIII ns (t = 0, df = 16)

Conclusion

There is no significant influence of alcohol use on the average amount of alpha activity in several stages.

	<u>Alcohol group</u>	<u>Control group</u>
Correlation coefficient	0.63	0.40
P < 0.01		ns

Conclusion

There is a significant correlation between PII + PIV and PIII for the alpha activity in the alcohol group.

Summary

<u>Beta activity</u>	<u>Alcohol group</u>		<u>Control group</u>	
Average PII + PIV - PIII	3.55	3.4	3.35	3.24
SD	1.6	1.07	1.71	1.89

Alcohol group beta activity PII + PIV - PIII ns (t = 0.38, df = 19)

Control group beta activity PII + PIV - PIII ns (t = 0.33, df = 16)

Conclusion

There is no significant influence of alcohol use on the average amount of beta activity in several stages.

	<u>Alcohol group</u>	<u>Control group</u>
Correlation coefficient	0.19	0.58
	ns	$P < 0.01$

Conclusion

There is only a significant correlation between PII + PIV and PIII for the beta activity in the control group.

Table VI²³ gives a summary of the occurrence of the theta and delta activity in various stages of the examination both in control- and alcohol group. In this case also use was made of the 4-point scale, whereby 1 is the score for the smallest amount present and 4 stands for the amount that occurs most.

With the help of the t-test 2 tailed it was also tested if the average amount of theta respectively delta activity in PII - PIV stage differed significantly from the average amount of occurrence in the PIII stage in control- and alcohol group.

Table VI²³: Amount of theta activity

Amount of delta activity									
Alcohol group n = 20					Control group n = 17				
Pat. No.	PII	PIII	PIII	PIV	Pat. No.	PII	PIII	PIII	PIV
2	1	1	1	1	1	2	3	4	1
5	3	1	2	2	18	2	1	3	2
10	-	-	-	-	20	1	2	3	1
11	1	1	1	1	24	1	3	1	1
15	1	4	2	3	26	3	2	3	1
16	2	1	2	2	27	2	3	1	1
17	2	2	2	1	33	1	3	2	2
19	2	1	1	1	36	1	-	-	-
30	1	1	1	1	43	2	2	2	1
34	-	-	-	-	44	3	2	4	1
35	2	3	1	2	45	1	2	3	4
37	1	1	3	2	46	3	2	1	1
38	2	1	2	2	47	3	2	3	2
39	1	1	1	1	49	2	2	1	2
40	3	4	2	1	52	1	1	1	1
41	1	1	2	1	53	1	2	2	3
42	1	1	1	1	54	1	3	1	4
48	1	3	1	2					
50	2	2	3	1					
51	1	1	1	2					

PII = preliminary stage

PIII = alcohol stage

PIV = final stage

Summary

<u>Theta activity</u>	<u>Alcohol group</u>		<u>Control group</u>	
Average PII + PVI - PIII	2.8	2.9	3.41	4.
SD	1.33	1.61	1.46	1.57

Alcohol group theta activity PII + PIV - PIII ns ($t = 0.40$, $df = 17$)

Control group theta activity PII + PIV - PIII ns ($t = 1.38$, $df = 15$)

Conclusion

There is no significant influence of alcohol intake on the average amount of theta activity.

	<u>Alcohol group</u>	<u>Control group</u>
Correlation coefficient	0.74	0.36
	$P < 0.001$	ns

Conclusion

There is a significant correlation between PII + PIV and PIII for the theta activity in the alcohol group.

Summary

<u>Delta activity</u>	<u>Alcohol group</u>		<u>Control group</u>	
Average PII + PIV - PIII	1.15	1.35	1.29	1.06
SD	1.65	2.01	1.87	1.55

Alcohol group delta activity PII + PIV - PIII ns ($t = 0.78$, $df = 7$)

Control group delta activity PII + PIV - PIII ns ($t = 1.76$, $df = 5$)

Conclusion

There is no significant influence of alcohol intake on the average amount of delta activity.

	<u>Alcohol group</u>	<u>Control group</u>
Correlation coefficient	0.83	0.97
	$P < 0.001$	$P < 0.001$

Conclusion

There is a significant correlation between PII + PIV and PIII for the delta activity in the alcohol- and control group.

c Reaction on hyperventilation and on stroboscopy

Table VI²⁴ gives a summary of the reaction on hyperventilation and on stroboscopy in various stages of the study both in control- and alcohol group. Again a 4-point scale was used, whereby 1 represents the smallest reaction and 4 the largest one.

With the help of the t-test 2 tailed it was tested if the reactions in stage PII + PIV showed large differences from the reactions in stage PIII.

Table VI²⁴: Reaction on hyperventilation

Reaction on stroboscopy

Alcohol group					Control group					Alcohol group					Control group				
Pat. No.	PII	PIII	PIII	PIV	Pat. No.	PII	PIII	PIII	PIV	Pat. No.	PII	PIII	PIII	PIV	Pat. No.	PII	PIII	PIII	PIV
2	2	2	1	3	1	1	1	2	1	2	-	-	3	2	1	-	-	-	-
5	3	2	1	1	18	1	1	1	1	5	-	-	-	-	18	-	-	-	-
10	3	2	1	4	20	2	3	3	1	10	-	-	-	-	20	1	1	1	2
11	3	2	2	1	24	1	4	3	2	11	-	-	2	1	24	-	-	-	-
15	1	1	2	3	26	1	1	1	1	15	1	1	-	-	26	-	-	-	-
16	3	1	4	2	27	1	1	1	2	16	1	4	3	1	27	-	-	-	-
17	1	1	1	1	33	1	1	1	1	17	-	-	-	-	33	-	-	-	-
19	2	2	2	2	36	1	1	1	1	19	-	-	-	-	36	-	-	-	-
30	2	2	1	2	43	1	1	1	1	30	-	-	-	-	43	-	-	-	-
34	1	1	1	1	44	3	3	1	2	34	-	-	-	-	44	-	-	-	-
35	2	2	1	1	45	1	1	1	1	35	1	1	1	2	45	-	-	-	-
37	2	2	3	2	46	2	1	1	1	37	1	2	3	2	46	-	-	-	-
38	2	2	1	1	47	2	1	3	2	38	-	2	2	2	47	-	-	-	-
39	1	1	1	1	49	2	2	1	2	39	2	1	1	1	49	1	2	2	1
40	2	2	2	1	52	1	2	2	1	40	2	2	1	1	52	-	-	-	-
41	1	1	1	1	53	1	1	1	1	41	-	-	-	-	53	-	-	-	-
42	1	1	1	1	54	1	1	1	1	42	-	-	-	-	54	-	-	-	-
48	1	1	2	1						48	4								
50	4	3	1	1						50	-								
51	2	2	1	2						51	-								

PII = preliminary stage

PIII = alcohol stage

PIV = final stage

Summary

Alcohol group hyperventilation PII + PIV - PIII ns ($t = 1.36$, $df = 19$)

Control group hyperventilation PII + PIV - PIII ns ($t = 1.02$, $df = 16$)

Stroboscopy: The number was too small to permit any conclusion.

Conclusion

There is no significant influence of alcohol intake on the reaction on hyperventilation. For the reaction on stroboscopy the number of subjects was too small to permit any conclusion.

Correlation between stage PII + PIV and stage PIII for the reaction on hyperventilation both in control- and alcohol group.

	<u>Alcohol group</u>	<u>Control group</u>
Correlation coefficient	0.49	0.44
	$P < 0.05$	$P < 0.01$

Conclusion

There is a good correlation between the reaction on hyperventilation in both alcohol- and control group in various stages.

d Amount of epileptic activity

Table VI²⁵ gives a summary of the amount of epileptic activity per EEG in various stages. Use was made of a 4-point scale, whereby 1 represents the smallest amount of epileptic activity. With the help of the t-test 2 tailed it was tested if the average amount of epileptic activity in stage PII + PIV differed significantly from the amount of epileptic activity in stage PIII.

