

J. Clin. Chem. Clin. Biochem.  
Vol. 22, 1984, pp. 79-96

## Detection and Exclusion of Alcoholism in Men on the Basis of Clinical Laboratory Findings<sup>1)</sup>

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(Received December 27, 1982/October 3, 1983)

In honour of Prof. Dr. Dr. h.c. mult. Adolf Butenandt on the occasion of his eightieth birthday

**Summary:** Alcoholism is a common disease; it is found in 10% to 15% of all patients admitted to general hospitals.

There is no single characteristic finding, but on the other hand, changes as compared with normal values have been reported in the literature for more than 30 frequently assayed clinical chemical and haematological parameters.

In the project reported here all 24 clinical chemical parameters and all 8 haematological parameters frequently assayed were studied in each of 82 hospitalized men with a confirmed diagnosis of alcoholism.

The diagnosis of alcoholism was made on the basis of the Munich Alcoholism Test (MALT) together with the following standardized assessments and examinations: past history, an alcohol questionnaire, general physical examination and neurological examination. All forms were filled in completely.

All steps in the clinical laboratory investigations were standardized, and all were subject to ongoing reliability control.

The clinical problem is usually not to differentiate alcohol abusers or alcoholics from healthy persons but rather to identify the alcoholics among a population of patients with a variety of illnesses.

For this reason 70 patients from two hospitals who were clearly neither alcohol abusers nor alcoholics were studied in exactly the same manner as the alcoholics.

In this combined group of 152 hospitalized patients significant differences were found in the distribution of the values for the alcoholics and the non-alcoholics for the following clinical chemical and haematological parameters: at the 0.1% level  $\gamma$ -glutamyltransferase, aspartate aminotransferase, urea, creatinine and mean corpuscular volume (MCV), and at the 1% level glutamate dehydrogenase, alanine aminotransferase and alkaline phosphatase.

From these eight parameters those combinations of between two and six parameters were selected that discriminated best between the alcoholics and the non-alcoholics. Using *conventional decision limits* the following was found: For the *alcoholics* two or more of the results for the following five parameters were outside the decision limits given in parentheses:  $\gamma$ -glutamyltransferase ( $\geq 28$  U/l), aspartate aminotransferase ( $\geq 18$  U/l), alanine aminotransferase ( $\geq 22$  U/l), MCV ( $\geq 96$  fl), creatinine ( $\leq 66.3$   $\mu$ mol/l). The diagnostic sensitivity (alcoholics) is 85%, the diagnostic specificity (non-alcoholics) is 64%.

For the *non-alcoholics* three or fewer results were outside the decision limits given in parentheses:  $\gamma$ -glutamyltransferase ( $< 28$  U/l), aspartate aminotransferase ( $< 18$  U/l), MCV ( $< 96$  fl), creatinine ( $> 66.3$   $\mu$ mol/l), urea-N ( $> 5.0$  mmol/l).

<sup>1)</sup> This research project was partially supported by funds provided by the Bayerisches Staatsministerium für Arbeit und Sozialordnung (Bavarian State Ministry of Labour and Welfare).

With the decision limits given above and this combination of parameters the diagnostic specificity (non-alcoholics) is 96% and the diagnostic sensitivity (alcoholics) is 50%.

This procedure thus enables the detection and exclusion of alcoholism in men on the basis of clinical laboratory findings.

By *optimizing the decision limits*, the diagnostic test criteria sensitivity, specificity and efficiency can be improved. Optimized decision limits for the discrimination of definite alcoholics from other patients who are definitely not alcoholics are shown in tables 3-14 to 3-16. A sensitivity (alcoholics) of 86% and a specificity (non-alcoholics) of 87% and thus an efficiency of 173 are obtained if the decision limits are fixed as follows and individuals are diagnosed as alcoholics if they have at least five results within these limits:  $\gamma$ -glutamyltransferase  $\geq 27$  U/l, aspartate aminotransferase  $\geq 9$  U/l, aspartate/alanine aminotransferase  $\geq 0.63$ , MCV  $\geq 89$  fl, creatinine  $\leq 70.7$   $\mu\text{mol/l}$  and urea-N  $\leq 6.4$  mmol/l.

Findings in recent papers on clinical chemical and haematological markers of alcohol abuse are compared with the findings in this study regarding both methodology and information obtained. A realistic picture is obtained only if alcoholics are compared with other patients who are not alcoholics, not if they are compared with "healthy persons". A *complete* separation between alcoholics and non-alcoholics in patient populations based on the parameters evaluated in this study is not possible with any procedure.

Corresponding data for a population of female alcoholics and non-alcoholics have been collected and are now being evaluated.

#### *Erkennung oder Ausschluß des Alkoholismus bei Männern aufgrund klinisch-chemischer Befunde*

**Zusammenfassung:** Der Alkoholismus ist eine häufige Erkrankung; seine Prävalenz bei den Patienten Innerer Kliniken beträgt 10 bis 15%.

Einerseits gibt es keinen charakteristischen Befund für den Alkoholismus, andererseits sind für alle diese Fälle Veränderungen gegenüber der Norm für mehr als 30 der häufig untersuchten klinisch-chemischen und hämatologischen Kenngrößen in der Literatur beschrieben.

In der vorliegenden Arbeit wurden bei 82 Patienten (Männer) mit sicher diagnostiziertem Alkoholismus gleichzeitig alle 24 klinisch-chemischen Kenngrößen und alle 8 hämatologischen Kenngrößen untersucht.

Die Diagnose des Alkoholismus erfolgte aufgrund des Münchner Alkoholismustests (MALT) sowie folgender standardisierter vollständiger Erhebungen oder Untersuchungen: Anamnese, Alkoholerhebungsbogen, internistische Untersuchung und neurologische Untersuchung.

Alle Teilschritte der klinisch-chemischen Untersuchungen waren standardisiert und unterlagen einer ständigen Zuverlässigkeitskontrolle.

Die klinische Fragestellung lautet meistens nicht, Patienten mit Alkoholabusus oder Alkoholismus von Gesunden zu unterscheiden, sondern sie verlangt, unter Patienten mit anderen Erkrankungen die Alkoholiker zu erkennen.

Es wurden deswegen aus zwei Krankenhäusern 70 Patienten mit anderen Erkrankungen, bei denen sicher kein Alkoholabusus oder Alkoholismus bestand (Nicht-Alkoholiker), in genau derselben Weise wie die Alkoholiker untersucht.

Bei diesen 152 Krankenhauspatienten bestanden signifikante Unterschiede in der Verteilung der Werte bei Alkoholikern und Nicht-Alkoholikern für die folgenden klinisch-chemischen und hämatologischen Kenngrößen: Auf dem 0,1%-Niveau  $\gamma$ -Glutamyltransferase, Aspartat-aminotransferase, Harnstoff, Kreatinin, mittleres Erythrocytenvolumen (MCV), und auf dem 1%-Niveau Glutamatdehydrogenase, Alanin-aminotransferase, alkalische Phosphatase.

Es wurden aus diesen Kenngrößen diejenigen Kombinationen von 2 bis 6 Kenngrößen herausgesucht, die bei den Patienten am besten die Alkoholiker von den Nicht-Alkoholikern diskriminieren. Bei der Verwendung von *konventionellen Entscheidungsgrenzen* gilt: Bei *Alkoholikern* werden 2 oder mehr Ergebnisse außerhalb der in Klammern angegebenen Entscheidungskriterien bei folgenden 5 Kenngrößen gefunden:  $\gamma$ -Glutamyltransferase ( $\geq 28$  U/l), Aspartat-aminotransferase ( $\geq 18$  U/l), Alanin-aminotransferase ( $\geq 22$  U/l), MCV ( $\geq 96$  fl), Kreatinin ( $\leq 66,3$   $\mu\text{mol/l}$ ). Die diagnostische Sensitivität (Alkoholiker) ist 85%, die diagnostische Spezifität (Nicht-Alkoholiker) 64%.

