REVIEW ARTICLE

Early identification of alcohol abuse: 2: Clinical and laboratory indicators*

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Despite awareness of the wide variety of clinical and laboratory abnormalities associated with alcohol abuse, drinking problems often remain undetected in hospital and in general medical practice. The diagnosis of alcohol abuse has been emphasized repeatedly in the literature but far less attention has been paid to indicators that would permit detection of excessive drinking at a stage when intervention might be more effective and less costly. The search for indicators of early alcohol abuse is complicated since many of the medical sequelae of alcoholism are nonspecific and may only be manifested after a number of years of excessive drinking. Part 2 of this two-part series considers various clinical and laboratory features related to alcohol abuse and highlights items that are potentially more sensitive for detecting early stages of problem drinking. Use by physicians of a composite profile of both biomedical and psychosocial indicators of excessive alcohol consumption is recommended for early identification of this problem.

Malgré la connaissance des multiples anomalies cliniques et de laboratoire reliées à l'abus de l'alcool, les problèmes d'alcoolisme échappent souvent à la détection, en milieu hospitalier comme en pratique générale. Dans la littérature, on a insisté sur le diagnostic de l'abus de l'alcool, mais on a accordé beaucoup moins d'attention aux indicateurs qui permettraient de déceler l'abus de l'alcool au stade où une intervention pourrait être plus efficace et moins coûteuse. La recherche des indicateurs du début de l'alcoolisme est compliquée par le fait que plusieurs des séquelles médicales sont non spécifiques et qu'elles peuvent ne se manifester qu'après un certain nombre d'années de consommation exagérée. Dans la deuxième partie de cette série de deux, on envisage diverses caractéristiques cliniques et de laboratoire rattachées à la consommation excessive d'alcool et on met en lumière les items susceptibles d'être plus sensibles pour détecter les premiers stades de l'alcoolisme. Afin de pouvoir identifier tôt ce problème, on recommande l'emploi par le médecin d'un profil associant des indicateurs biomédicaux et psychosociaux de la consommation excessive d'alcool.

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An increasing awareness that excessive drinking is a major medical problem has prompted research aimed at determining reliable indicators of hazardous alcohol consumption.[1,2] Although many of the alcohol-induced symptoms, clinical signs and abnormal laboratory findings are nonspecific, it is reasonable to assume that the more alcohol-related problems a patient has, the greater the probability that excessive alcohol consumption has been or is present. Despite considerable interest in the medical sequelae of alcohol abuse, there is relatively little information on the value of using alcohol-related diseases as predictors of past or present problem drinking. Few epidemiologic studies have compared the disease patterns of patients who abuse alcohol with the patterns of control subjects. Without adequate prevalence data, the value of a variety of alcohol-associated disorders for detecting problem drinking in the general population cannot be adequately assessed.

Alcohol-related problems are known to be a common cause for medical consultation, and knowledge of the protean manifestations of hazardous alcohol consumption should aid in detecting alcohol abuse. This approach is encouraged by the successful use of a variety of medical factors known or believed to be associated with a high prevalence of alcoholism for the screening of patient populations in order to identify the "hidden alcoholic".[3-9] A recent World Health Organization (WHO) study group indicated that an important objective of future research on alcohol abuse should be the "development of methods for screening and early detection of alcohol-related disabilities, with correlation of questionnaire and laboratory methods".[1]

Although a number of reviews on the detection of alcohol abuse have appeared in recent years,[8-11] few

studies have focused on biomedical factors associated with both early and later clinical manifestations of excessive alcohol consumption. The aim of this paper is to discuss the value of various symptoms, signs and clinical investigations for identifying alcohol abuse. Particular attention is given to describing the morbidity profile at progressive stages in the development of alcohol abuse and on a critical appraisal of the growing number of laboratory tests and biochemical markers of such abuse.

This paper was prepared during the planning of a series of tests for identifying problem drinking. Before this research began at the Clinical Institute of the Addiction Research Foundation of Ontario in Toronto, attempts were made to justify including various biomedical and sociobehavioural items that might form the basis of an identification battery for the detection of alcohol abuse. The major thrust of this research is to determine accurate indicators of excessive alcohol consumption and related problems, and to incorporate these into a brief medical examination and a questionnaire for the patient that may be used in a variety of settings, including hospitals, industrial clinics and private practices.

Disorders related to alcohol abuse

Chronic hazardous drinking results in a wide spectrum of disorders causing a multitude of clinical symptoms and signs, many of which may be useful in detecting alcohol abuse. It is accepted that the functional and morphologic changes in many organs of the body that accompany or result from excessive alcohol consumption can provide reliable evidence of excessive drinking. However, relatively few clear correlations between clinical data and prolonged heavy drinking have been adequately demonstrated. Although alcohol abuse and problem drinking have diverse clinical manifestations, the most specific disorders usually represent advanced and often irreversible effects of alcohol and therefore may not be relevant to the early identification and treatment of these problems. Nevertheless, by accepting the assumption that the larger the number of alcohol-related alterations, the greater the probability that excessive alcohol consumption is present, a physician may compensate for the lack of specificity of some clinical items by using combinations of symptoms and signs.

In his excellent study on the hidden alcoholic in general practice Wilkins[8] drew attention to items in a patient's history that are valuable clues to alcohol abuse. These items, known or believed to be associated with a higher prevalence of alcoholism, were compiled in an "alcoholic at risk" register for detecting individuals whose drinking habits were already advanced. Wilkins recognized that earlier detection of alcohol abuse would improve the chances of arresting this disorder but concentrated his attention mainly on individuals with established alcoholism.