Table VI²⁵: Amount of epileptic activity

Alcohol group					Control group				
Patient No.	PII	PIII	PIII	PIV	Patient No.	PII	PIII	PIII	PIV
2	3	1	2	-	1	1	1	1	1
5	-	-	-	-	18	-	1	-	-
10	2	1	2	1	20	1	2	1	1
11	1	1	2	1	24	2	3	1	3
15	-	-	-	-	26	2	4	3	1
16	-	1	-	-	27	1	1	1	2
17	1	3	2	1	33	2	3	1	1
19	2	1	2	1	36	3	2	3	1
30	-	2	1	0	43	1	1	1	1
34	-	1	-	-	44	2	3	3	1
35	-	-	-	-	45	2	1	4	3
37	2	1	3	4	46	-	-	-	-
38	-	-	-	-	47	2	1	3	1
39	-	-	-	-	49	2	1	1	1
40	3	4	2	1	52	-	-	-	-
41	3	2	1	4	53	2	1	2	1
42	1	3	2	1	54	1	2	2	1
48	-	-	-	-					
50	4	3	1	2					
51	2	1	1	3					

PII = preliminary stage

PIII = alcohol stage

PIV = final stage

Summary

Alcohol group amount of epileptic activity PII + PIV - PIII ns
(t = 0.36, df = 9)

Control group amount of epileptic activity PII + PIV - PIII ns
(t = 1.96, df = 13)

Conclusion

Alcohol intake does not have a significant influence on the average amount of epileptic activity.

Correlation between stage PII + PIV and stage PIII as for the amount of epileptic activity both in control- and alcohol group.

	<u>Alcohol group</u>	<u>Control group</u>
Correlation coefficient	0.64	0.72
	$P < 0.01$	$P < 0.001$

Conclusion

There is a good correlation in various stages in both groups on the amount of epileptic activity.

7 Summary

The following was investigated.

1 The influence of alcohol on seizures: no effect was demonstrable.

2 a The influence of alcohol on blood levels of carbamazepine, phenobarbital and phenytoin was not affected by alcohol.

b The number of subjects taking primidone or ethosuximide was too small to permit any conclusion.

c The concentration of valproic acid was possibly influenced by alcohol, but requires further investigation.

3 Influence of alcohol on EEG

a The frequency of background rhythms was not altered.

b The amount of alpha, beta and theta activity did not change.

The number of subjects with delta activity was too small to permit any conclusion, as was the proportion showing abnormal reactions to photic stimulation.

c The amount of epileptic activity was not affected.

CHAPTER VII: SURVEY OF ATTITUDES TO ALCOHOL AND EPILEPSY IN 25 COUNTRIES

1 Introduction

In this chapter a review is given of the uses and limitations of a mail questionnaire. Likewise a review is given of the response rate in the various mail questionnaires reported by several authors and also more information is given on the methods that are used to increase the response rate. An explanation of the survey plan can be found after which the results of the inquiry are discussed. The response rate reported advice with regard to use of alcohol and counseling policy will be detailed, as well as to what extent the respondents believe that alcohol provokes seizures.

An analysis is made of a possible correlation between the advice with regard to alcohol use and belief in a possible provocative action of alcohol on the seizures. Subsequently the opinions will be examined of the influence of alcohol use on the blood levels of the anti-epileptics and the epileptic activity in the EEG. In Holland it was asked if, when advising patients, a distinction was made between the various alcoholic drinks.

These results will also be discussed.

Finally an analysis is made of a correlation between the answers to questions in the survey.

2 Uses and limitations of a mail questionnaire

In the lexicon of the Dutch Language by M.J. KOENEN/J. ENDEPOLS (1960) the word survey is explained as follows: "an investigation on a matter of public interest, of which the results usually are published".

'T HART (1974) gives in his thesis 'Selection and self-selection of inquiries' as explanation of the word survey: "no more or less than investigation, especially by interrogation". There are, in his opinion, 5 characteristics of the survey as a method to collect facts:

- 1 A method to collect facts specifically for purposes of scientific investigation.
- 2 To collect these facts informants are important. Verbal or written information can be given.
- 3 The number of informants is relatively large. The interview of 3

persons usually is not described as a survey, the questioning of 1.000 people is. The number of respondents to be surveyed depends on the degree of reliability, which the investigator requires.

- 4 In a survey the questions and observations are more or less the same for every participant. This 'more or less' indicates that the interviewer has some influence on the answering of the questions.
- 5 Information is collected in the field. The respondents are not therefore required to travel in order to be interviewed.

A survey can be verbal or written. The aim of the present survey among the Dutch neurologists was to get an insight into usual advice on the use of alcohol by epileptic patients. This survey was a postal one and will be discussed later. First some notes on the advantages and disadvantages of the mail questionnaire (SELLITZ et al. 1966, V. WILK 1975), the usual response and a way to increase the response.

a Advantages of the mail questionnaire

- The questionnaire is likely to be a less expensive procedure than a personal interview.
- It requires much less skill to administer than an interview; questionnaires are often simply mailed or handed to respondents with a minimum of explanation.
- Usually more informants can participate in the research.
- It is usually possible to cover a wider area and to obtain information from more people by means of questionnaires than by personally interviewing each respondent.
- The interviewer has no influence because of the standardization of the questions and the covering letter.
- The respondents may have greater confidence in their anonymity and thus feel free to express their views they fear might be disapproved of or might get them into trouble.
- Another characteristic of the questionnaire that sometimes it may be desirable, though not always, to place less pressure on the subject for immediate response. When the subject is given ample time for filling out the questionnaire, he can consider each point carefully rather than replying with the first thought that comes to

his mind, as often happens under the social pressure of long silences in an interview.

b Disadvantages in the mail questionnaire

- When questionnaires are mailed to a random sample of the population the proportion of returns is usually low, varying from about 10 to 50%.
- If the subject misinterpretes a question or records his responses in an unclear manner, there is usually little that can be done to remedy the situation.
- Complicated questionnaires requiring extensive written responses can be used with only a very small percentage of the population; only simple questions can be asked.
- The answers are final and no further explanation to the answers can be given.
- There is no stimulating influence of the interviewer.
- There is no control on the sequence in which the questions are answered.
- The interviewing situation offers a better opportunity than the questionnaire to appraise validity of reports.
The interviewer is in a position to observe not only what the respondent says but also how he says it. In a questionnaire there is no information concerning the circumstances of its completion.
- There is no insight in which way the non-response group diverge of the response group.

c Response rate in mail questionnaires

In the literature various authors consider the same response rate 'high' in mail questionnaires.

- GADOUREK (1976) mentions that a response rate of 40-50% is very high for a mail questionnaire (see table VII¹).
- HENSLEY (1974) reports that the response increases by stamping the pre-addressed letter to the respondent and the return envelope with different stamps. When the same stamps are used the response rate will be about 51%, but when these 2 letters are prepaid with different stamps, this will lead to a response rate of 61%.

- HOUSE et al. (1977): an average response rate of 53-60% can be registered as very high. However, it is less than the average response rate gained with personal interviews.
- KERLINGER (1970): the response on mail questionnaires is usually poor. A varying response rate of 40-50% is normal. Higher percentages hardly ever are obtained. A very satisfying response rate is 50-60%.
- MOOY (1978): the average response rate is 40-50%. He took a sample at random from the Dutch mailing list of educational workers and teachers of regional schools for training in vocational guidance.
Response of educational workers 58,8% (n = 305)
Response of teachers 54,1% (n = 269)
- BLUMBERG and co-authors (1974) are not optimistic about the response to mail questionnaires. They traced the influence of the day of the month the survey was sent, the length of the questionnaire, the fact if the respondent had to formulate his own answers or tick off fixed items. He also considered if promising money or presents increased the response. His average response rate was between 11 and 30% and only sometimes over 30% : 42 and 56%.