Bei *Nicht-Alkoholikern* werden 3 oder weniger Ergebnisse außerhalb der in Klammern angegebenen Entscheidungsgrenzen gefunden:  $\gamma$ -Glutamyltransferase (<28 U/l), Aspartat-aminotransferase (<18 U/l), MCV (<96 fl), Kreatinin (>66,3  $\mu$ mol/l), Harnstoff-N (>5,0 mmol/l).

Die diagnostische Spezifität (Nicht-Alkoholiker) beträgt bei dieser Kombination bei den vorgegebenen Entscheidungsgrenzen 96% und die diagnostische Sensitivität (Alkoholiker) 50%.

Danach ist es möglich, aufgrund klinisch-chemischer Befunde bei Männern einen Alkoholismus zu erkennen oder auszuschließen.

Durch eine *Optimierung der Entscheidungsgrenzen* können die diagnostischen Prüfkriterien Sensitivität oder Spezifität oder Effizienz noch verbessert werden. Die optimierten Entscheidungsgrenzen für die Diskrimination der sicheren Alkoholiker von anderen Patienten, die sicher keine Alkoholiker sind, werden in den Tabellen 3-14 bis 3-16 mitgeteilt. Dabei werden bei einer Sensitivität (Alkoholiker) von 86% und einer Spezifität (Nicht-Alkoholiker) von 87% eine Effizienz von 173 erreicht, wenn die Entscheidungsgrenzen wie folgt festgelegt und Probanden als Alkoholiker diagnostiziert werden, wenn sie mindestens fünf Ergebnisse innerhalb dieser Grenzen aufweisen:  $\gamma$ -Glutamyltransferase  $\geq 27$  U/l, Aspartat-aminotransferase  $\geq 9$  U/l, Aspartat-/Alanin-aminotransferase  $\geq 0,63$ , mittleres Erythrocytenvolumen (MCV)  $\geq 89$  fl, Kreatinin  $\leq 70,7$   $\mu$ mol/l und Harnstoff-N  $\leq 6,4$  mmol/l.

Arbeiten der letzten Jahre über klinisch-chemische und hämatologische „Marker“ für Alkoholabusus werden mit den vorliegenden Daten methodisch und sachlich kritisch verglichen. Ein realistisches Bild ergibt sich nur aus dem Vergleich von Alkoholikern mit anderen Patienten, die keine Alkoholiker sind, aber nicht aus dem Vergleich mit „Gesunden“. Eine *vollständige* Trennung von Alkoholikern und Nicht-Alkoholikern in Patientenpopulationen ist bei unseren Daten mit keinem Verfahren möglich.

Die Untersuchungen bei Frauen sind abgeschlossen und werden ausgewertet.

## 0. Introduction and Description of the Problem

Alcoholism is a common disease. The prevalence among hospital patients who have been admitted for reasons other than drunkenness is between 10 and 15 percent (1, 2).

By alcoholism is meant here excessive consumption of alcohol leading to a disturbance of physical, mental and/or social function. This definition is consistent with the 1952 definition of the World Health Organization and with the term "alcohol-related disabilities" used by *Edwards* et al. (3). The development of alcohol dependence is intentionally not discussed in this paper.

Since once consumed alcohol can reach virtually all body cells, alcohol abuse leads to metabolic, functional and sometimes even irreversible anatomical changes in numerous organs (4, 5, 6). The symptoms of these changes are extremely diverse, variable and, frequently, uncharacteristic. Therefore, intensive efforts have been made to develop methods for the detection and exclusion of alcoholism.

Up to now no single characteristic symptom has been found on which to base a diagnosis of alcoholism.

Since 1977 there has been a reliable "combination" test for the detection of alcoholism (7, 8), the Munich Alcoholism Test (MALT). This test consists of two parts, the first requiring a self-rating by the patient (part S) and the second an assessment by a physician (part F) after a thorough examination of the patient. The two parts must be evaluated together. Part F contains one clinical chemistry criterion (the result for at least one of the three parameters aspartate aminotransferase, alanine aminotransferase and  $\gamma$ -glutamyltransferase must be outside of the normal range). For methodological reasons this criterion was omitted when evaluating the data in part F for use in this study.

The MALT requires the cooperation of the patient for part S. However, since alcoholism is an illness that patients tend to conceal both from themselves and from relatives for as long as possible, questions that could indicate the presence of alcoholism are answered inaccurately by uncooperative patients.

In clinical work a technique is therefore urgently needed that enables both the detection and the exclusion of alcoholism without interviewing the patient and his or her relatives.

The test developed by *Shaw & Lieber* (9) based on the ratio of plasma  $\alpha$ -amino-*n*-butyric acid to leucine (A/L) is unsuitable as a screening test because of the time-consuming analytical procedure. This test detects only 80 percent of alcoholics and produces false positive results 2 percent of the time. Furthermore, it can be carried out only in specialized laboratories and is thus not available for use in routine diagnosis. The ratio is dependent on diet and is altered by liver disease. In addition, the A/L ratio cannot be used as a screening test for alcoholism in populations that are heterogeneous with respect to nutrition or the extent of liver disease (5).

Thus there is still an urgent need for a test or a combination of tests for the detection of alcoholism that can be carried out easily and at any time both in hospitals and in physicians' offices.

Changes in a great many clinical chemical parameters have been observed in connection with alcoholism. These have been discussed in a previous paper on excessive consumption of alcohol as a biological influence factor (10). It is demonstrated clearly in that paper that the detection or exclusion of alcoholism by assessment of a single clinical chemical parameter, i. e. on the basis of a single clinical laboratory finding, is not possible. This observation led to the multivariate assessment of the same analytical results, which is the subject of the present paper.

In recent years a number of studies have also been published on combinations of clinical laboratory findings for the detection and exclusion of alcoholism (see Section 3.3). However, the findings in these studies are not comparable for the reasons given in the previous paper (10).

A group of known alcoholics was used in the present study. The subjects were all interviewed by a standard procedure, and all were given a thorough physical examination. The *purpose* of the study was to determine, with the highest possible probability of accuracy, those clinical chemical parameters that enable discrimination not only between these alcoholics and healthy persons but also between these alcoholics and patients with other disorders from the same population. The detection and exclusion of alcoholism are both dependent on diagnostic sensitivity and diagnostic specificity.

Those clinical chemical parameters were favoured that can be determined in all hospitals and in as many physicians' offices as possible. This would enable an early diagnosis or suspected diagnosis of alcoholism without the patient's cooperation.

This goal was achieved for a group of hospitalized men using six clinical chemical parameters. The present paper is a report on this project. The programme developed is now being validated on suitable patient populations in hospital departments of internal medicine.

## 1. Purpose of the Study and Experimental Design

### 1.1 Purpose of the study

#### 1.1.1 Detection of alcoholism

The goal here is as high a diagnostic sensitivity as possible coupled with an adequate level of specificity. This would permit the diagnosis of suspected alcoholism. The diagnosis could then be confirmed with the appropriate special investigations.

If it is known that a patient is an alcoholic then this can be taken into consideration when treating other disorders (e. g. by prescribing a higher dosage of a medication or a different drug). If alcoholism could be detected at the beginning of an organic or mental disorder the diagnostic process could be greatly simplified and thus also shortened.

The problem is not to differentiate alcoholics from "healthy" persons but rather from other patients who are not alcoholics, for example those who have chronic hepatitis or biliary cirrhosis, and thus for whom certain clinical parameters are outside the reference interval for healthy persons.

#### 1.1.2 Exclusion of alcoholism

The goal here is as high a diagnostic specificity as possible with adequate sensitivity. Many pathological findings and many disorders can be caused by alcoholism (4, 5, 6). Because of the high prevalence of alcoholism among hospitalized patients but also in the general population, it would be very helpful if alcoholism could be excluded as the cause with a sufficiently high degree of probability via clinical laboratory investigations.

#### 1.1.3 Monitoring of treatment in alcoholics

It would be most useful in the treatment of alcoholics to have a procedure for the detection of renewed alcohol consumption for a longer period after the event than is currently possible by measuring serum

ethanol. In addition, an attempt should be made to detect those patients whose alcohol consumption has already resulted in isolated physical damage but not to the extent that the MALT criteria for alcoholism are fulfilled.