A patient's social history, including marital status, social class, living conditions, ethnic origin and occupation, should be considered since circumstances such as divorce, low social class and poor housing may be associated with a higher prevalence of hazardous alcohol consumption.[8,12] Wilkins emphasized that the general practitioner may be in an almost ideal situation for detecting alcohol abuse, as clues to the presence of alcoholism can be obtained by studying demographic data reported on patients' records even before they are seen in a clinic or an office. Alcoholics have a higher incidence of sickness, absenteeism, accidents, neurologic disorders, pulmonary disease and hypertension than matched controls.[13-16] It has been suggested that these alcohol-related disabilities may follow a recognizable sequence, and that early complications of alcohol abuse may manifest themselves before the patient or clinician is aware that a drinking problem exists.[17] For example, trauma and gastrointestinal disease tend to occur earlier in the course of alcohol abuse than neurologic disease or cirrhosis of the liver. The recognition of certain disorders as earlier indicators of hazardous alcohol consumption could aid in the detection of problem drinking.[17]

This review will concentrate on the principal medical sequelae of alcohol abuse, emphasizing the signs and symptoms related to gastrointestinal disorders, liver disease, neurologic alterations, trauma, and cardiovascular and respiratory disease. Attempts will be made to indicate disorders that are useful for detecting early rather than more advanced stages of alcohol abuse (Table I).

Gastrointestinal disease

Morning retching, nausea, anorexia and vomiting occur frequently in persons who abuse alcohol, and may be associated with hangovers or withdrawal symptoms.[18,19] Alcohol ingestion has been causally associated with a number of inflammatory lesions in the upper gastrointestinal tract. Because alcohol reduces the pressure of the lower esophageal sphincter and interferes with esophageal peristaltis, short-term or long-term alcohol abuse may promote gastroesophageal reflux.[20] Smoking, a common habit in abusers of alcohol,[21] may also reduce sphincter pressure, predisposing the drinker who smokes to esophageal reflux.[22] Portal hypertension induced by alcoholic cirrhosis may lead to esophageal varices and severe gastrointestinal bleeding.[23] Severe vomiting after overindulgence in food and alcohol may tear the mucosa at the gastroesophageal junction and cause hematemesis (Mallory–Weiss syndrome).[24] Erosive gastritis and acute duodenal erosions can develop in heavy drinkers and may lead to gastrointestinal hemorrhage.[25,26] Endoscopic studies have shown an increased prevalence of gastric mucosal disease in alcoholics. Moderate to severe antral gastritis has been found in 46% of alcohol abusers (the proportion was about half in a control group),[27] and abnormal gastric tissue was noted in all the members of a group of 51 patients with chronic alcoholism.[28] However, the evidence that alcohol consumption causes chronic gastritis has been questioned.[29]

Many authors have stressed a high frequency of dyspeptic symp-

toms in alcohol abusers. In one study of absenteeism in office staff it was noted that one third of a group of heavy drinkers were absent from work because of upper gastrointestinal complaints.[30] It would appear that the clinical manifestations of peptic ulceration are twice as common in alcoholic patients as in control subjects.[13,31] Although a number of studies suggest that the incidence of peptic ulcer is higher with alcohol abuse,[13,15,16] further investigation is required to substantiate this apparent relationship.[12]

Alcohol consumption is an important etiologic factor in both acute and chronic pancreatitis. The incidence of alcohol-associated acute pancreatitis in younger age groups seems to be increasing.[32] Chronic pancreatitis, when advanced, can cause an insufficiency of digestive enzymes. This may account for certain abnormalities in nutrient absorption that are associated with chronic alcohol abuse.[33] Motor function of the stomach and small intestines is affected by alcohol.[34-37] Robles and colleagues[37] have shown that impeding peristaltic waves are decreased by alcohol, but that propulsive movement remains unchanged. This altered small bowel motility could increase the rate of transit in the small bowel and may contribute to the diarrhea that is associated with "binge drinking". In addition, chronic, heavy consumption of alcohol may interfere directly with absorption in the small intestine.[38] Recent evidence indicates that caffeine consumed in normal amounts may increase the serosa to mucosa flux of fluid in the intestines, leading to an intraluminal accumulation of fluid and subsequently to diarrhea.[39] Thus, the alcohol abuser who also consumes caffeine may be even more prone to diarrhea.

Both drinking in binges and chronic alcohol abuse may lead to the malabsorption of a variety of substances, including D-xylose,[40] calcium,[41] B-complex vitamins[40,42] and iron.[43] However, other factors are involved in the nutrient deficiencies of alcoholics. These include an inadequate diet and metabolic disorders secondary to chronic hazardous alcohol consumption.[44] Overt symptoms and signs of malnutrition represent relatively late-stage complications of alcoholism and appear to be more prevalent in the "skid-row" alcoholic.[45]