Table VII¹: Percentage response on mail questionnaire

Author	<u>Response on mail questionnaire</u>		
	Low response %	High response %	Very high response %
Gadourek	40	40-50	50
House a.o.			53-60
Kerlinger	40	40-50	50-60
Mooy		40-50	50-60

d Methods to increase the response to mail questionnaires

- Taking care that the questionnaire is easy.
- One can stamp the return envelopes; sometimes even more than one stamp is used, e.g. 4 stamps: of 2, 3, 5 and 10 cents instead of one 20 cent stamp, so that the respondent knows the investigator will

suffer a loss when he does not answer.

- The covering letter can be typed on personal correspondence paper and signed by the investigator. The nature of the accompanying letter requesting cooperation.
- A reminder can be sent to ask for response. This also can be done when the survey is anonymous: the investigator thanks the respondent in case he has already returned the completed questionnaire and asks the respondent to return it in case this has not yet been done.
- Promising a premium or money can also increase the response rate.

3 Survey plan

In Holland a survey was held among all neurologists. Through the Dutch League for Neurologists names and addresses were obtained. Addresses of practising neurologists abroad were merely obtained through the World of Learning (1980) in which addresses of several universities per country are mentioned.

In 26 countries the professor of neurology/psychiatry of several universities was approached. He was asked to distribute the survey forms among a number of colleagues, who had to return the forms to the investigator after they had been filled in. No reminders were sent. In some countries (Belgium, Denmark, United Kingdom, Canada and the United States) the cooperation was asked of the National Branch of the International League against Epilepsy.

In principle the survey was anonymous. The questionnaire was sent with an accompanying letter, in which the reason of this survey was explained.

Covering letter:

"Dear Colleague,

In December 1977 a research project was set up in the Epilepsy Centre Kempenhaeghe in Heeze, the Netherlands, on the influence of social use of alcohol on epileptic seizures. Here, social use of alcohol means a total of 1-3 glasses of alcoholic drinks in 1½-2 hours. The ethical aspects of this investigation are guaranteed by a committee of which the expert members are not related to the Epilepsy Centre. Chairman of this committee is professor P. VAN DER LUGT, neurologist. On the

subject whether to approve or not of the use of some alcohol by epileptic patients opinions differ. In a way this is understandable as there has never been any thorough scientific investigation of this matter.

We would like to have an impression of the opinion of the neurologists throughout the world on this matter. We will send this questionnaire to various clinics in different countries. The intention is not to gain some scientific justification but to learn what is usually advised in practice.

We enclose herewith some questionnaires. Would you be so kind to hand them over to your colleagues and ask them to return them completed. The results of the inquiry will be used for the purposes of a thesis concerning the influence of the social consumption of alcohol on epilepsy. We will send you in due course the results of the survey, which show the opinions prevailing in various countries.

We are looking forward to your reaction and thank you in advance".

Sincerely yours,

R.J.E.A. Höppener, neurologist

In Holland it was also checked by way of the questionnaire if a distinction was drawn between the various alcoholic drinks with regard to the advice (question 4). For the other countries this question was not included in the survey.

4 Questionnaire

- 1 Do you advise an epileptic patient spontaneously about the use of alcohol or do you wait until patient brings up the matter himself?
 - a spontaneous advice
 - b wait until patient himself asks
- 2 What is your advice to an epileptic patient on this matter?
 - a no use of alcohol
 - b incidental use of alcohol
 - c moderate use of alcohol
 - d no limitation

- 3 Do you think a few alcoholic drinks per evening can provoke epileptic seizures?
- a no
 - b to a limited extent
 - c yes
- 4 Do you see any difference in the various alcoholic drinks with respect to your advice?
- a yes
 - b no
- 5 Do you think a few alcoholic drinks per evening can change the blood levels of antiepileptic medication?
- a no
 - b to a small extent
 - c yes
- 6 Do you think that moderate use of alcohol increases epileptic activity on the electroencephalogram?
- a no
 - b sometimes
 - c often
 - d usually

Please send your questionnaire to:

Medical Secretariat Alcoholcommittee
Epilepsiecentrum Kempenhaeghe
Sterkselseweg 65
5591 VE HEEZE
The Netherlands

5 Results of the survey

a Response rate

In Holland everybody was addressed individually. In the rest of the countries a random sample had been taken whereby several (average 3) survey forms were sent to one person with the request to spread these among colleagues. Through this some distortion of the response rate may have been caused. In Holland 519 survey forms were sent, of

which 328 were returned (response rate of 63,2%).

Of the respondents 51 could not answer the questions, either because they treated too few epileptic patients where an advice with regard to alcohol use was relevant, or because they were no longer practising as clinical neurologists, so in total 277 completed survey forms were returned. 1.180 Questionnaires were sent to the other 26 countries. The response from 2 countries was so inadequate that these are excluded from further consideration.

From the other 24 countries in total 478 out of 1.120 forms have been completed and returned, giving a response rate of 42,7%.

Table VII² gives a review of the response rates per individual country.

Table VII²: Response Rate World Survey

Name of country	Forms sent	Response Number	%	Name of country	Forms sent	Response Number	%
Australia	30	10	33,3	Belgium	40	24	60,0
Finland	30	11	36,7	Chili	40	20	50,0
France	30	12	40,0	Denmark	40	20	50,0
Italy	30	12	40,0	United Kingdom	40	21	52,5
Yugoslavia	30	14	46,6	S.Africa	40	24	60,0
Norway	30	12	40,0	Czechoslovakia	20	5	25,0
Austria	30	6	20,0	Canada	60	27	45,0
Switzerland	30	17	56,6	China	60	10	16,6
Spain	20	9	45,0	India	60	14	23,3
Hungary	20	6	30,0	Germany	100	46	46,0
Poland	20	11	55,0	Japan	150	61	40,6
Ireland	20	5	25,0	United States	150	79	52,6
				Holland	519	328	63,2

Conclusion

The response rate on the survey was to be qualified as normal to high both nationally and internationally. This is probably caused by the great interest that exists for this problem as well as the lack

of literature on which an opinion can be based.

b Advice with regard to use of alcohol

Since an opinion about alcohol use by epileptic patients was not based on scientific investigations, one could expect a great variety in the advice within a country as well as between the several countries. The 25 countries who took part in the investigation were divided into 3 categories: permissive, moderate and strict with reference to their attitude with regard to the advice on alcohol use.

Criteria:

- 1 Category permissive: 40% or more of the respondents allow social use of alcohol
- 2 Category moderate : 10-39% of the respondents allow social use of alcohol
- 3 Category strict : 0-9% of the respondents allow social use of alcohol

Similar numbers of countries fell in each category, so that in the category permissive, moderate, strict respectively 9, 8, 8 countries were represented.

Table VII³ gives a review of the countries per category.

Table VII³: Attitude with regard to Alcohol advice per country

Cat. permissive > 40% positive		Cat. moderate 10-40% positive		Cat. strict 0-9,9% positive	
Denmark	80 %	Japan	32,8%	Yugoslavia	7,1%
United Kingdom	61,9%	Australia	30,0%	Germany	6,5%
Ireland	60,0%	Finland	27,3%	Hungary	0 %
India	57,1%	Switzerland	17,6%	Austria	0 %
S.Africa	52,4%	Italy	16,7%	Poland	0 %
France	50,0%	Chili	15,0%	Spain	0 %
Canada	48,1%	China	10,0%	Czechoslovakia	0 %
Norway	46,2%			Belgium	0 %
United States	44,3%				

Factor determining attitudes are not immediately obvious. Countries with a high social alcohol consumption fall in all 3 categories (e.g. Ireland, France - 'permissive'; Australia, Japan - 'moderate'; Hungary, Poland, Spain - 'strict'). An influence of a prevailing or state religion is also inapparent. The predominantly catholic countries are also distributed between all 3 groups (Ireland, France - 'permissive'; Chili - 'moderate'; Austria, Belgium, Poland, Spain - 'strict'). The 4 socialist countries are all to be found in the strict group. This association is highly significant ($P < 0,01$ by FISCHER's exact probability test 2 tailed), but considering that Germany and Austria fall in the same category the effect may well be geographical rather than political. A striking effect more readily acceptable at its face value is the association of permissive attitudes with former membership of the British Empire ($P < 0,01$ by FISCHER's exact probability test 2 tailed).