## 1.2 Subjects

The analytical results that served as the basis for this study were also used in another part of the same project. They were obtained from carefully evaluated patients and thus from patients whose diagnosis with regard to alcoholism was definite. The details have been reported elsewhere (10).

A few points should be stressed here, however.

For the questions raised in this study a reference sample group of "healthy" persons would not have been the most meaningful control group. Rather, it was essential that comparisons also be made with non-alcoholics who had been selected from the same hospital population as the alcoholics. Therefore, the patients in this study were selected from a general city hospital (Munich-Schwabing City Hospital), a psychiatric hospital (Haar Regional Hospital) and (alcoholics only) a hospital specializing in the treatment of alcoholism (Annabrunn Alcoholism Treatment Centre).

## 1.3 Statistical evaluation

The following kinds of statistical evaluation were carried out:

1. Comparison of the results for alcoholics and healthy persons. The decision limits used were the upper and lower limits of the relevant reference interval (11, 12) and the location parameter for healthy persons. In the previous paper (10) these comparisons were made only for individual constituents, whereas in the present study combinations of constituents were assessed.

2. Comparison of the results for alcoholics and non-alcoholics, both groups of subjects having been selected from the same populations of hospitalized patients. The decision limits were the same as in the comparisons with healthy persons. The comparisons were made for both individual constituents and combinations of constituents.

3. Optimization of the decision limits with regard to the diagnostic criteria sensitivity, specificity and efficiency.

## 2. Materials and Methods

The patients and methods have been described in the report on another part of this project (10). The reader is therefore referred to the following sections of the report on the earlier study:

### 2.1 Patient selection

### 2.2 Examination of the patients

### 2.3 Clinical chemical parameters studied, analytical methods used and reliability criteria

### 2.4 Biological influence factors and interference factors

Further information is necessary only regarding the statistical procedures used.

### 2.5 Statistical procedures

Numerous comparisons were made in connection with this project. The statistical procedures used in these comparisons are listed below.

#### 2.5.1 Comparison of the results for alcoholics and healthy persons

Here the results were compared using the relevant reference interval for healthy persons. This is a purely descriptive procedure, with the number and percentage of results above and below the reference interval being determined.

In addition, the location of the results for the alcoholics was compared with the location parameter of the reference values for the healthy persons in order to detect any systematic deviation; significance was assessed using the sign test (13).

#### 2.5.2 Comparison of the results for alcoholics and non-alcoholics

For each individual constituent the distribution of the results for the alcoholics was compared with the distribution for the non-alcoholics using the chi-square test.

Since in these comparisons the number of degrees of freedom (number of classes minus 1) and thus the critical values were not the same for all constituents, a standardized parameter  $\tilde{X}^2$  was introduced where

$$\tilde{X}^2 = \frac{X^2 - f}{\sqrt{2f}}$$

and  $f$  is the number of degrees of freedom.

For the values of  $f$  occurring in this study a  $\tilde{X}^2$  value of more than 3 can be regarded as indicating a significant difference at the 1% level and a value above 5 a significant difference at the 0.1% level. For  $X^2 \leq f$ ,  $\tilde{X}^2$  is defined as 0.

In comparing combinations those parameters were selected where the distributions for the alcoholics and non-alcoholics showed the largest differences.

The differences between distributions of combinations were analysed only with regard to discrimination between alcoholics and non-alcoholics, not with regard to significance.

#### 2.5.3 Optimization of the decision limits

The usual procedure for achieving optimal discrimination between two populations such as alcoholics and non-alcoholics is linear discriminant analysis. However, the application of this procedure with the analytical results obtained here did not yield

satisfactory results. This is not surprising since linear discriminant analysis is based on the model of normal distributions with identical matrices of covariance, i.e. especially with identical standard deviations for the individual values. Quadratic discriminant analysis, which is sometimes used, also assumes a normal distribution. But usually, and especially in this case, not even a normal distribution can be assumed, quite apart from identical standard deviations. Therefore a system was developed that is as simple as possible and still effective. This procedure is based on the direct transfer of the term "decision limit" to several dimensions and the division of the multidimensional space into simple discriminance areas defined by such multiple decision limits. A detailed description of this procedure and a discussion of its application are the subject of another paper (14). The fact that this simple method yielded substantially better results than the parametric procedure shows that, in contrast to the view sometimes expressed (15), the form of the distribution can have a decisive influence on the result of a parametric analysis.

A number of other well-known statistical procedures were also used in connection with this project. They are listed in table 2-1 according to the area of application.

### 3. Results and Discussion

The analytical results obtained for the alcoholics were compared with the reference intervals (11, 12) and location parameters of the analytical results obtained for healthy persons. Then the results for the alcoholics were compared with those for patients who were definitely not alcoholics, but who had been treated for some other problem on the same hospital wards as the alcoholics. This comparison and the in-

formation obtained from it provide the basis for achieving the goals initially set. The comparisons and the strategies for investigation derived from them are a practical example of the models developed in general clinical chemistry (17, 18, 19, 20) and their applicability in connection with clinical questions.

Each section of results is followed immediately by a discussion of those results.

#### 3.1 Comparison of the analytical results for alcoholics and healthy persons

Medical assessment of analytical results (21) usually involves a comparison with the reference interval (earlier termed "normal range") for a group of people considered to be healthy. Thus a transverse assessment is usually made (22, 21). Most of the published reports on changes in clinical chemical parameters in alcoholics are also based on this kind of comparison (l.c. (10) and Section 3.3). This was the case, too, for the group of alcoholics reported on by the present authors in the previous paper (10). An assessment was made of the percentage of the analytical results for the alcoholics above and below the reference interval or the location parameter for a representative sample of healthy persons.

The disorders found in the two groups of patients are listed in table 3-1.

Tab. 2-1. Special statistical evaluations.

Question	Procedure	References
1. Normal distribution of individual constituents (alcoholics and non-alcoholics)	<i>Sarkadi-Stoermer</i>	(15a)
2. Comparison of the institutions for the 7 most important individual constituents	<i>Kruskal-Wallis</i>	(16, 13)
3. Comparison alcoholics/non-alcoholics for		
- Age	Chi-square	(16, 13)
- Height	<i>Wilcoxon-Mann-Whitney</i>	
- Weight	<i>Wilcoxon-Mann-Whitney</i>	
- Difference between weight and ideal weight		
4. Correlation between the 7 most important constituents		
- Creatinine/body weight	Both product-moment correlation and	(13)
- Urea/body weight	<i>Spearman</i> rank correlation	(16)
5. Comparison of the subjects with low/high MALT scores for the 7 most important constituents (alcoholics and non-alcoholics)	<i>Wilcoxon-Mann-Whitney</i>	(16, 13)
6. Comparison of the subjects without liver disease for		
- $\gamma$ -Glutamyltransferase	<i>Wilcoxon-Mann-Whitney</i>	(16, 13)
- MCV		
- Creatinine		
7. Number of subjects (alcoholics) with liver disease within/outside the reference limits for the 7 most important constituents	Description	

Tab. 3-1. Disorders found in the two groups of patients (more than one possible).

Kind of disorder/organ	Alcoholics	Non-alcoholics
No other physical disorder	29	—
Liver	41	1
Pancreas	1	1
Gastrointestinal tract	4	7
Blood and haematopoietic tissues	1	—
Neurological disorders	4	3
Mental disorders:		
Alcohol delirium	3	—
Schizophrenia	—	27
Affective psychoses	—	1
Neuroses	—	2
Personality disorders	—	3
Suicide attempt	—	3
Chronic brain syndrome	1	—
Adjustment reaction	—	3
Mineral metabolism	—	—
Metabolic disorders	9	7
Endocrine disorders	—	2
Drug abuse	4	—
Kidneys	—	4
Orthopaedic disorders	1	4
Skin	5	—
Respiratory system	2	2
Traumas	1	1
N =	82	70

### 3.2 Comparison of alcoholics with other patients

The first step in comparing the analytical results for the alcoholics and non-alcoholics was to determine whether the distributions were significantly different. If there were significant differences between the distributions for alcoholics and non-alcoholics for a given constituent, then the diagnostic importance of that constituent in the detection and exclusion of alcoholism was assessed.