Table I—Clinical symptoms and signs of alcohol abuse

Symptoms and signs	Stage of appearance*	Diagnostic value†
General appearance		
Hand tremor	E	+
Excitability, irritability, nervousness	E	
Unkempt appearance	L	
Jaundice	L	+
Alcoholic facies	E	?
Mouth		
Coated tongue	E	
Peridontal disease	L	
Alcoholic fetor by day	E	+
Gastrointestinal tract		
Dyspepsia	E	
Morning nausea and vomiting	E	+
Recurrent diarrhea	E	
Recurrent abdominal paln	L	
Acute and chronic pancreatitis	E, L	+
Hepatomegaly	E	+
Splenomegaly	L	
Ascites	L	
Gastrointestinal bleeding	E, L	
Genitourinary system		
Polyuria	E	
Amenorrhea	L	
Impotence	E	
Face, skin and hands		
Rosacea, seborrheic dermatitis	L	
Parotid swelling	L	
Spider nevi	L	
Finger clubbing	L	
Dupuytren's contracture	L	+
Scars unrelated to surgical procedure	E	+
Cardiovascular and respiratory system		
Palpitations	E	
Cardiomyopathy	L	
Hypertension	E	
Chronic obstructive airways disease	L	
Recurrent chest infection and pneumonia	L	
Central nervous system		
Poor memory for recent events	E	
Blackouts	L	
Seizures	L	
Ataxia	L	
Peripheral neuropathy, myopathy	L	
Insomnia, nightmares	E	
Hallucinations	L	
Delirium tremens	L	
Wernicke–Korsakoff syndrome	L	
Miscellaneous		
Trauma	E	+
Random blood alcohol level > 65 mmol/l (300 mg/dl)	E	+
No gross incidents of intoxication with blood alcohol level > 33 mmol/l (150 mg/dl)	E	+

*E = usually early; L = usually late.
†+ = probably a good indicator of alcohol abuse.

Liver disease

Liver disease occurs frequently with chronic alcohol abuse, and alcoholic liver disease in adult populations is positively correlated with the overall per capita consumption of alcohol.[46] About 10% of alcohol abusers have cirrhosis, which is more likely to develop in the "continuous imbiber" than in the "spree drinker".[47] The correlation between per capita alcohol consumption and rates of death from cirrhosis is well recognized.[46,48-53] In one large study the observed death rate from cirrhosis in 6478 alcoholics was about 13 times more frequent than would be expected in the general population.[54] Although

cirrhosis may present a number of characteristic clinical symptoms and signs, it occurs at a relatively late stage in the morbidity sequence of alcoholism.[55] It may take 5 to 10 years of chronic alcohol abuse before cirrhosis appears.[46] Important precursors of cirrhosis, including fatty liver, alcoholic hepatitis and fibrosis, may frequently be asymptomatic and have few or even no clinical signs.[56-61] For example, the spectrum of those with alcoholic hepatitis may range from an asymptomatic individual to a patient with fever, jaundice, encephalopathy and ascites.[53] Rankin and coworkers[61] drew attention to the problems of diagnosing alcoholic liver disease by demonstrating a lack of correlation between clinical signs and the severity of underlying liver disease as assessed by liver biopsy. The degree of overlap of clinical manifestations of the various liver disorders is such that differentiation on clinical grounds is not possible with any degree of accuracy.[61]

It has been suggested that a composite index, derived by multivariate statistical analyses of various clinical signs and tests of liver function, provides greater diagnostic accuracy than consideration of any single test.[62] An important attempt to overcome some of the problems surrounding the clinical diagnosis of alcoholic liver disease is the development of a composite index to assess severity of alcoholic liver disease.[63] This clinical and laboratory index is based on 11 clinical signs (hepatomegaly, splenomegaly, ascites, encephalopathy, a clinically overt tendency to bleed, spider nevi, palmar erythema, collateral venous circulation on the anterior abdominal wall, circulation, peripheral edema, anorexia and weight loss) and six laboratory findings (levels of glutamic oxaloacetic transaminase [SGOT], γ-glutamyl transpeptidase [GGT], alkaline phosphatase, albumin and bilirubin in the serum, and prothrombin time). The scoring system of this index is based on the concept that the severity of the underlying liver disease is proportional to the number of abnormal clinical and laboratory findings. Certain items, such as encephalopathy, ascites, a raised level of serum bilirubin and a prolonged prothrombin time, are weighted because they are known to be associated with more advanced disease and a poorer prognosis.

Neurologic disease

Both periodic heavy drinking and chronic alcohol abuse produce a variety of complex metabolic and pathophysiologic alterations in the central and peripheral nervous systems. However, the precise cause of many of the neurologic sequelae of alcohol abuse is unknown. Neurologic disorders in the alcoholic have been classified on phenomenologic, etiologic and neuropathologic bases.[64-68] The main neurologic disturbances in alcohol abusers are acute intoxication, withdrawal symptoms (e.g., tremulousness), hallucinations, epilepsy, delirium tremens, Wernicke–Korsakoff syndrome, polyneuropathy, cerebellar degeneration, central pontine myelinolysis, Marchiafava–Bignami disease, neurologic sequelae of chronic hepatic disease (e.g., hepatic encephalopathy), cerebral atrophy with neuropsychologic impairment and alcoholic dementia.[68] In addition to neurologic dysfunction, alcohol abusers may have an uncommon but well defined syndrome of acute alcoholic myopathy, with muscle pain, tenderness, swelling and variable myoglobulinuria.[69-71] A chronic myopathy may occur with an insidious onset of muscle weakness and atrophy.[69-71]