Table VII⁴ gives a summary per category with regard to the advice: no alcohol use, incidental alcohol use and moderate alcohol use allowed.

Table VII⁴: Advice Alcohol Use

Advice	The Netherl. %	Cat. permissive %	Cat. moderate %	Cat. strict %
No use	33	19	44	82
Incidental use	42	29	31	15
Moderate use	25	52	25	3
	100 n = 277	100 n = 215	100 n = 141	100 n = 121

Conclusion

With regard to the advice on alcohol use by epileptic patients there is a great variety. The percentage of respondents allowing alcohol varies per country for 0-80%. Since this attitude can not be

supported by scientific investigations the basis of this attitude will probably be underlined by special cultural and social factors.

c Advice attitude

With regard to the advice of alcohol use the specialist himself can take the initiative to inform the patient on the possible influence of alcohol use on his epilepsy or take a more passive attitude and only give an advice after the patient asked for it. For the greater part of the respondents there is an active policy with regard to the advice. In the category 'strict' 97,5% of the specialists pursue an active policy while this varies between 77,7 and 84,4% in the other categories.

Table VII⁵ gives a summary with regard to initiative.

Table VII⁵: Advice attitude

Advice	The Netherl. %	Cat. permissive %	Cat. moderate %	Cat. strict %
Spontaneously offered	83	78	84	97
Given when requested	17	22	16	3
	100 n = 277	100 n = 215	100 n = 141	100 n = 121

$$x^2 = 23,18$$

$$df = 3$$

$$P < 0,001$$

Conclusion

Among the categories 'the Netherlands', 'permissive', 'moderate' and 'strict' there is a significant difference in advisory attitude. The most active advisory policy is pursued in those countries which most discourage alcohol use. In all countries the greater part of the specialists advice actively.

d Use of alcohol - provocation of seizures

The opinion about the provocative action of alcohol on the seizures showed great differences between the various countries as well. In Denmark only 5% of the respondents ascribed a provocative action to alcohol (lowest score), while in Hungary 83% was of the opinion that alcohol use most certainly caused seizures (highest score). In the categories 'permissive', 'moderate' or 'strict', with regard to their advice on alcohol use, opinions on the provocative action of alcohol were also very varying. Although Ireland was allocated to the category 'permissive' with regard to the advice, it reached the highest score after Hungary concerning the provocative action of alcohol on the seizures. Poland arranged in the category 'strict', ranked 8th of the countries which ascribed little provocative action to alcohol.

Table VII⁶ gives a review of the percentage of respondents per country who certainly ascribe a provocative action of alcohol on seizures. In this table also the rank number is mentioned which the country takes in its attitude with regard to alcohol advice. Denmark, where 80% of the specialists allow alcohol, has rank number 1, United Kingdom rank number 2, etc. See also table VII³. Holland ranks 13 as for its attitude with regard to the allowance of alcohol use.

There is a positive correlation between the advice on alcohol use and the opinion with regard to the provocation of seizures by alcohol (SPEARMAN's $r = 1.247$, $P < 0,02$). The rank correlation coefficient of SPEARMAN R_s comes to 0,52.

Table VII⁶: Provocation of seizures by alcohol

No.	Country	%	Rank number adv. on alc. use	No.	Country	%	Rank number adv. on alc. use
1	Denmark	5	1	14	Yugoslavia	50	18
2	India	7	4	15	Norway	54	8
3	Japan	16	10	16	Finland	55	12
4	Italy	17	15	17	France	58	6
5	United Kingdom	19	2	18	Czechoslovakia	60	22,5
6	China	20	17	19	Chili	60	16
7	S.Africa	25	5	20	Austria	67	22,5
8	Poland	36	22,5	21	Spain	67	22,5
9	The Netherl.	36	13	22	Germany	72	19
10	United States	38	9	23	Belgium	74	22,5
11	Canada	41	7	24	Ireland	80	3
12	Switzerland	41	14	25	Hungary	83	22,5
13	Australia	50	11				

SPEARMAN test quantity $r = 1.247$

Rank correlation coefficient of SPEARMAN $R_s = 0,52$

Significance $P < 0,02$

Table VII⁷ gives a review of the average scores in the several categories as for the provocative influence of alcohol on seizures. In Holland 16 respondents did not have an opinion on this subject; in the category 'permissive', 'moderate' and 'strict' this were 6, 1 and 0 respondents respectively. Therefore they are not mentioned in this table.

There is a clear significance for the correlation between the category in which a country is classified on the principle of alcohol use and the opinion if alcohol whether or not provokes seizures.

Table VII⁷: Review average scores of provoked seizures by alcohol use

Provocation	The Netherl. %	Cat. permissive %	Cat. moderate %	Cat. strict %
No	28	24	16	7
Small amount	36	42	52	27
Yes	36	34	32	66
	100 n = 261	100 n = 209	100 n = 140	100 n = 121

$$\chi^2 = 57,29$$

$$df = 6$$

$$P < 0,001$$

Conclusion

In more than half of the investigated countries the greater part of the specialists is of the opinion that alcohol use provokes seizures. However, this opinion does not always imply that in consequence of this with respect to the social use of alcohol a negative attitude is taken. The specialist rather often allows social use of alcohol in spite of his opinion that it provokes seizures.

e Relation alcohol use - influence of blood levels on antiepileptic drugs

In the literature the information on the influence of alcohol on the blood levels of antiepileptic drugs is very scarce. Articles on this subject usually are published in magazines which are not in the field of interest of the clinical specialists. In fact the expectation was a considerable variety of answers on the questions in the survey. Table VII⁸ gives a review of this.

The great number of respondents in Holland who, in comparison with the other categories, answered this question with 'no opinion' is

striking. Consequently there is a significant difference in answers in the several categories.

At the same time the relation was studied between the advice with regard to alcohol use and the expected influence of alcohol on the blood levels. This was done per category 'permissive', 'moderate', 'strict' and 'the Netherlands'.

The respondents who answered the question with 'no opinion' were not mentioned in the tables.

Table VII⁸: Influence of alcohol use on blood levels

Influence	The Netherl. %	Cat. permissive %	Cat. moderate %	Cat. strict %
None	32	45	32	26
Small amount	19	26	37	26
Yes	14	18	24	31
No opinions	35	11	7	17
	100 n = 277	100 n = 215	100 n = 141	100 n = 121

$$\chi^2 = 97,98$$

$$df = 9$$

$$P < 0,001$$

As appears from the tables VII⁹⁻¹⁰⁻¹¹⁻¹² only in the category 'permissive' there is a significant association between the advice and the expected influence on the blood levels.

Table VII⁹: Crosstabulation Advice - Influence on Blood levels

The Netherlands

Advice	Effect on blood levels		
	Yes %	Small amount %	No %
No use	46	26	28
Incidental	39	42	44
Moderate	15	32	52
	100 n = 39	100 n = 53	100 n = 89

$$\chi^2 = 6,14$$

$$df = 4$$

No significance

Table VII¹⁰: Crosstabulation Advice - Influence on Blood levels

Permissive

Advice	Effect on blood levels		
	Yes %	Small amount %	No %
No use	32	19	12
Incidental	42	30	27
Moderate	26	51	61
	100 n = 38	100 n = 57	100 n = 97

$$\chi^2 = 14,05$$

$$df = 4$$

Significance $P < 0,007$

Table VII¹¹: Crosstabulation Advice - Influence on Blood levels

Moderate

Advice	Effect on blood levels		
	Yes %	Small amount %	No %
No use	47	42	47
Incidental	29	31	33
Moderate	24	27	20
	100 n = 34	100 n = 52	100 n = 45

$$\chi^2 = 0,74$$

No significance

Table VII¹²: Crosstabulation Advice - Influence on Blood levels

Strict

Advice	Effect on blood levels		
	Yes %	Small amount %	No %
No use	76	88	77
Incidental	24	6	16
Moderate	0	6	7
	100 n = 37	100 n = 32	100 n = 31

$$\chi^2 = 6,19$$

$$df = 4$$

No significance

Conclusion

When excluding the respondents who have 'no opinion', there is within the category usually no significant relation between advice on alcohol use and the expected influence on the blood level. Only in the category 'permissive'. However, there are significant differences between the categories.

f Relation alcohol use - influence epileptic activity EEG

With an increase of the amount of seizures, an increase of the amount of registered epileptic activity can also be expected. In the literature there is a lot of information on the activation of the desynchronisation of the EEG by alcohol in low dosages, but there is no information whether epileptic activity is provoked by this. In fact the expectation was a great variety of answers on the question posed in the survey.