This assessment consisted of determining the diagnostic sensitivity, diagnostic specificity and diagnostic efficiency, each expressed as a percentage.

*Diagnostic sensitivity (%) =*

$$\frac{\text{number of positive findings}}{\text{number of alcoholics}} \times 100$$

*Diagnostic specificity (%) =*

$$\frac{\text{number of negative findings}}{\text{number of non-alcoholics}} \times 100$$

*Diagnostic efficiency* is defined in this paper as the sum of diagnostic sensitivity and diagnostic specificity:<sup>2)</sup>

$$\text{sensitivity} + \text{specificity} = \text{efficiency}$$

Since sensitivity and specificity are given as percentages, the highest possible value for diagnostic efficiency is 200. For quantitative tests the decision about whether a finding is positive or negative is based on a comparison with a *decision limit*. For transverse assessment in medicine this usually takes the form of a comparison with what is termed the reference interval. The initial decision limits used were therefore parameters for a reference population of healthy persons (upper and lower limits of the reference interval and the location parameter). First, each clinical chemical parameter was assessed alone.

Since it is well known that the diagnostic validity of clinical chemical tests can be improved by combining two or more tests, various combinations were then assessed for their diagnostic efficiency.

Finally, an attempt was made to optimize the diagnostic importance of individual investigations and combinations of investigations by altering the decision limits.

#### 3.2.1 Differences between the distributions of analytical results for the alcoholics and the non-alcoholics

The differences were assessed with the chi-square test. A standard measure was introduced because of the different degrees of freedom for the different constituents (see Section 2.5.2 above). The results of this assessment (performed as described in Section 2.5.2) are shown in table 3-2. The level of efficiency with optimal decision limits (14 and Section 5.2) is given only for those constituents for which the differences between the distributions were significant at the 1% level or better. The significant difference at the 0.1% level in the distributions for alcoholics and non-alcoholics for creatinine is of greatest interest: For all the other parameters with significant differences between the distributions for alcoholics and non-alcoholics, the altered values in the alcoholics were already evident using the conventional assessment system, as demonstrated in tables 3-1 and 3-2 of the previous paper (10).

<sup>2)</sup> Another common definition of *efficiency* is the percentage of "correct" findings in the total sample. The reasons for using the above definition instead are discussed elsewhere (14). For subsamples of the same size the definitions are the same except for a factor of 2.

Tab. 3-2. Comparison of the distributions of the analytical results for alcoholics and non-alcoholics.

Constituent	(Unit)	$\bar{X}^2$	Signifi- cance 1%: * 0.1%: **	Maximum efficiency	Optimized decision limit	Reference limits	
						lower	upper
Haemoglobin	(g/l)	2.74					
Haematocrit	(l)	0					
Erythrocytes	(10 <sup>12</sup> /l)	1.76					
MCV	(fl)	5.18	**	138	95	80	96
MCH	(pg)	3.91	*	130	32		
Reticulocytes	(l)	0.95					
Leukocytes	(10 <sup>9</sup> /l)	0					
Granulocytes	(%)	6.70	*	124	1		
Lymphocytes	(%)	0.55					
Thrombocytes	(10 <sup>9</sup> /l)	0					
Glucose	(mmol/l)	0.16					
Total protein	(g/l)	2.21					
Albumin fraction	(l)	0.83					
Globulin fractions							
α <sub>1</sub> -	(l)	0					
α <sub>2</sub> -	(l)	0					
β-	(l)	0.62					
γ-	(l)	0					
Bilirubin	(μmol/l)	2.58					
Uric acid	(μmol/l)	0					
Sodium	(mmol/l)	0.31					
Potassium	(mmol/l)	0					
Calcium	(mmol/l)	0					
Chloride	(mmol/l)	0.64					
Phosphorus	(mmol/l)	0.28					
Magnesium	(mmol/l)	1.84					
Serum iron	(μmol/l)	1.25					
Serum copper	(μmol/l)	0					
Cholesterol	(mmol/l)	0					
Triglycerides	(mmol/l)	0					
Creatinine	(μmol/l)	5.19	**	137	71	44	97
Urea-N	(mmol/l)	6.78	**	135	4.3	2.1	7.8
γ-Glutamyltransferase	(U/l)	14.26	**	151	45	6	28
Aspartate aminotransferase	(U/l)	15.14	**	145	16	2	18
Alanine aminotransferase	(U/l)	3.28	*	132	15	2	22
Cholinesterase	(U/l)	0.25					
Alkaline phosphatase	(U/l)	3.16	*	125	145	60	200
Glutamate dehydrogenase	(U/l)	4.86	*	132	1.6		4
Creatine kinase	(U/l)	0.69					

If the distributions for a given constituent were significantly different, then the efficiency, assuming optimal decision limits, was determined (see Section 3.2.4). It was found that there was not always a correlation between the results of the chi-square test and the efficiency levels.

### 3.2.2 Diagnostic sensitivity, diagnostic specificity and efficiency of individual findings

Diagnostic sensitivity, specificity and efficiency were determined for each of the clinical chemical parameters studied as illustrated with γ-glutamyltransferase

in table 3-3, assuming the usual decision limits (limits of the reference interval or location parameter of the reference values). As already pointed out, the diagnostic efficiency can have a maximum value of 200.

Table 3-4 shows all constituents for which the diagnostic efficiency was greater than or equal to 118, assuming conventional decision limits.

1. Diagnostic sensitivity always refers to the alcoholics.
2. Diagnostic specificity always refers only to the non-alcoholics.



Tab. 3-3. Determination of diagnostic sensitivity, specificity and efficiency for the assay of  $\gamma$ -glutamyltransferase.  $b$  = catalytic activity concentration (of  $\gamma$ -glutamyltransferase)

Alcoholics			Non-alcoholics		
No.	Code	U/l	No.	Code	U/l
1.	6033	11	1.	2641	8
2.	6023	13	2.	2627	9
3.	4146	14	3.	4631	9
4.	6062	16	4.	4634	10
5.	2019	18	5.	4632	10
6.	6032	18	6.	2640	11
7.	6049	19	7.	4609	11
8.	4161	20	8.	4624	11
9.	2145	21	9.	4633	11
10.	6055	21	10.	4673	11
11.	6064	21	11.	2602	12
12.	6066	22	12.	2612	12
13.	6041	23	13.	4625	12
14.	6030	25	14.	4642	12
15.	6007	26	15.	4665	12
16.	4184	27	16.	4698	12
17.	4190	27	17.	2649	13
18.	6052	27	18.	2607	13
19.	4101	30	19.	4668	13
20.	6040	30	20.	4618	14
21.	6042	30	21.	2608	14
22.	4114	31	22.	4635	14
23.	2057	32	23.	4704	14
24.	4201	32	24.	4637	15
25.	6051	32	25.	2648	16
26.	2036	35	26.	2638	16
27.	2029	36	27.	4703	16
28.	6045	39	28.	4692	17
29.	4139	41	29.	4694	17
30.	6044	41	30.	4695	17
31.	4159	45	31.	2652	18
32.	2038	45	32.	2624	18
33.	2012	49	33.	4636	19
34.	1002	50	34.	2617	20
35.	6010	52	35.	2619	20
36.	2028	56	36.	4667	20
37.	2143	56	37.	2631	22
38.	4202	57	38.	2625	23
39.	1004	59	39.	2637	23
40.	4158	60	40.	2633	23
41.	6043	60	41.	2650	23
42.	6050	62	42.	2647	25
43.	6008	67	43.	4678	25
44.	6021	72	44.	2611	26
45.	6046	72	45.	4623	26
46.	6048	77	46.	4693	26