Although symptoms and signs of withdrawal from drinking alcohol may be useful clinical indicators of alcohol abuse, they are extremely variable. It is especially important to be aware of mild withdrawal reactions such as tremor, anxiety, insomnia, hyperreflexia, and a lowered seizure threshold.[18,19] All of these symptoms may appear within a few hours of withdrawal from drinking alcohol and may last for approximately 2 days.[72] Severe withdrawal reactions, manifested by confusion, hallucinations, seizures and full-blown delirium tremens, are often most evident between 2 and 4 days after withdrawal but may persist for up to 10 days.[72]

Although peripheral neuropathy may be present in up to 10% of cases of chronic alcohol abuse,[73,74] it may occur only after a number of years of heavy alcohol use.[75] The onset of symptoms of this disorder is variable but usually extends over weeks or months. The neurologic deficit is frequently bilateral, symmetric and sensorimotor in type. It is important to be aware that subclinical neuropathy is common. Clinical findings include weakness, muscle wasting and tenderness, a loss of reflexes and distal sensory impairment or loss. Patients may complain of burning feet or of trophic skin changes in the lower limbs. The legs alone are affected in approximately 70% of all cases.[73,74] Significant defects in memory and other cognitive processes are often present in alcohol abusers,[75-79] but clinically overt intellectual impairment may be present in a smaller proportion of patients.[80,81] Dementia occurs in about 9% of abusers of alcohol, its incidence increases with age and it is more common in women than men.[68]

Many of these neuropsychologic deficits have been presumed to be related to cerebral atrophy.[78] Recent studies have indicated that both abnormal results of neuropsychologic tests and cerebral atrophy, as measured by computer-assisted transaxial tomography, are present in abusers of alcohol.[80,81] However, these measures may not reflect the duration of heavy drinking, and the neuropsychologic test results do not always correlate with the amount of cerebral atrophy.[79] Although physicians do not generally use neuropsychologic tests, it seems likely that such tests would be effective in detecting early stages of alcohol abuse.

Trauma and accidents

Alcohol abuse plays a major role in accidents, criminal behavior, acts of violence, suicide and other serious events.[1,2] Numerous studies have implicated alcohol as a cause of many traffic, industrial and recreational accidents.[54,82-85] A direct result of an increased accident rate among abusers of alcohol is a high incidence of traumatic injuries. Past or present traumatic events are among the most common diagnoses in heavy drinkers admitted to treatment units.[86,87] One survey estab-

lished that 36% of regular drinkers had reported at least two accidental injuries in the preceding year, compared with an accident rate of only 8% in nondrinkers.[88] The extent to which alcohol is involved in accidents and emergency admissions to hospitals has been substantiated by a recent study that demonstrated that approximately one third of all patients attending a casualty department in a large general hospital in the evening had a blood alcohol concentration of over 17.4 mmol/l (80 mg/dl).[89] Bone fractures occur commonly in heavy drinkers,[90-92] and since injuries are known to be among the most common causes for medical consultation in inebriated patients,[93] an awareness of the prevalence of such alcohol-related morbidity can aid in detecting alcohol abuse.

In an investigation conducted by the Addiction Research Foundation of Ontario in Toronto, rib or thoracic vertebral fractures or both were found on the routine chest roentgenograms of 28.9% of a group of alcoholic men but in only 1.3% of a matched control group of social drinkers.[92] An increased exposure to trauma was the most likely cause of this 16-fold increase in the number of thoracic fractures. Since trauma occurs early among the problems related to alcohol abuse, evidence of fractures may be an early indicator of past or present hazardous alcohol use.

A number of studies have drawn attention to the association between acute alcohol intoxication and head injury.[94-98] In one prospective study 62% of the men and 20% of the women admitted to hospital with a head injury had detectable levels of alcohol in their blood.[97] Galbraith and associates[97] observed that assaults and falling while under the influence of alcohol were common modes of head injury, whereas road traffic accidents accounted for only 25% of cases. Preliminary data from a study of patients with chronic subdural hematoma admitted to a large district general hospital in Toronto indicate that between 30% and 40% of such patients may be abusers of alcohol (M.S. Jacobs, P.L. Carlen: personal communication, 1979).

Cardiovascular and respiratory disease

A number of investigations have documented an association between alcohol consumption and hypertension.[99-101] In a study of the alcoholic employees of a large company, Pell and D'Alonzo[14] found a two- to threefold greater prevalence of hypertension (a systolic blood pressure higher than 160 mm Hg or a diastolic pressure higher than 95 mm Hg) in alcohol abusers than in matched controls. From a survey of 84 000 people Klatsky and associates[102] reported that the prevalence of hypertension was 11.2% in individuals ingesting six or more drinks a day compared with 4.6% in nondrinkers. Alcohol abusers have an increased risk of premature death from diseases of the cardiovascular system.[103] It seems likely that alcohol consumption, by contributing to hypertension, increases the risk for such disease. However, additional investigation is required to define the level of alcohol consumption that is associated with an increased risk of cardiovascular disease and to ascertain the underlying mechanisms.[104]

The relation between alcohol abuse and coronary artery disease requires further clarification, since it appears that the prevalence of coronary artery disease decreases as the quantity of alcohol consumed increases, up to an intake of about 70 ml of ethanol a day.[2] Those who drink more than this amount may have a higher risk of coronary artery disease than nondrinkers.[2] A clear association between alcohol abuse and cardiomyopathy is well recognized, and is usually manifested by congestive cardiac failure in alcohol abusers under the age of 50.[71,105] Alcoholic cardiomyopathy may be acute or chronic, and is often manifested by tachycardia and hypotension.[71] Cardiac arrhythmias may occur in association with cardiomyopathy[106] or with intoxication in patients without other clinical evidence of underlying heart disease.[99,107]