Table VII¹³ gives a review of this.

Table VII¹³: Influence of alcohol use on the epileptic activity in the EEG

Influence	The Netherl. %	Cat. permissive %	Cat. moderate %	Cat. strict %
None	28,2	48,0	22,0	17,3
Incidental	22,0	38,1	59,5	49,6
<i>Rather often</i>	12,3	0,5	6,4	7,4
Often	3,2	0,9	6,4	16,6
No opinion	34,3	12,5	5,7	9,1
	100 n = 277	100 n = 215	100 n = 141	100 n = 121

$$\chi^2 = 193,8$$

$$df = 12$$

$$P < 0,001$$

Just as with the reaction on the questions concerning blood levels, the large number of respondents in Holland who answered this question with 'no opinion' is remarkable. In Holland this percentage was about 34, in the rest of the categories this percentage varied between circa 6 and 12,5. Here too there is a statistical significant difference in answers in the various categories.

At the same time the relation was studied between the advice with regard to alcohol use and the expected influence of alcohol on the epileptic activity in the EEG. This was done per category 'permissive', 'moderate', 'strict' and 'the Netherlands'. The respondents who had no opinion on this question are not included in the tables.

As appears from the tables VII¹⁴⁻¹⁵⁻¹⁶⁻¹⁷ with the exception of the category 'strict', there is a significant association between the advice and the expected influence on the epileptic activity in the EEG.

Table VII¹⁴: Crosstabulation Advice - Influence on EEG

The Netherlands

Advice	Effect on EEG			
	Yes %	Small amount %	Incidental %	No %
No use	67	53	29	15
Incidental	33	35	38	46
Moderate	0	12	33	39
	100 n = 9	100 n = 34	100 n = 61	100 n = 78

$$\chi^2 = 25,37$$

$$P < 0,001$$

Table VII¹⁵: Crosstabulation Advice - Influence on EEG

Permissive

Advice	Effect on EEG			
	Yes %	Small amount %	Incidental %	No %
No use	100	0	26	13
Incidental	0	100	34	27
Moderate	0	0	40	60
	100 n = 2	100 n = 1	100 n = 82	100 n = 103

$$\chi^2 = 19,17$$

$$df = 6$$

$$P < 0,01$$

Table VII¹⁶: Crosstabulation Advice - Influence on EEG

Moderate

Advice	Effect on EEG			
	Yes %	Small amount %	Incidental %	No %
No use	89	56	43	32
Incidental	0	44	30	42
Moderate	11	0	27	26
	100 n = 9	100 n = 9	100 n = 84	100 n = 31

$$\chi^2 = 13,01$$

$$df = 6$$

$$P < 0,05$$

Table VII¹⁷: Crosstabulation Advice - Influence on EEG

Strict

Advice	Effect on EEG			
	Yes %	Small amount %	Incidental %	No %
No use	95	78	80	76
Incidental	5	22	17	14
Moderate	0	0	3	10
	100 n = 20	100 n = 9	100 n = 60	100 n = 21

$$x^2 = 5,42$$

$$df = 6$$

No significance

Conclusion

With the exclusion of the respondents who had no opinion there is except for the category 'strict' a significant relation between advice of alcohol use and the expected influence on the epileptic activity in the EEG.

g Relation alcohol advice - distinction

The Dutch respondents were also asked whether a distinction was made between different alcoholic drinks with regard to the advice. From this there appeared to be a significant relation between the advice and the distinction that was made between the various alcoholic drinks. See table VII¹⁸.

Table VII¹⁸: Crosstabulation advice - distinction alcoholic drinks

Advice	Distinction	
	Yes %	No %
No use	15	40
Incidental	59	35
Moderate	26	25
	100 n = 78	100 n = 198

$$\chi^2 = 18,34$$

$$df = 2$$

$$P < 0,0001$$

Conclusion

There is a significant relation between the advice concerning alcohol use and the distinction of alcoholic drinks.

h Correlation between the questions in the survey

It might be expected that if the views of the respondents were consistent, then their classification of general attitude as 'strict', 'moderate' or 'permissive' should be paralleled by the answers to the other questions. Those clinicians, who take a restrictive view, might be expected to justify this by the assertion that alcohol provokes seizures, adversely effects blood levels of drugs and changes the EEG. In general this was the case both for the Dutch respondents (table VII¹⁹) and for those from the rest of the world (table VII²⁰). In both groups the weakest correlation was found between 'attitude' and 'blood level'. Thus it was evident that a general position adopted by physicians concerning alcohol and epilepsy influenced not only their views on subjective matters but also their views concerning factual matters, which they could readily determine both from their own practice and from the published literature.

Table VII¹⁹: Correlation coefficients the Netherlands, n = 150

	Attitude	Advice	Provoc.	Blood level	EEG
Attitude	1,00	0,32	0,36	0,16	0,31
Advice		1,00	0,65	0,19	0,38
Provoc.			1,00	0,39	0,52
Blood level				1,00	0,38
EEG					1,00

P = 0,05

when $r \geq 0,16$

Table VII²⁰: Correlation coefficients rest of the world, n = 552

	Attitude	Advice	Provoc.	Blood level	EEG
Attitude	1,00	0,23	0,24	0,12	0,18
Advice		1,00	0,40	0,21	0,38
Provoc.			1,00	0,28	0,40
Blood level				1,00	0,27
EEG					1,00

P = 0,01

when $r \geq 0,12$

Conclusion

Both in the Netherlands and in the rest of the world there is a reasonable correlation between the answers on the various questions, whereby it is striking that both in the Netherlands and in other countries the smallest correlation exists between 'attitude' and 'blood level'.

CHAPTER VIII: DISCUSSION

1 Social aspects

When someone suffers from seizures which are diagnosed as epileptic in nature this is likely prove a source of considerable inconvenience and distress. After only a few attacks have occurred the patient's friends, relatives and physician are liable to attempt to impose a variety of restrictions which impair the patient's social functioning. Friends and relatives are concerned by the still wide-spread though totally unfounded belief that each seizure causes a loss of brain cells leading to eventual dementia. The possibility of successful treatment is generally viewed with a pessimism which is not justified by the relevant literature. From recent studies it appears that it is possible to achieve freedom from seizures in some 70% of patients and in 85% the quality of seizure control is sufficient to permit a normal life-style. In children this anxiety leads to overprotection which itself limits social interaction and leads to isolation from other children. Similarly the patient's self-confidence is diminished and his academic achievements are likely to be impaired. The psychosocial and educational disfunction of the patient is thus determined not so much by the epilepsy itself as by social attitudes towards the disease. A variety of unnecessary restrictions are imposed on the daily activities of adults. This practice can be explained only on the basis of prejudice, for numerous published studies have indicated that employed persons with epilepsy have an accident rate no higher than others.

The patient's chances of obtaining employment in the first place are prejudiced by a variety of misconceptions concerning the physical risks of the major convulsion, personality problems, frequent sick leave etc.

Consequently many patients conceal their epilepsy when applying for a job, with some justification, in that in 75% their epilepsy apparently has no adverse effect upon their work performance. Similarly, sporting activities are frequently restricted without adequate grounds and persons with epilepsy can in fact indulge in most field sports without

restriction. Swimming is perhaps a special case as it is particularly difficult and sometimes impossible to lift an adult out of the water during a convulsive seizure. Regarding driving licences, there are legal restrictions which are frequently ignored. In fact it appears that a patient with well-controlled seizures causes no more accidents in urban traffic than the rest of the population. People who have epilepsy do suffer more road traffic accidents, not involving other vehicles, on quiet country roads. The strict rule that for possession of a driving licence freedom of seizures is mandatory is clearly not regularly enforced and this would appear to be a favourable and not unreasonable development.