Alcoholics			Non-alcoholics		
No.	Code	U/l	No.	Code	U/l
47.	6065	77	47.	2644	26
48.	6063	80	48.	4645	28
49.	4112	83	49.	2632	28
50.	2024	93	50.	4626	30
51.	6031	100	51.	2651	30
52.	2017	100	52.	2030	31
53.	4186	102	53.	4652	32
54.	4102	104	54.	4691	32
55.	6020	119	55.	4616	32
56.	6047	124	56.	4611	35
57.	2059	125	57.	2613	38
58.	2027	132	58.	2642	38
59.	2067	134	59.	4654	39
60.	4200	147	60.	4628	42
61.	6053	151	61.	4627	42
62.	6006	170	62.	2634	47
63.	4103	186	63.	4653	58
64.	6061	190	64.	4670	60
65.	2025	224	65.	2620	60
66.	2035	248	66.	4615	64
67.	4185	249	67.	4705	77
68.	6009	250	68.	2601	80
69.	4156	252	69.	4655	136
70.	6022	253	70.	4617	218
71.	4160	270			
72.	4151	282			
73.	2068	352			
74.	6054	360			
75.	2005	370			
76.	2015	450			
77.	2014	450			
78.	2039	484			
79.	1001	580			
80.	1003	670			
81.	2034	930			
82.	2056	1430			

Example with conventional decision limits:

Diagnostic sensitivity (%) =

$$\frac{\text{Alcoholics with } b \geq 28 \text{ U/l}}{\text{No. of alcoholics}} \times 100 = \frac{64}{82} \times 100 = 78.0\%$$

Diagnostic specificity (%) =

$$\frac{\text{Non-alcoholics with } b < 28 \text{ U/l}}{\text{No. of non-alcoholics}} \times 100 = \frac{47}{70} \times 100 = 67.1\%$$

Diagnostic efficiency =

$$\text{diagnostic sensitivity} + \text{diagnostic specificity} = 78.0 + 67.1 = 145.1$$

Tab. 3-4. Diagnostic sensitivity, specificity and efficiency for individual constituents.

Constituent	(Unit)	Abbreviation	Criterion	Sensitivity (%)	Criterion	Specificity (%)	Efficiency
$\gamma$ -Glutamyltransferase	(U/l)	$\gamma$ -GT	$\geq 28$	78.0	$< 28$	67.1	145.2
Aspartate aminotransferase	(U/l)	GOT	$\geq 18$	47.6	$< 18$	91.4	139.0
Urea-N	(mmol/l)	urea-N	$\leq 5.0$	80.5	$> 5.0$	52.9	133.6
Creatinine	( $\mu\text{mol/l}$ )	creat	$\leq 66.3$	48.8	$> 66.3$	84.3	133.1
Mean corpuscular volume	(fl)	MCV	$\geq 96$	72.8	$< 96$	60.0	132.8
Alanine aminotransferase	(U/l)	GPT	$\geq 22$	45.1	$< 22$	72.9	118.0

In contrast to table 3-2, conventional decision limits have been used here, as is the case for all subsequent tables through 3-10.

3. Both are dependent on the decision limit used (e. g. limit of the reference interval, location parameter of the reference values or some other decision limit). If non-alcoholics are replaced by healthy persons and the decision limit is held constant a different specificity usually results.

4. Thus *diagnostic sensitivity* and *diagnostic specificity* are completely *independent of one another*. Knowledge of the value of one of these diagnostic criteria does not provide any information about the value for the other (see example in table 3-3).

5. A particular level of efficiency is valid only for the combination of two specific distributions, in this case for the combination of the distributions for alcoholics and non-alcoholics.

#### *Detection and exclusion*

From the logical point of view the use of diagnostic sensitivity and diagnostic specificity is based on the exclusion principle, in analogy with statistical test procedures (14).

If a test based on positive results has a high sensitivity (as, for example, 92.6% in table 3-6, constituent combination 10, or 95.1% in table 3-16), a negative test result signifies the exclusion of alcoholics, i. e. the detection of non-alcoholics. In this case a positive test result taken alone does not necessarily mean the detection of alcoholics. If the test has a high specificity (as, for example, 97.1% in table 3-7, constituent combination 5, or 95.7% in table 3-15), a positive test result signifies the exclusion of non-alcoholics, i. e. the detection of alcoholics.

Here a negative test result taken alone does not necessarily mean the detection of non-alcoholics. A single test criterion can be used both to detect and to exclude alcoholics or non-alcoholics only if it has both sufficiently high sensitivity and sufficiently high specificity and thus sufficiently high efficiency. Otherwise different criteria must be used for detection and exclusion.

#### *3.2.3 Diagnostic sensitivity, specificity and efficiency of constituent combinations*

When differentiating between alcoholics and non-alcoholics on the basis of individual findings and conventional criteria (tab. 3-4), the highest level of efficiency was 145 and thus still unsatisfactory. It therefore seemed reasonable to try to obtain better discrimination by using combinations of findings.

Table 3-5 shows the combinations of positive findings found, including the number of alcoholics and non-alcoholics with each combination. There are numerous different patterns of findings, and it seemed useful to assess the efficiency of differentiation with these different patterns. Here it must be emphasized that the assessments were always made parallel to each other, not sequentially.

In the following, the findings for a subgroup of alcoholics and a subgroup of non-alcoholics serve to illustrate the kinds of information contained in table 3-5.

In the *group of alcoholics* ( $n = 82$ ) with 3 positive findings ( $k = 3$ ) there are 18 alcoholics ( $H_k$ ). Of these 18 alcoholics, one-third had no elevation of  $\gamma$ -glutamyltransferase, and 4 had no positive liver findings at all. All alcoholics without elevated  $\gamma$ -glutamyltransferase had elevated MCV and a drop in either creatinine or urea or both. Of the 82 alcoholics, 65 had between 3 and 6 positive findings ( $H_k^*$ ).

In the *group of non-alcoholics* ( $n = 70$ ), 20 ( $H_k$ ) had 2 positive findings ( $k = 2$ ) and 52 had 2 or fewer positive findings ( $H_k^{**}$ ). Of these 52, 6 had elevated  $\gamma$ -glutamyltransferase but no elevation of aspartate aminotransferase or alanine aminotransferase; 2 had elevated MCV, 1 decreased creatinine and 3 a drop in urea-N below the location parameter of the reference sample group.

Table 3-5 also shows that 2 ( $H_k$ ) of the 82 alcoholics had no pathological findings at all ( $k = 0$ ). Among the non-alcoholics the number was 14. In addition, 18 of the 82 alcoholics did not have elevated  $\gamma$ -glutamyltransferase, 26 did not have elevated MCV and 6 had no elevation in either. Both  $\gamma$ -glutamyltransferase and MCV were elevated in 44 of the 82 alcoholics.

Tab. 3-5. Patterns of findings seen in alcoholics and non-alcoholics.  
 Explanation of symbols, with examples given in parentheses:

k: Number of positive findings (e. g. 4)

H<sub>k</sub>: Number of subjects with k positive findings (e. g. 22 alcoholics and 8 non-alcoholics had 4 positive findings)

H<sub>ki</sub>: Number of subjects with a given pattern (e. g. 3 alcoholics but no non-alcoholics had positive findings for the combination  $\gamma$ -glutamyltransferase, aspartate aminotransferase, MCV and urea)

H<sub>k</sub><sup>\*</sup>: Number of subjects with at least k positive findings (e. g. 47 alcoholics had 4, 5 or 6 positive findings)

H<sub>k</sub><sup>\*\*</sup>: Number of subjects with k positive findings at the most (e. g. 70 non-alcoholics had 1, 2, 3 or 4 positive findings)

Abbreviations and decision limits as in Tab. 3-4.

k	Alcoholics			Patterns of findings						Non - alcoholics		
	H <sub>k</sub>	H <sub>k</sub> <sup>*</sup>	H <sub>ki</sub>	$\gamma$ -Glutamyl- transferase	Aspartate aminotransferase	Alanine aminotransferase	Mean corpuscular volume	Creatinine	Urea	H <sub>ki</sub>	H <sub>k</sub> <sup>**</sup>	H <sub>k</sub>
6	8	8	8								70	0
5	17	25	1								70	0
			2									
4	22	47	12									
			2									
			3							3	70	8
			3									
3	18	65	1									
			2									
			5									
			4									
			1									
			1									
2	12	77	4									
			1									
			2									
			2									
			2							5	52	20
			2							3		
1	3	80	3									
			1									
			1							6	32	18
0	2	82	1									
			1							8		
			2							14	14	14

*Combinations of two*

The power of differentiation for 10 combinations of two in which at least one finding is positive are shown in table 3-6, arranged according to level of efficiency. A marked increase in sensitivity (alcoholics) is evident for the combination  $\gamma$ -glutamyltransferase/MCV (92% rather than 78% and 73% respectively for the individual constituents); however, the specificity (non-alcoholics) of this combination at 40% is lower than that for the individual findings.