Alcohol abuse is frequently associated with pulmonary disease, and especially with chronic obstructive airways disease, pulmonary fibrosis, tuberculosis and bronchiectasis.[108-110] A predisposition to pulmonary disease may be a direct result of the toxic effect of alcohol on the lung or an indirect result of the fact that alcoholics tend to be malnourished, to suffer from aspiration pneumonia and repeated respiratory tract infections and to be heavy cigarette smokers.[109,110] It seems likely that excessive smoking is a major cause of cardiac and pulmonary disease in alcoholics.[21,109]

Miscellaneous symptoms and signs

Normal sleep patterns are disrupted by alcohol consumption.[111] Sleep problems such as insomnia and frightening dreams are frequently experienced by abusers of alcohol.[112] Detailed studies of the sleep of alcohol abusers and of normal volunteers following alcohol ingestion have shown that both the quality and the quantity of sleep are disturbed by alcohol.[112,113] Complaints of sleep disturbance, especially from young patients, should prompt a clinician to enquire about drinking habits.

Reduced libido and impotence are recognized as being associated with chronic alcohol abuse. Masters and Johnson[114] indicated that secondary impotence in men is frequently caused by the excessive consumption of alcohol. Lemere and Smith[115] reported impotence in 8% of over 17 000 alcoholic men but found little evidence of sexual dysfunction in women who abused alcohol. Most alcoholic patients report that sexual performance has been normal for a number of years, but in the later stages of their heavy drinking sexual ability tends to be reduced.[116] The wide variability in what is considered normal sexual performance and the problem of obtaining accurate accounts of sexual function render sexual activity difficult to study. Important components of impotence that the alcoholic man may experience are a reduction or absence of sexual drive and a failure to achieve erection or ejaculation or both.[117] The causes of sexual dysfunction in the alcoholic are not understood completely but Lemere and Smith[15] have suggested that alcohol may damage the complex of neurologic reflexes subserving erection and that

psychologic factors may often be of secondary importance.

Margolis and Roberts[118] reported that 24% of a population of "chronic drinkers" derived from 500 consecutive admissions to hospital medical wards had significant skin lesions. Metabolic derangements, poor hygiene, inadequate nutrition and trauma may cause cutaneous lesions in alcohol abusers.[119] A wide variety of cutaneous stigmata may provide useful clues for the detection of alcohol abuse.[118,120-122]

The face of the habitual drinker often shows persistent erythema with or without telangiectasia, capillary engorgement of the conjunctiva, edema of the forehead and periorbital region, and grooving and thickening at the eyelid margins. A "whiskey nose" or rhinophyma may be present.[3,123] Young[122] has usefully divided cutaneous signs of alcohol abuse into three categories describing the sequelae of acute alcoholism, the sequelae of chronic alcoholism and the dermatoses that are influenced by alcohol. Trauma and injury, which occur commonly in alcohol abusers and problem drinkers, may cause bruises and scars in unusual numbers or sites.[119] Uncommon or unusual cutaneous signs, such as pressure sores,[124] widespread insect stings,[125] tattoos,[126] frostbite scars,[120] extensive varicose ulcerations in the lower leg,[127] eruptions caused by drug reactions,[128] cutaneous signs of drug abuse,[129] abnormal sweating,[130,131] and cutaneous infections[120] may all provide a clue to alcohol abuse. A growing dependence on alcohol frequently leads to self neglect.[132] The patient may be unkempt and practise poor skin and oral hygiene. In addition, there appears to be an increased incidence of rosacea, neurodermatitis, dermatophytosis, seborrhea capitis, seborrheic dermatitis, eczematoid dermatitis, aggravated acne and psoriasis in alcoholics.[118,119,122]

When chronic alcohol abuse is associated with underlying liver disease, more specific skin changes appear.[55] Vascular skin lesions such as spider angiomas and wiry telangiectasia[133,134] are among the more specific indicators of underlying liver disease in an alcohol abuser,[61] although they may also occur in healthy people.[134] Other signs of alcoholic liver disease include jaundice, purpura, abdominal varices (caput medusae), "paper money skin", the venous star, Campbell de Morgan's spots (cherry angiomas),[135] sparse axillary and pubic hair, with testicular atrophy,[136] gynecomastia,[136] generalized itchiness with scratch marks,[119] palmar erythema,[134] Dupuytren's contracture,[137] pigmentary changes with pellagroid melanosis of areas exposed to the sun,[122] and a variety of finger-nail changes, such as clubbing,[135] white nails,[138] white-banded nails,[139] opaque nails[140] and thinned nail folds with a wide cuticle.[122]

Painless unilateral or bilateral enlargement of the parotid gland caused by fatty infiltration of acinar tissue is sometimes present in alcoholic patients.[141,142] In one study 41 out of 50 patients with asymptomatic parotid gland enlargement were alcoholic, and 25 of this group had cirrhosis of the liver.[143] Wolfe and collaborators[144] also drew attention to the increased incidence of parotid enlargement in patients with alcoholic liver cirrhosis, but other investigators have noted this condition in patients who did not have cirrhosis and drank only moderate amounts of alcohol.[145] In an analysis of the clinical features of 60 new patients referred to a joint psychiatric and medical outpatient clinic for alcohol abusers, Shaw and Thomson[146] found that 3.3% of the group had parotid enlargement. A compensatory type of enlargement of this gland may also be associated with calcific pancreatitis in non-alcoholic patients,[147] and transient parotid enlargement with excessive salivation has been recorded in an alcoholic man in association with recurrent attacks of acute pancreatitis.[148] The cause of parotid swelling in abusers of alcohol is unknown, but could be related to poor nutrition or to vitamin A deficiency.[149] A reduction of alcohol intake may decrease the amount of enlargement of the parotid gland, as will an improvement in liver function in patients with cirrhosis.[150] The relative size of the parotid gland may be a useful clinical sign for detecting chronic alcohol abuse and perhaps provide an indication of reduced or continued alcohol consumption.