The use of alcohol plays an important role in normal social behaviour. Refusal of alcoholic drinks elicits a variety of reactions and questions. If abstinence is not voluntary but imposed on account of epilepsy it is experienced as distressing and discriminatory. The forbidding of the use of alcohol without specific reasons is therefore unjustifiable. The sedative effect of alcohol and possible antiepileptic action are rarely mentioned as positive arguments for its use. For these reasons the above study was carried out. Some further comments may be necessary concerning the composition of the experimental groups, the influence of alcohol on seizures, blood levels of antiepileptic drugs, biochemical variables, alcohol concentrations and EEG effects. Finally, some comments will be made concerning the results of the questionnaire.

2 The groups that were examined

In respect of the items type of epilepsy, age, sex, medication and seriousness of brain damage, the control- and alcohol group were completely comparable. In our study the distribution of the types of epilepsy, 54% generalized epilepsy, of which 50% secondary generalized epilepsy and 46% partial epilepsy, differs from the findings of BICARD et al. (1955), VAN HEYCOP TEN HAM (1974) and GASTAUT (1975). BICARD et al. (1955) found in a group of epileptic patients who were chosen at random the following: 27,5% generalized epilepsy, 72,5% partial epilepsy. VAN HEYCOP TEN HAM (1974) found the following division: primary generalized epilepsy in about 30%, secondary generalized epilepsy in about 10% and partial epilepsy in about 60% of

the total population of epileptic patients. In the age category over 15 years GASTAUT (1975) came to a division of 22,3% generalized epilepsy of which 1,9% was secondary generalized and in 77,7% partial epilepsy. In our material the occurrence of primary generalized epilepsy and partial epilepsy is much lower, while the number of patients with secondary generalized epilepsy is much higher. This reflected the fact that the persons participating in our study were mostly resident in an institution on account of amongst other factors, therapy-resistant epilepsy. The percentage of brain damage often combined with a difficult therapeutic control was in our group 59,6. These findings agree with those of GASTAUT (1976) who, during computerized tomography examination with patients with a primary generalized epilepsy, found abnormalities in 11%, with secondary generalized epilepsy in 61% and with focal epilepsy in 53%.

The number of prescribed drugs, about 2,8 per epileptic patient, also reflects the difficulties of therapeutic control. However, this number is considerably lower than the average of ca. 3,8 medicament that was prescribed to the Dutch epileptic patient in 1974 (GUELEN and VAN DER KLEYN 1978).

Although the division of the kinds of epilepsy in the groups examined differs from the findings in literature there are no indications that alcohol intake has a selective provocative effect in a particular form of epilepsy.

3 Seizure control

In several textbooks the use of alcohol is considered to be one of the provocative factors for the precipitation of attacks. However, none of the authors refers to published studies on which they base their pronouncements. There are some authors with a more or less qualified opinion who do draw the attention to the possibility that alcohol intake can be accompanied by lack of sleep, or an unreliable intake of drugs, which may provoke seizures. In this study RODIN (1961) could not prove an influence on the epileptic attacks, when administering a single high dose of alcohol. However, his findings must be viewed with some reservations. In view of the large spontaneous fluctuations in the seizure frequency (see findings of our study) it is very difficult to

check a possible change in seizure frequency during an experiment that was only performed once and in a short period.

How far alcohol use influences the blood levels of the anticonvulsants and thus changes the seizure frequency also was not discussed. In view of the plan of his study a strong seizure provocation by alcohol can be excluded; no opinion can be given upon the provocative effect of a smaller quantity of alcohol during a longer time. The often negative attitude with respect to alcohol intake is possibly also caused by several studies on the relations of alcohol abuse and the occurrence of seizures. These seizures occur after cessation of alcohol use and can be considered as abstinence symptoms and were wrongly termed alcohol epilepsy. In other withdrawal seizures, e.g. phenobarbital, we do not use the term phenobarbital epilepsy.

In our study no influence of alcohol could be proved when using 1-3 glasses of alcohol, twice a week during 16 weeks. This agrees with the practical experience of LIVINGSTONE (1972) who allows his epileptic patients moderate alcohol use during the treatment and who has never been able to establish provocation of the seizures by such use, in more than 5.000 adult patients treated by him.

4 Blood levels

a Carbamazepine

The serum concentration of carbamazepine shows large fluctuations in the course of the day (HOPPENER et al. 1980). In this study we could also ascertain that with one and the same patient there usually are large differences between the blood level concentration in the morning and in the evening. No studies were known on the influence of ethanol on the pharmacokinetics of carbamazepine. Our study proves that the carbamazepine serum concentration is not influenced by social use of alcohol.

b Ethosuximide

In view of the long half-life of ethosuximide, between 35-50 hours, the differences between blood level concentrations will be small in the morning and in the evening. We also notice that the fluctuations

between the serial determinations per patient are small and thus there is a high reproducibility of the concentration that was measured once. Until now no studies were known on the influence of ethanol on the ethosuximide blood level concentration. Though the number is small, $n = 5$, in our study no alcohol effect on the ethosuximide level can be proved.

c Phenobarbital

Phenobarbital has a half-life varying between 53 and 140 hours. In consequence of this the fluctuations in the serum concentrations will be small in the course of the day, while also the reproducibility of the once measured concentration was so large that DRIESSEN and HOPPENER (1977) used this stability as an indicator for otherwise reliable intake of the medication.

By adding valproic acid to phenobarbital the serum concentration of phenobarbital is influenced very varyingly. In ca. 50% of the persons an increase of the phenobarbital level is caused, which increase can vary from 30 to more than 100%. The valproic acid concentration also shows strong fluctuations in the course of the day, the differences between 2 concentrations can be 300%, while also the reproducibility of a single measurement of valproic acid concentration is poor. It is possible that those mechanisms played a part in the development of the slightly significant differences in the control group, where 4 patients used a combination of phenobarbital and valproic acid, between the phenobarbital levels in the 2 stages at 8 a.m. In the literature little information was known on the influence of ethanol on the steady state phenobarbital levels.

CURRY (1973) observed a faster absorption of phenobarbital when it was administered simultaneously with ethanol, but the total amount of the absorbed phenobarbital remained the same. Thus he could not prove an influence of ethanol on the steady state levels of phenobarbital. Our investigation proved also that ethanol does not have an influence on this.

d Phenytoin

The relationship between phenytoin dosage and the observed plasma concentrations in a patient is not linear, as higher doses of phenytoin will yield superelevated plasma concentrations (REMMER 1969). In man, the most important step in the elimination of phenytoin is its conversion into parahydroxy-phenytoin in the liver cell. It is assumed that the enzyme system in the endoplasmatic reticulum will already become saturated or inhibited in the therapeutic dose range (GLAZKO 1972, PERUCCA et al. 1978), which explains the observed non-linear relationship. By this and dependent on the serum concentration the reproducibility of the once measured concentration can be very varying per individual. With heavy practising alcoholics there is an accelerated break-down of phenytoin by ethanol.

The results of the study of DE LEACY (1979) showed that incidental social alcohol intake had no significant effect on the plasma phenytoin level. In our study we found that the phenytoin level was not altered by regular social alcohol intake.

e Valproic acid

VREE and VAN DER KLEIJN (1977) proved with laboratory animals that a high dosage mg/kg of valproic acid leads to an interaction between alcohol and valproic acid expressing itself in a retarded elimination of both components. SCHOBEN (1979) proved with a volunteer that the combination of the usual dose of valproic acid and ethanol is not likely to cause serious interference with elimination in man. This study was, however, too small to draw a definite conclusion.