Tab. 3-6. Combinations of two findings, at least one of which is positive.

Constituent combinations	Sensitivity alcoholics (%)	Specificity non-alcoholics (%)	Efficiency alcoholics/non-alcoholics
Positive findings	1	0	
1 GOT/creat	76.8	75.7	152.6
2 $\gamma$ -GT/creat	90.2	56.3	146.6
3 $\gamma$ -GT/GOT	79.3	64.3	143.6
4 $\gamma$ -GT/GPT	80.5	58.6	139.1
5 MCV/creat	86.4	51.4	137.8
6 Creat/urea-N	87.8	48.6	136.4
7 GOT/urea-N	85.4	50.0	135.4
8 GOT/MCV	80.2	54.3	134.5
9 GPT/creat	75.6	57.2	132.8
10 $\gamma$ -GT/MCV	92.6	40.0	132.6

Constituent abbreviations and decision limits as in table 3-4.

The specificity improves very markedly, to 87%, if the requirement is made that both findings are abnormal (tab. 3-7).

Tab. 3-7. Combinations of two findings, both of which are positive.

Constituent combinations	Sensitivity alcoholics (%)	Specificity non-alcoholics (%)	Efficiency alcoholics/non-alcoholics
Positive findings	2	1	
1 $\gamma$ -GT/urea-N	69.5	78.6	148.1
2 $\gamma$ -GT/MCV	58.0	87.1	145.2
3 $\gamma$ -GT/GOT	46.3	94.3	140.6
4 GOT/urea-N	42.7	94.3	137.0
5 GOT/MCV	39.5	97.1	136.6
6 MCV/urea-N	59.3	77.1	136.4
7 Creat/urea-N	41.5	88.6	130.0
8 $\gamma$ -GT/creat	36.6	93.0	129.6
9 GOT/GPT	37.8	91.4	129.2
10 MCV/creat	35.8	92.9	128.7

Constituent abbreviations and decision limits as in table 3-4.

*Combinations of three*

For these combinations, if it is required that at least two findings be positive (tab. 3-8) the efficiency can be increased over that shown in table 3-7; specificity is then somewhat poorer, but sensitivity is much better.

Tab. 3-8. Combinations of three findings, at least two of which are positive.

Constituent combinations	Sensitivity alcoholics (%)	Specificity non-alcoholics (%)	Efficiency alcoholics/non-alcoholics
Positive findings	2	1	
1 $\gamma$ -GT/MCV/creat	76.5	80.0	156.5
2 $\gamma$ -GT/GOT/urea-N	75.6	78.6	154.2
3 GOT/MCV/creat	63.0	90.0	153.0
4 GOT/creat/urea-N	69.5	81.9	152.4
5 $\gamma$ -GT/GOT/creat	63.4	88.6	152.0
6 $\gamma$ -GT/creat/urea-N	79.3	70.0	149.3
8 $\gamma$ -GT/GOT/MCV	66.7	81.4	148.1
9 $\gamma$ -GT/GPT/MCV	70.4	72.9	143.2

Constituent abbreviations and decision limits as in table 3-4.

*Combinations of four*

For the combinations shown in table 3-9 the highest sensitivity is obtained if only 2 positive findings are required, whereas the highest specificity is obtained (with a different combination) if at least 3 positive findings are required.

Tab. 3-9. Combinations of four findings.

Constituent combinations	Sensitivity alcoholics (%)	Specificity non-alcoholics (%)	Efficiency alcoholics/non-alcoholics
Positive findings	2	1	
1 $\gamma$ -GT/GOT/MCV/creat	81.5	74.3	155.8
2 $\gamma$ -GT/GOT/creat/urea-N	82.9	70.0	152.9
3 $\gamma$ -GT/GPT/MCV/creat	84.0	65.7	149.6
4 GOT/GPT/creat/urea-N	75.6	71.4	147.0
5 GOT/GPT/MCV/creat	69.1	77.1	146.2
6 GOT/GPT/MCV/urea-N	85.2	60.0	145.2
Positive findings	3	2	
1 $\gamma$ -GT/MCV/creat/urea-N	66.7	87.1	153.8
2 $\gamma$ -GT/GOT/creat/urea-N	61.0	90.0	151.0
3 $\gamma$ -GT/GOT/MCV/urea-N	61.7	88.6	150.3
4 $\gamma$ -GT/GOT/MCV/creat	53.1	95.7	148.8
5 GOT/MCV/creat/urea-N	56.8	91.4	148.2

Constituent abbreviations and decision limits as in table 3-4.

**Combinations of five**

The following can be seen in table 3-10:

1. For the combination  $\gamma$ -glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, MCV and creatinine and a requirement of at least 2 positive findings, 85% of the alcoholics are included (see sensitivity) and 64% of the non-alcoholics are identified as such with 1 positive finding at most (see specificity).

2. For the combination  $\gamma$ -glutamyltransferase, aspartate aminotransferase, MCV, creatinine and urea and a limit of 3 positive findings, 96% of the non-alcoholics are included (see specificity) and 51% of the alcoholics are identified as such with at least 4 positive findings (see sensitivity).

Tab. 3-10. Combinations of five findings.

Constituent combinations	Sensitivity	Specificity	Efficiency
	alcoholics (%)	non-alcoholics (%)	
Positive findings	2	1	
$\gamma$ -GT/GOT/GPT/MCV/creat	85.2	64.3	149.5
Positive findings	3	2	
$\gamma$ -GT/GPT/MCV/creat/urea-N	76.5	75.7	152.2
$\gamma$ -GT/GOT/MCV/creat/urea-N	74.1	82.9	157.0
$\gamma$ -GT/GOT/GPT/creat/urea-N	65.8	84.3	150.2
Positive findings	4	3	
$\gamma$ -GT/GOT/MCV/creat/urea-N	50.6	95.7	146.3

Constituent abbreviations and decision limits as in table 3-4.

**Combinations of six** do not bring any improvement in power of differentiation.

**3.2.4 Optimization of the decision limits: Increasing diagnostic efficiency with reference to other patients**

The decision limits were optimized first for individual constituents and then for constituent combinations.

**3.2.4.1 Individual constituents**

For individual constituents only the efficiency can be optimized. The process is illustrated using the distribution of  $\gamma$ -glutamyltransferase activity for alcohol-

ics and non-alcoholics (tab. 3-11). The effects on efficiency, sensitivity and specificity of a change in the decision limit are shown in table 3-12. The highest efficiency is obtained when the decision limit is  $45 \geq U/l$ .

All individual constituents for which it was possible to obtain a maximum level of efficiency of at least 130 are shown in table 3-13 along with the optimized decision limits.

Tab. 3-11. Frequency distribution for  $\gamma$ -glutamyltransferase.

Class limit (U/l)	Sensitivity for the lower class limit	Alcoholics (N)	Non-alcoholics (N)	Specificity for the upper class limit
0- 10	100	0	0	5.7
11- 20	100	8	31	47.1
21- 30	90.2	13	15	70.0
31- 40	74.4	7	8	84.3
41- 50	65.9	6	3	88.6
51-100	59.8	18	6	97.1
101-200	39.0	12	1	98.6
>200	22.0	18	1	100

Tab. 3-12. Example of the process of optimizing the decision limit for a single constituent with regard to efficiency, constituent:  $\gamma$ -glutamyltransferase.