Laboratory tests and biochemical markers

As with many of the clinical signs and symptoms used to diagnose alcohol abuse, laboratory tests used for this purpose are often relatively nonspecific.

The only true indicator of alcohol consumption is the detection of alcohol or one of its metabolites in the patient's body fluids. However, the relatively short half-life of these compounds and the fact that their presence alone does not predict the patient's drinking habits or tolerance of alcohol detract from their usefulness as markers of alcohol abuse. Both the circumstances under which alcohol is detected in body fluids and its concentration may be strong indicators of the presence of hazardous alcohol consumption. The National Council on Alcoholism (NCA) criteria for diagnosing alcohol abuse regard a blood alcohol level of greater than 65 mmol/l (300 mg/dl), recorded at any time, or a level of more than 22 mmol/l (100 mg/dl), recorded during a routine clinical examination, as important indicators of alcoholism.[151] A blood alcohol level of more than 33 mmol/l (150 mg/dl) in a patient who is not obviously intoxicated is evidence of tolerance to alcohol and is also a strong indicator of alcohol abuse.

The laboratory tests that may be used to detect alcohol abuse will be reviewed. A summary of key findings to date is given in Table II.

Alcohol and acetaldehyde

Estimates of the level of alcohol in urine or blood have an established role in the diagnosis of intoxication,[152] and repeating these estimations may provide an indication of chronic hazardous alcohol consumption.[153,154] Clinical signs such as slurred speech, muscular incoordination, alcoholic fetor and erythema of the conjunctiva are often unreliable indicators of intoxication since a medical practitioner may consider a patient sober when blood alcohol concentrations are recorded at a level consistent with marked

inebriation.[155] When difficult management decisions occur because of suspected intoxication, a test that will give an immediate result is required. This has led to the analysis of alcohol in the breath as a diagnostic tool in clinical practice.[156] Inaccuracies in the use of breath alcohol analysers have prompted studies of saliva and sweat as indicators of alcohol abuse[157,158] and these methods seem promising. It may be possible to obtain an objective estimate of the amount of alcohol consumed over a period of time by analysing sweat,[158] but the value of this technique in general clinical practice has not been explored in detail.

Acetaldehyde and acetate, which are products of the oxidation of alcohol in the body, can be measured in blood. However, technical difficulties in their measurement in the laboratory, their low concentrations in blood and their short half-life render it impractical to use them as a diagnostic test, and they offer little advantage over measuring blood alcohol levels.[2]

Multitest approaches

There are many examples of the use of a battery of laboratory tests, especially in patients in hospital, to diagnose alcohol abuse.[159-171] In a large survey of patients attending a multiphasic health screening centre, alcohol consumption, within the range that may be considered normal, was found to affect a number of biochemical and hematologic findings, including the serum levels of GGT, uric acid, triglycerides, aspartate aminotransferase (ASAT) and the mean corpuscular volume (MCV).[167] Age- and sex-related differences were noted in the results of a number of tests, and fewer abnormalities were detected in younger patients. From these data Whitfield and colleagues[167] suggested that these laboratory tests could be used to compare alcohol intake within groups of individuals over a period of time. However, if such tests were used for the early identification of alcohol abuse there might be false-negative and false-positive results. Therefore, it is necessary to interpret laboratory findings in conjunction with other medical or sociobehavioural data.[168]

Blood lipids

Alcohol exerts an effect on the metabolism and transport of lipids, tending to raise serum concentrations of triglycerides and high-density-lipoprotein (HDL) cholesterol.[172-179] Results of the Cooperative Lipoprotein Phenotyping Study indicated that alcohol consumption was correlated with HDL-cholesterol levels in all populations, and that lipid levels appeared to show a graded response even over lower ranges of alcohol consumption.[177] In addition, it was noted that serum triglyceride levels showed a modest positive correlation and low-density-lipoprotein (LDL) cholesterol levels a consistently negative correlation with alcohol consumption.[177] Other studies in large populations have confirmed these observations.[180-182] It has been demonstrated in healthy volunteers that when alcohol is added to a normal diet HDL-cholesterol levels rise, whereas with a cessation of drinking these levels fall.[183-184]

Despite the strong association between changes in blood lipids and alcohol consumption, there have been relatively few studies of HDL-cholesterol levels in alcoholic populations. Johansson and Medhus[185] measured serum HDL-cholesterol levels in 69 alcoholic men who had been on drinking bouts for various periods (5 to 10 days) before admission to hospital. They observed that HDL-cholesterol levels were increased in 60 of the patients but tended to return to normal within 2 weeks after the patients stopped drinking. However, they found no correlation between HDL-cholesterol concentrations and liver damage as assessed from the serum levels of bilirubin, SGOT, glutamic pyruvic transaminase (SGPT) and GGT, and the retention of sulfobromophthalein. In a study of similar design an increase in serum HDL-cholesterol levels was noted in 25 of 39 alcoholic men while they