In the course of the day the valproic acid concentrations show large fluctuations, the differences between 2 serum levels of valproic acid in one patient on the same day can vary more than 200%. The reproducibility of the measured valproic acid serum level is also very bad. This means that in the same patient 2 determinations on different days on the same conditions (same time of blood sampling, unchanged medication) show large differences in valproic acid level (HOPPENER 1979). This is perhaps the reason for the significant difference of the valproic acid concentration at 8 a.m. in the control group. Therefore the interpretation of the significant differences between

the 2 stages in the alcohol group both at 10 p.m. and 8 a.m. is very difficult. The increase of the valproic acid concentration could be caused by the ethanol as well as by coincidence. Before giving an opinion upon this a more detailed study is required.

5 Chemical blood examination

During the course of the investigation all concentrations of the determined substances remained within the norm. The sensitiveness of the gamma-GT concentration for alcohol use was known and it was not surprisingly that this concentration was elevated in the evening following the alcohol use. No data were known concerning the influence of alcohol on the alkaline phosphatase concentration. It is possible that the use of antiepileptic drugs enhances the sensitivity of the liver to alcohol. It is not evident whether or not the elevation of alkaline phosphatase arises from bone or liver. Further detailed investigation will be necessary to get an insight into which fraction of the alkaline phosphatase is raised.

6 Alcohol concentration

The alcohol metabolism is different from person to person. However, one can roughly estimate that having a glass of beer on an empty stomach gives a blood level of 0,15 to 0,20 ‰. Whenever food is present in the stomach while drinking, the contribution per glass has to be estimated 20 to 40% lower, so minimum 0,09 ‰ and maximum 0,16 ‰. To the patients taking part in the examination, vodka with orangeade was administered, whereby the alcohol concentration per 100 ml was similar to the alcohol concentration of a glass of beer, so that the contribution to the blood alcohol level per glass of alcoholic beverage is comparable to that of beer. At 6 p.m. the patients ate a warm meal. At 8 p.m. when they started drinking there certainly was still some food left in the stomach. Without making allowance for the elimination, the use of 3 glasses of alcohol on a stomach with food would lead to an alcohol concentration of minimum $3 \times 0,09 = 0,27$ ‰ and maximum $3 \times 0,16 = 0,48$ ‰ (see above). The average alcohol elimination is 0,15 ‰ per hour. At judicial inquiry in Holland, when estimating the alcohol permillage one starts from the principle of an elimination of

0,20 ‰ per hour. Theoretically the maximum alcohol concentration in our investigation at 10 p.m. could be $3 \times 0,16 = 0,48$ ‰ minus 0,15 ‰ for the elimination = 0,33 ‰. This level will only be reached under the following optimum circumstances:

- 1 Maximum contribution per glass to the absorption 0,16 ‰.
- 2 Use of maximum glasses of alcohol, 3.
- 3 Very slow elimination, 0,15 ‰ in $1\frac{1}{2}$ hour. In our investigation the first glass of alcohol was always used a half hour past 8 p.m. Blood sampling for alcohol determination was at 10 p.m.
- 4 Hardly any use of phenobarbital since this might increase the elimination of alcohol.

The value of 0,33 ‰ was also obtained once. Usually the alcohol concentration will be much lower. Theoretically the alcohol concentration can be zero at 10 p.m., when 1 or 2 glasses are used in the first half hour of the 2 hours period and there is a fast elimination. We did not see it in our study.

7 EEG registration

In total 4 EEG registrations were made; 2 in the alcohol stage and 2 in the stage without alcohol. The EEG registrations in the alcohol stage were made on the morning following the evening of alcohol intake. The blood alcohol was then reduced to zero. In case of chronic abundant alcohol intake an over-excitement of the brain can still be proved some days after alcohol consumption has been stopped. With social alcohol use it was not to be expected that a change in frequency bands, alpha, beta, theta and delta would be found. This was also confirmed during our investigation. There also were no signs of changed over-excitement during provocation with hyperventilation and light-flash stimulation. Finally the average amount of epileptic activity also stayed unchanged in both periods, indicating that when using this amount no rebound effect occurs. One may assume that the amount of epileptic activity strongly varies per registration through which the change in the amount of epileptic activity per individual is no indication for a provocative action of alcohol or otherwise; but in case of provocation a tendency would have to be perceptible in the entire group.

This agrees with the findings of KUYER (1979) who made extensive EEG

registrations during and after abundant alcohol use with some patients in whom alcohol was expected to have a provocative action. She too had never been able to perceive an increase of the epileptic activity.

8 Survey

In our mail questionnaire the response rate could be qualified as normal to high, both nationally and internationally. This reflects the great interest that exists for this problem. With the advice on alcohol use by epileptic patients there was a great variety with regard to the advice. This was not surprising because there is a lack of studies on which an opinion on this topic can be based. Remarkably nevertheless was the great variety in answers in several neighbouring countries as France and Spain, Denmark and Germany, etc.

In view of the association of permissive attitudes to the use of alcohol with English speaking countries and the predominance of central European countries in the category 'strict', it appears that the advice concerning use of alcohol is principally determined by cultural factors. The percentage of respondents permitting alcohol ranged from 0-80. The attitudes in the Netherlands were less permissive than might have been expected and only 25% of the Dutch respondents permitted social use of alcohol. There was a general attitude of the respondents expressing itself in a good correlation between the answers on the various questions. It also appears that general attitude influences reply to factual questions concerning EEG and blood levels. In the Dutch respondents and those from the rest of the world the weakest correlation was found between 'attitude' and 'blood level'. The ignorance of the pharmacokinetics of the antiepileptic drugs on the part of most of the neurologists probably plays a part in this small correlation.

Although there are doctors who sometimes are of the opinion that alcohol use provokes seizures, they will not always dissuade a patient from alcohol use. An explanation for this can be:

- 1 The doctor knows that his advice (prohibition) is neglected by the patient.
- 2 He thinks it an unacceptable intervention in the personal freedom of the patient.
- 3 When weighing the interests the social aspects seem to prevale

against the medical objections. So before he makes a decision the doctor also implicates several non-medical aspects in his opinion.

9 How to advice in practice

An absolute alcohol prohibition for epileptic patients can no longer be justified. However, when advising one will have to check per patient if there are no objections against incidental or social alcohol use. There can be some reservations because:

- 1 The patient does not follow the prescribed advice, or follows it badly, expressing itself in e.g. a bad compliance of his medication intake.
- 2 In the history there was question of alcohol abuse.
- 3 There exists an 'individual sensitiveness' for alcohol. Although these patients did not occur in our investigation, this can not be excluded with certainty.

The attitude of the attending specialist should not play a part in the advice.

10 Further studies

In this thesis not all the changes that occurred could be explained with certainty.

- 1 Does social alcohol use have an influence on the valproic acid levels. Although there were positive indications, further investigation would be necessary in order to come to a more reliable pronouncement.
- 2 Which mechanism is responsible for the increase of the alkaline phosphatase serum concentration after alcohol use. Which fraction of the alkaline phosphatase is responsible for this increase.
- 3 A follow up questionnaire after some years.

SUMMARY AND CONCLUSION

People suffering from epileptic seizures are often confronted with restrictions resulting from their attacks, as exclusion from several professions, not being allowed to drive a car, being excluded from some sports and prohibition of alcohol.

This absolute alcohol prohibition could not always be realized. However, after relaxation of this prohibition no influence of alcohol on the seizure frequency could be perceived.

Consultation of manuals in order to trace the literature studies on which this prohibition was based, was unsuccessful since there was no mention of the original research from which it appeared that alcohol was provocative of seizures.

To be able to give a well-founded pronouncement on the influence of social alcohol intake on epilepsy research was undertaken with epileptic patients who had never before or very sporadically used alcohol.

During 16 weeks - twice a week - in a clinical setting 1 to 3 glasses of alcoholic beverage were used within a period of 2 hours. The examination could be carried out double blind since the drink that was chosen - vodka - is odourless and can not be tasted when mixed with orangeade.

The following items were examined

- 1 Does the seizure frequency change in case of social use of alcohol?
- 2 What is the effect of alcohol intake on the blood levels of anti-convulsants?
- 3 Are there any changes in the epileptic EEG activity induced by alcohol intake?
- 4 What are the attitudes of the Dutch neurologist and his foreign colleagues with regard to alcohol intake by epileptic patients?