Criterion (U/l)	Sensitivity alcoholics (%)	Specificity non-alcoholics (%)	Efficiency alcoholics/non-alcoholics
$\geq 220$	22.0	100	122.0
$\geq 60$	52.4	90.0	142.4
$\geq 45$	63.4	87.1	150.6
$\geq 27$	81.7	67.1	148.9
$\geq 21$	90.2	51.4	141.7
$\geq 11$	100	7.1	107.1

Tab. 3-13. Decision limits optimized for maximum efficiency for six individual constituents.

Constituent	(Unit)	Max. efficiency alcoholics/non-alcoholics	Limit
$\gamma$ -GT	(U/l)	151	$\geq 45$
GOT	(U/l)	143	$\geq 16$
MCV	(fl)	138	$\geq 95$
Urea-N	(mmol/l)	137	$\leq 4.3$
Creat	( $\mu$ mol/l)	134	$\leq 70.7$
GPT	(U/l)	130	$\geq 15$

Constituent abbreviations as in table 3-4.

## 3.2.4.2 Combinations

The following can be seen in table 3-14:

1. For combination no. 5, consisting of the 6 constituents  $\gamma$ -glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, MCV, creatinine and urea, 83% of the alcoholics can be included if there are at least 5 positive findings (see sensitivity) and 89% of the non-alcoholics can be recognized as such (see specificity) if there are 4 positive findings at the most. This means that this combination with these restrictions can be used to detect the non-alcoholics.
2. The complementary situation for the same combination is that 89% of the non-alcoholics can be included with 4 positive findings at the most (see specificity) and 83% of the alcoholics can be identified as such if there are at least 5 positive findings. This means that this combination in this form can be used

to detect the alcoholics. The two applications complement each other if both the sensitivity of 83% and the specificity of 89% are regarded as being high enough.

3. For the combination of  $\gamma$ -glutamyltransferase, aspartate aminotransferase, the ratio aspartate/alanine aminotransferase, MCV, creatinine and urea, 86% of the alcoholics are included if at least 5 positive findings are required (see sensitivity) and 87% of the non-alcoholics can be identified as such (see specificity) if there are at least 4 positive findings.

If a sensitivity or specificity of 100% is required, then for a combination of six either a maximum sensitivity of 59% or a maximum specificity of 53% can be attained. Considering the marked overlapping of the distributions, such requirements must be regarded as unrealistically severe. Therefore in tables 3-15 and 3-16 respectively specificity and sensitivity were set at 95%.

Tab. 3-14. Examples of decision limits optimized for maximum efficiency for various combinations of constituents.

Constituent combination	(Unit)	Limit	Criterion for positive test, minimum no. positive	Sensitivity alcoholics (%)	Specificity non-alcoholics (%)	Efficiency alcoholics/non-alcoholics
1 $\gamma$ -GT MCV	(U/l) (fl)	$\geq 18$ $\geq 90$	2	90.1	68.6	158.7
2a $\gamma$ -GT GOT MCV	(U/l) (U/l) (fl)	$\geq 18$ $\geq 19$ $\geq 90$	2	93.8	67.1	161.0
2b $\gamma$ -GT GOT MCV	(U/l) (U/l) (fl)	$\geq 18$ $\geq 11$ $\geq 90$	3	85.2	80.0	165.2
3 $\gamma$ -GT GOT MCV Urea-N	(U/l) (U/l) (fl) (mmol/l)	$\geq 18$ $\geq 9$ $\geq 89$ $\leq 5.4$	4	85.2	82.9	168.0
4 $\gamma$ -GT GOT MCV Creat Urea-N	(U/l) (U/l) (fl) ( $\mu$ mol/l) (mmol/l)	$\geq 19$ $\geq 15$ $\geq 94$ $\leq 68.1$ $\leq 2.9$	3	81.5	88.6	170.0
5 $\gamma$ -GT GOT GPT MCV Creat Urea-N	(U/l) (U/l) (U/l) (fl) ( $\mu$ mol/l) (mmol/l)	$\geq 26$ $\geq 10$ $\geq 9$ $\geq 93$ $\leq 67.2$ $\leq 6.4$	5	82.7	88.6	171.3
6 $\gamma$ -GT GOT GOT/GPT MCV Creat Urea-N	(U/l) (U/l) (U/l) (fl) ( $\mu$ mol/l) (mmol/l)	$\geq 27$ $\geq 9$ $\geq 0.63$ $\geq 89$ $\leq 70.7$ $\leq 6.4$	5	86.4	87.1	173.6

Constituent abbreviations as in table 3-4.

The following can be seen in tables 3-15 and 3-16:

1. For the combination of  $\gamma$ -glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, MCV, creatinine and urea, if 95.7% of the non-alcoholics are included, 67% of the alcoholics with at least 4 positive findings will be detected (see maximum sensitivity, table 3-15).
2. For the same combination, if 95.1% of the alcoholics are included, 74% of the non-alcoholics with 3 positive findings at the most will be identified as such (see maximum specificity, table 3-16).

The decision limits for the two procedures are different.

### 3.3 Clinical laboratory findings as markers of alcoholism and alcohol abuse

Because of the increase in alcoholism over the last 3 decades, numerous attempts have been made during

the past 10 years to find combinations of clinical chemical findings that would be useful in the detection or exclusion of alcohol abuse (23). Table 3-17 shows the combinations of findings suggested in selected papers published in the last 3 years. In some of the papers alcoholics were compared with "healthy" persons, with the result that the figures on discrimination of alcoholics from non-alcoholics are too optimistic. A realistic picture is obtained only if alcoholics are compared with non-alcoholics who have other disorders that can lead to changes in clinical chemical parameters.

Furthermore, from the data structure of the analytical results for alcoholics and non-alcoholics reported here it can be seen that for most of the parameters studied the prerequisites for use of linear or quadratic discriminant analysis are not fulfilled (see Section 2.5.3).

Tab. 3-15. Examples of decision limits optimized for maximum sensitivity of constituent combinations.  
Required specificity: 95.7% (non-alcoholics)

Constituent combination	(Unit)	Limit	Minimum no. of positive tests	Maximum sensitivity (%) alcoholics
1 $\gamma$ -GT	(U/l)	$\geq 67$	2	48.2
MCV	(fl)	$\geq 84$		
2 $\gamma$ -GT	(U/l)	$\geq 24$	3	55.6
GOT	(U/l)	$\geq 15$		
MCV	(fl)	$\geq 92$		
3 $\gamma$ -GT	(U/l)	$\geq 29$	4	60.5
GOT	(U/l)	$\geq 9$		
MCV	(fl)	$\geq 92$		
Urea-N	(mmol/l)	$\leq 4.6$		
4 $\gamma$ -GT	(U/l)	$\geq 62$	3	65.4
GOT	(U/l)	$\geq 16$		
MCV	(fl)	$\geq 95$		
Creat	( $\mu$ mol/l)	$\leq 61.9$		
Urea-N	(mmol/l)	$\leq 2.9$		
5 $\gamma$ -GT	(U/l)	$\geq 27$	4	66.7
GOT	(U/l)	$\geq 15$		
GPT	(U/l)	$\geq 11$		
MCV	(fl)	$\geq 97$		
Creat	( $\mu$ mol/l)	$\leq 61.9$		
Urea-N	(mmol/l)	$\leq 2.9$		
6 $\gamma$ -GT	(U/l)	$\geq 18$	5	67.9
GOT	(U/l)	$\geq 9$		
GOT/GPT	(U/l)	$\geq 1.05$		
MCV	(fl)	$\geq 90$		
Creat	( $\mu$ mol/l)	$\leq 67.2$		
Urea-N	(mmol/l)	$\leq 6.4$		

Constituent abbreviations as in table 3-4.