Table II—Laboratory markers of excessive alcohol, or ethanol, consumption

Marker	Diagnostic value
Serum γ-glutamyl transpeptidase level	Raised in 70% to 80% of alcoholic patients. Responds to ethanol consumption in excess of 40 to 60 g/d. Probably one of the best early indicators except in individuals with nonalcoholic liver disease and those taking other drugs.
Mean corpuscular volume	Raised in 75% to 90% of alcoholic patients. Appears to respond to ethanol consumption in excess of 60 g/d.
Serum aspartate aminotransferase level	Raised in 30% to 75% of alcoholic patients. Primarily indicative of liver disease and probably not responsive to low levels of alcohol consumption.
Serum high-density-lipoprotein cholesterol level	Raised in 50% to 80% of alcoholic patients. Probably sensitive to moderate ethanol consumption (40 to 60 g/d) but not in patients with severe alcoholic liver disease.
Serum glutamate dehydrogenase level	Raised in alcoholic patients with severe liver disease and in patients with fatty liver following excessive alcohol ingestion. Not responsive to consumption of 140 g/d for 4 weeks in normal individuals. Actual prevalence of abnormal values in alcoholic patients not clear.
Serum transferrin level	Raised in 81% of alcoholic patients who consume over 60 g/d of ethanol. Not present in patients with nonalcoholic liver disease and raised levels of serum glutamic oxaloacetic transaminase. Sensitive to low to moderate ethanol consumption. Quantitation and methodologic simplification of test methods should render this determination valuable.
Ratio of α-amino-*n*-butyric acid to leucine	Raised in some types of alcoholic patients but not in others. Apparently dependent on liver dysfunction and nutritional status.

were intoxicated,[186] but again no correlation was found between HDL-cholesterol levels and other measures of liver function. However, these studies did not provide data on the patients' dietary and nutritional status, the type or amount of alcohol they consumed, the results of liver biopsy or details of prior drug treatment, all of which may modify serum concentrations of HDL-cholesterol.

Since liver disease exerts a major effect on the level of HDL-cholesterol in the serum, using this test as a marker of alcohol consumption may not be useful in patients with alcoholic hepatitis or cirrhosis. To further examine the relationship between serum HDL-cholesterol levels and alcohol consumption in patients with liver disease, liver function and alcohol consumption (assessed objectively by estimating the amount of alcohol in the urine) were measured in 57 alcoholic patients with liver disease.[187] HDL-cholesterol levels were also determined in a control group of 67 hospital employees with no known history of hazardous alcohol consumption. There was no significant difference between the HDL-cholesterol levels of the patients and the controls. However, within the patient group HDL-cholesterol was found to be significantly higher in those who were still drinking (positive urine tests) than in those who had not been drinking. Nevertheless, serum HDL-cholesterol levels were found to be inversely correlated with the severity of liver disease as assessed by laboratory measures of prothrombin time, total bilirubin, albumin and alkaline phosphatase. Although HDL-cholesterol has a tendency to be higher in alcoholic patients who are still drinking it may be within normal limits in patients with liver disease, largely because impaired liver functions will tend to lower HDL-cholesterol levels. Thus, a measure of HDL-cholesterol may not be a reliable test for detecting alcohol abuse in patients with liver disease.[187]

Enzymes

The concentration of a number of enzymes in the blood is known to increase with excessive alcohol consumption. These enzymes include SGOT (ASAT), SGPT (alanine aminotransferable [ALAT]), glutamate dehydrogenase (GDH), lactate dehydrogenase (LDH) and alkaline phosphatase. Skude and Wadstein[188] found that in a group of patients admitted to a Swedish hospital for the treatment of alcohol abuse 77% had raised SGOT values and 50% had raised SGPT values. Rosalki and Rau[189] reported that 32% of a similar group of patients had raised SGOT levels. Orrego and coworkers[63] studied alcoholic patients with mild liver disease and found that 76% had raised SGOT values. Although levels of SGOT and SGPT are nonspecific indicators of liver damage, an SGOT/SGPT ratio greater than 2 is considered highly suggestive of alcoholic hepatitis or cirrhosis or both.[190]

The serum GGT level appears to be a good early indicator of alcoholic consumption and has been shown to be raised in about three quarters of a group of alcoholic patients who had no evidence of hepatomegaly or other clinical signs of liver disease.[188,189] While the serum GGT level is known to be raised in patients with a variety of liver diseases, it may also be raised in alcoholic patients at a time when the SGOT, SGPT and alkaline phosphatase levels are normal.[191] GGT is stored mainly in the liver as a membrane-bound constituent of the microsomal fraction.[192] Since an increase in microsomal mass is one of the earliest results of chronic alcohol consumption, the location of GGT probably accounts for its special sensitivity as an indicator of liver disturbances in heavy drinkers. Although an increased level of GGT may correlate with liver cell necrosis,[193] in many cases it probably reflects microsomal induction. It may also be raised because of drug therapy.[194]