Since the use of alcohol belongs to one of the social aspects of epilepsy, in this thesis full attention is also paid to several other social aspects of epilepsy, for instance the influence of the onset of epilepsy on the education of the child, outlook on the future, school attainment and what factors can influence employment. Consideration is also given to the relation epilepsy-exercise as well as the conditions on which various

countries allow driving licences to epileptics and the accident frequency of epileptic patients in comparison with a control group.

It goes without saying that special attention is paid to alcohol metabolism and the influence of alcohol intake on drugs and the electric activity of the brain cells.

There is also a review of literature on the relation alcohol use and seizures in which case it is conspicuous that this is virtually confined to the relation of alcohol abuse with the occurrence of attacks. The cooperation in the inquiry into the attitude of the attendant specialist with regard to alcohol intake with epileptic patients was very large. The response of the Dutch neurologists was very high and came to 63%. From the other 24 countries in total 478 forms have been completed and returned, giving a response rate of 42,7%.

The differences in attitude between the various countries were very large and so it could happen that in one country 90% of the respondents believed in an absolute alcohol prohibition, while in another country 80% of the respondents believed in social alcohol use.

Conclusions

- 1 No influence of social alcohol use on epileptic seizures is demonstrable.
- 2 The blood levels of carbamazepine, phenobarbital and phenytoin are not influenced by alcohol intake. The valproic acid concentration is possibly slightly increased. However, this needs further examination before pronouncements can be made.
- 3 Both in frequency bands and in the amount of epileptic activity no change is produced by alcohol use.
- 4 The attitude of specialists with regard to alcohol intake by epileptic patients is very contradictory and differs very strongly between countries.

SAMENVATTING EN CONCLUSIE

De mensen die last hebben van epileptische aanvallen worden hierdoor nogal eens geconfronteerd met diverse beperkingen, voortvloeiende uit hun aanvallen, zoals onder andere het onbereikbaar zijn van diverse functies, het niet mogen autorijden, het uitgesloten zijn van sommige sporten en het verbieden van alcohol.

Dit absolute alcoholverbod was in de praktijk niet altijd realiseerbaar. Na ontheffing van dit verbod kon echter geen invloed van alcohol op de aanvalsfrequentie worden waargenomen.

De raadpleging van handboeken om na te gaan op welke literatuurstudies dit verbod gebaseerd was, leverde een teleurstellend resultaat op daar er geen bronvermelding was waaruit bleek dat alcohol aanvalsprovocerend was.

Ten einde een goed gefundeerde uitspraak te kunnen doen over de invloed van sociaal alcoholgebruik op epilepsie werd een onderzoek gestart bij epilepsiepatiënten, die voordien nooit of zeer sporadisch alcohol gebruikt hadden.

Gedurende 16 weken werd in een klinische setting 2 maal per week 1 tot 3 glazen alcoholhoudende drank geconsumeerd in een periode van 2 uur. Door de keus van de drank - wodka, reukloos en in sinas niet te proeven - kon het onderzoek dubbelblind worden uitgevoerd.

Onderzocht werden

- 1 Verandert door sociaal alcoholgebruik de aanvalsfrequentie?
- 2 Wat is het effect van alcoholgebruik op de bloedspiegels van de anti-epileptica?
- 3 Treden door alcoholgebruik veranderingen op in de epileptische activiteit geregistreerd met behulp van het EEG?
- 4 Hoe is de houding van de Nederlandse neuroloog en die van zijn buitenlandse collega's ten opzichte van het alcoholgebruik bij epileptische patiënten?

Daar alcoholgebruik tot één van de sociale aspecten van epilepsie behoort, is in deze thesis ook uitvoerig aandacht besteed aan diverse andere sociale aspecten van epilepsie, zoals aan: wat is de invloed van het ontstaan van epilepsie op de opvoeding van het kind, toekomstoriëntatie,

schoolniveau en welke factoren kunnen de arbeidsrelatie beïnvloeden. Daarnaast wordt ingegaan op de relatie epilepsie en inspanning, alsmede welke voorwaarden zijn er in de diverse landen voor het verlenen van rijbewijzen aan epileptici en hoe is de ongevalsfrequentie van epilepsiepatiënten in vergelijking met een controlegroep?

Vanzelfsprekend is er uitvoerig stilgestaan bij het alcoholmetabolisme en wat de invloed van alcoholgebruik is op geneesmiddelen en de elektrische activiteit van de hersencellen.

Ook is er een overzicht van de literatuur over de relatie alcoholgebruik en aanvallen, waarbij opvalt dat er bijna uitsluitend literatuur is over de relatie alcoholmisbruik en het optreden van aanvallen.

De medewerking aan de enquête om een inzicht te krijgen in de houding van de behandelend specialist ten opzichte van het alcoholgebruik bij epilepsiepatiënten was groot. Het responspercentage van de Nederlandse neurologen was hoog en bedroeg 63. Vanuit de overige 24 landen die deelnamen aan de enquête werden 478 formulieren ingevuld en geretourneerd, hetgeen een responspercentage gaf van 42,7.

De verschillen in attitude tussen de landen onderling waren zeer groot en zo kon het voorkomen dat in het ene land 90% van de respondenten voorstander was van een absoluut alcoholverbod, terwijl in een ander land 80% van de respondenten voorstander was van sociaal alcoholgebruik.

Conclusies

- 1 Er is geen invloed aantoonbaar van sociaal alcoholgebruik op epileptische aanvallen.
- 2 De bloedspiegels van carbamazepine, phenobarbital en phenytoïne worden niet door het alcoholgebruik beïnvloed. De valproïnezuurconcentratie wordt mogelijk licht verhoogd. Hiervoor is echter verder onderzoek nodig alvorens tot een zekere uitspraak te komen.
- 3 In zowel de frequentiebanden als in de hoeveelheid epileptische activiteit treedt door alcoholgebruik geen verandering op.
- 4 De houding van de specialisten ten aanzien van het alcoholgebruik bij epilepsiepatiënten is zeer tegenstrijdig en kon tussen de landen onderling sterk verschillen.

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CURRICULUM VITAE

The author was born in Brunssum, the Netherlands, on August 3, 1944. He attended the 'Bishops College' in Roermond and passed the HBS-B examination in June 1962.

In June 1965, after having passed his B.A.-examination at the Catholic University in Nijmegen, he continued his study on the State University in Leiden, where he passed his examination with success on June 1967 and on September 5, 1969 he obtained his medical qualifying examination. From October 1969 till March 1971 he fulfilled his military service, most of the time of which he was employed on the neurological department of the 'Dr. A. Mathijssen' Hospital in Utrecht, tutor Dr. J.C. GATHIER. Within the framework of his specialist training he completed his term of probation in psychiatry at the Psychiatric Hospital Rosenberg in The Hague, tutor Dr. J. BIJL. After that he continued his study in neurology at the University Hospital in Leiden under the leadership of the late professor Dr. A. VERJAAL. On October 1, 1974 he was entered in the specialist register. Ever since he has worked at the Epilepsy Centre Kempenhaeghe in Heeze, where he carried out from 1977-1980 his investigation concerning the influence of social alcohol intake on epilepsy. This study was financially supported by a grant from the Dutch Research Committee on Epilepsy (CLEO) of the organization for Health Research (TNO).

From October 1, 1976 till November 1, 1977 he worked in the Wever Hospital in Heerlen to obtain his endorsement in clinical neurophysiology, tutor Dr. J. MOL. Both he and Dr. O. DRIESSEN, scientific collaborator pharmacology department of the State University in Leiden, were engaged in research concerning drug compliance in epileptic patients.

After that he was a co-researcher with a study concerning the theoretical and practical aspects of phenytoin administration.

At the moment he is engaged in pharmacokinetic studies on carbamazepine and valproic acid, as well as the correlation between the cause of side effects and the serum concentration.

He is also making an exploratory study on the value of the changes in the prolactin level in the differential diagnosis with epileptic and psychogenic attacks.