Tab. 3-16. Examples of decision limits optimized for maximum specificity of constituent combinations.  
Required sensitivity: 95.1% (alcoholics)

Constituent combination	(Unit)	Limit	Minimum no. of positive tests	Maximum specificity (%) non-alcoholics
1 $\gamma$ -GT	(U/l)	$\geq 13$	2	48.6
MCV	(fl)	$\geq 89$		
2 $\gamma$ -GT	(U/l)	$\geq 16$	2	60.0
GOT	(U/l)	$\geq 19$		
MCV	(fl)	$\geq 90$		
3 $\gamma$ -GT	(U/l)	$\geq 15$	3	65.7
GOT	(U/l)	$\geq 14$		
MCV	(fl)	$\geq 90$		
Urea-N	(mmol/l)	$\leq 5.0$		
4 $\gamma$ -GT	(U/l)	$\geq 18$	3	70.0
GOT	(U/l)	$\geq 10$		
MCV	(fl)	$\geq 94$		
Creat	( $\mu$ mol/l)	$\leq 70.7$		
Urea-N	(mmol/l)	$\leq 2.5$		
5 $\gamma$ -GT	(U/l)	$\geq 18$	4	74.3
GOT	(U/l)	$\geq 10$		
GPT	(U/l)	$\geq 9$		
MCV	(fl)	$\geq 97$		
Creat	( $\mu$ mol/l)	$\leq 66.3$		
Urea-N	(mmol/l)	$\leq 4.3$		
6 $\gamma$ -GT	(U/l)	$\geq 25$	5	72.9
GOT	(U/l)	$\geq 10$		
GOT/GPT	(U/l)	$\geq 0.60$		
MCV	(fl)	$\geq 90$		
Creat	( $\mu$ mol/l)	$\leq 80.4$		
Urea-N	(mmol/l)	$\leq 6.4$		

Constituent abbreviations as in table 3-4.

Tab. 3-17. Combinations of clinical chemical findings as markers of alcohol abuse and alcoholism.

System analysed	Investigator; year (reference)						
	<i>Whitehead</i> et al.	<i>Whitfield</i> et al.	<i>Ryback</i> et al.	<i>Wisser &amp; Knoll</i>	<i>Chalmers</i> et al.	<i>Eckardt</i> et al.	<i>Glud</i> et al.
Constituent	1978 (24)	1978 (25)	1980 (26)	1980 (27)	1981 (28)	1981 (29)	1981 (30)
<b>Whole blood</b>							
Sedimentation rate							
Haemoglobin			xxx				
Haematocrit			xxx				
Erythrocytes			xxx				
MCV	xxx	xxx	xxx	xxx	xxx	xxx	
Reticulocytes							
Leukocytes			xxx				
Differential blood count							
Thrombocytes							
<b>Capillary blood</b>							
Glucose			xxx				
<b>Serum</b>							
Total protein			xxx				
Albumin			xxx				
γ-Globulin							
Bilirubin			xxx				
Uric acid	xxx	xxx	xxx				
Sodium			xxx				
Potassium			xxx				
Calcium			xxx				
Chloride			xxx				
Phosphorus, inorg.			xxx				
Magnesium							
Iron							
Copper							
Cholesterol			xxx				
Triglycerides		xxx	xxx				
Creatinine							
Urea			xxx				
γ-Glutamyltransferase	xxx	xxx		xxx	xxx	xxx	xxx
Aspartate aminotransferase	xxx	xxx	xxx	xxx			xxx
Alanine aminotransferase				xxx	xxx		
Cholinesterase							
Alkaline phosphatase			xxx		xxx		xxx
Glutamate dehydrogenase							
Creatine kinase							
Lactate dehydrogenase			xxx				

For this reason the procedure described in Section 2.5.3 (14) was developed and used to discriminate between alcoholics and non-alcoholics. This procedure made possible an assessment on the same groups of subjects of all combinations of constituents suggested so far as "markers of alcohol abuse". Moreover, the alcoholics have been carefully described via the outside criterion MALT and additional investigations.

In the course of the present project those combinations of constituents were determined that enable the best discrimination. Tables 3-6 to 3-10 show the values for the diagnostic criteria sensitivity, specificity and efficiency with conventional decision limits.

Tables 3-14 through 3-16 contain the same information assuming optimized decision limits.



In our statistical evaluations, marked overlapping of distributions was also found for combinations of constituents. As a result, a *complete* separation of alcoholics and non-alcoholics is not possible with any procedure. The combinations of six with optimized decision limits shown in Section 3.2.4.2 appear to us to be the best combinations of clinical laboratory findings for the differentiation of alcoholics and non-alcoholics in patient populations.

The levels of discrimination reported by *Ryback* et al. (26) and *Eckardt* et al. (29) appear to us to be unrealistic. This is because

(1) alcoholics were compared with individuals who were apparently healthy and

(2) quadratic discriminant analysis was used (the structure of our data and our results indicate that the prerequisites for this procedure are not fulfilled).

#### 4. Conclusions

The investigations reported here were performed on men only. The conclusions are therefore valid for men only. In an analogous study with the same design but with women as subjects all tests have been completed and the data are now being evaluated.

With regard to the *purpose of the study* the following has been learned:

##### 1. Detection of alcoholism

Detection of alcoholism on the basis of a statistical discrimination procedure is synonymous with exclusion of non-alcoholism.

If the 5 parameters  $\gamma$ -glutamyltransferase ( $\geq 28$  U/l), aspartate aminotransferase ( $\geq 18$  U/l), alanine aminotransferase ( $\geq 22$  U/l), MCV ( $\geq 96$  fl) and creatinine ( $\leq 66.3$   $\mu$ mol/l) are studied, alcoholism can be detected on the basis of 2 or more of the results being outside the conventional decision limits given in parentheses (tab. 3-10). The diagnostic sensitivity is 85%, the diagnostic specificity 64% and thus the diagnostic efficiency 149.

If the decision limits are optimized and the sensitivity maintained about as above, the specificity can be increased to about 89% and the efficiency to 171 for 6 parameters, no ratio, or 174 for 6 parameters with ratio (tab. 3-14).

Thus it appears possible to detect alcoholism with a high degree of probability using simple means and without the cooperation of the patient.

##### 2. Exclusion of alcoholism

The exclusion of alcoholism on the basis of a statistical discrimination procedure is synonymous with the detection of non-alcoholism.

If the 5 parameters  $\gamma$ -glutamyltransferase ( $< 28$  U/l), aspartate aminotransferase ( $< 18$  U/l), MCV ( $< 96$  fl), creatinine ( $> 66.3$   $\mu$ mol/l) and urea ( $> 5.0$  mmol/l) are studied, alcoholism can be detected if 4 or more of the results are outside the conventional decision limits given in parentheses (tab. 3-10). For this combination the diagnostic specificity is 96%, the diagnostic sensitivity 50% and thus the efficiency 146.

If the decision limits are optimized and the specificity maintained as above, the sensitivity can be increased to about 67% (tab. 3-15). Efficiency can be increased to 171 for 6 parameters, no ratio, or 174 for 6 parameters with ratio (tab. 3-14).

It thus appears to be possible to exclude alcohol abuse very quickly with a high level of probability, using simple investigations.

3. It is essential that these patterns of findings in alcoholics and non-alcoholics be validated with patients who have disorders of the liver, the blood and blood-forming organs, the kidneys and the circulatory system. A validation study with men is in progress.

#### 5. Acknowledgments

The extensive study reported here would not have been possible without the efficient collaboration of three departments within the Max-Planck-Institut für Psychiatrie.

The patients were selected and examined by Dr. *Sigrid Seidel* and Dr. *V. Geiger* of the Psychiatric Outpatient Department. The clinical chemical and haematological studies were performed in the routine laboratory of the Department of Clinical Chemistry. Special thanks are due to the head technologist, Ms. *Liselotte Hofmann*, to Mrs. *Elisabeth Stiegler* (née *Roesch*) and to all of the other laboratory technicians.

Ms. *Ingrid Bickert* and Ms. *Eva Müller* (Department of Biostatistics) carried out the data processing, compiled the tables and prepared the diagrams with great attention to detail. The reference list was compiled and the manuscript typed with great care by Ms. *Elisabeth Geirhos* and Ms. *Ursula Grau*.

Professors *Ellen Schmidt* and *Johannes Büttner* of Hannover were kind enough to discuss the results and their evaluation with us; they made valuable suggestions for the future validation of our findings.

We wish to express our appreciation to all concerned.

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