Rollason and associates[195] compared the levels of GGT, SGOT and alkaline phosphatase in groups of subjects with different drinking habits. They were able to demonstrate significant differences in these levels between nondrinkers and heavy drinkers. Whitehead and collaborators[169] found an increased level of GGT in 17% of 2034 men in London, England and suggested that excessive alcohol consumption caused the raised levels of the enzyme in over 60% of cases. Pomerleau and colleagues[196] confirmed this observation by finding a significant correlation between the ethanol consumption reported by a group of subjects seeking treatment for alcohol abuse and the subjects' GGT levels. Although the relation between alcohol consumption and raised serum levels of GGT has been demonstrated by numerous studies,[197-203] its use as a diagnostic marker of alcohol abuse may have certain limitations.[204,205]

Studies of LDH concentrations in blood obtained from chronic abusers of alcohol while they were intoxicated indicated that LDH isoenzyme levels change in most drinkers, with a tendency to increases in the LDH-1, LDH-2 and LDH-5 fractions.[206,207] In a study of 100 alcoholic patients the GDH level was found to be a reliable marker of liver cell necrosis.[194] Raised GDH concentrations in the blood discriminated between patients with hepatic necrosis and those without, as assessed by liver biopsy. Furthermore, GDH measurement was able to detect cases of alcoholic hepatitis that were considered "clinically silent" and seemed to yield few false-positive results. However, data from other studies have not confirmed these findings. Jenkins and associates[208] reported that in alcoholic patients with fatty livers, those who had recently consumed an excessive amount of alcohol also showed increased serum levels of GDH. In addition, the level of this enzyme was not markedly raised in nonalcoholic volunteers consuming 2 g ethanol/kg every day for 4 weeks.[209]

Ratio of plasma α-amino-n-butyric acid to leucine

Recently interest has focused on using the ratio of α-amino-*n*-butyric acid (AANB) to leucine in the plasma as a potential biochemical marker of alcohol abuse. Shaw and Lieber[210] have shown that chronic alcohol abuse produces an increase in the level of AANB in the plasma. However, this increase does not

result from a single bout of heavy drinking, which suggests that AANB might be a useful indicator of long-term alcohol consumption. Since the level of AANB is known to be depressed by a deficiency of dietary protein, and since the diet of alcoholics is frequently deficient in protein,[210] it has been proposed that a more accurate marker of alcoholism might be obtained by expressing the level of AANB relative to that of leucine.[211] Expression of the ratio to leucine was chosen because the concentration of leucine in the blood is depressed by protein malnutrition.

Conflicting data have been reported on the use of the AANB:leucine ratio for diagnosing alcohol abuse. Shaw and coworkers[211] reported an increased ratio in well nourished baboons fed alcohol and in both ambulatory and hospitalized alcoholic patients. Furthermore, these investigators found a significant positive correlation between the AANB:leucine ratio and the degree of alcohol abuse as assessed by separate criteria (e.g., NCA criteria and reports of average daily ethanol intake) in a sample of alcoholic and nonalcoholic patients taking methadone. These findings were confirmed in two subsequent studies.[212,213] Using the AANB:leucine ratio in combination with GGT levels was reported to detect alcohol abuse in 28 out of 33 heavy drinkers, with a false-positive rate of only 2%.[212] Recently Shaw and collaborators[213] reported that the level of AANB decreased during withdrawal from alcohol and during abstinence.

Other investigators have disagreed with the findings of Shaw's group. Morgan and colleagues[214] concluded that the AANB:leucine ratio provides an indication of hepatic dysfunction rather than long-term alcohol abuse. Data from Dienstag and associates[215] showed that this ratio increased nonspecifically in humans with liver disease unrelated to alcohol and in animals with liver cell injury. These findings indicate that a raised AANB:leucine ratio is not necessarily characteristic of chronic alcohol abuse. Ellingboe and coworkers[216] confirmed these findings and concluded that this ratio cannot be used as an empirical biochemical marker of long-term alcohol abuse. Finally, Hilderbrand and collaborators[217] found no significant correlation between the AANB:leucine ratio and either reported drinking or GGT levels.

Thus, the potential use of the AANB:leucine ratio to screen for alcohol abuse is questionable. Ellingboe and coworkers[216] suggested that these conflicting results might be explained by the fact that hepatocellular disease in general, rather than alcohol consumption alone, increases this ratio. It is likely that a considerable number of patients studied had liver disease, which could account for the raised AANB:leucine ratios. Even with unanimous evidence to support its value, this ratio is unlikely to be used routinely since AANB measures are expensive, requiring the use of an amino-acid analyser.

Hematologic tests

Excessive alcohol consumption may produce a variety of changes in the hematopoietic system, including anemia with suppression of erythropoiesis,[218] cytoplasmic and nuclear vacuolation of early myeloid and erythroid precursors in the bone marrow,[219,220] altered folate status and its hematologic consequences,[221] transient hemolysis with hyperlipidemia,[172,222] a reversible type of sideroblastic erythropoiesis,[223] leukopenic and leukocytopenic responses to bacterial infections,[224,225] thrombocytopenia,[226,227] hemostatic defects[228,229] and a variety of erythrocytic abnormalities, including macrocytosis,[230,231] acanthocytosis[232,233] and stomatocytosis.[234]

The most frequent hematologic findings a clinician may observe in an alcoholic patient are a normal hemoglobin concentration, a normoblastic marrow, normal serum B_{12} and folate concentrations and a raised MCV.[235] Several studies have indicated that an increased MCV indicates heavy alcohol consumption, and that estimation of the MCV may be important in the detection of alcohol abuse.[169,230,236-240] Unger and Johnson[231] found that 3% of the 8000 employees of a large insurance company had macrocytosis (MCV more than 96/fl for men and more than 100/fl for women); a large proportion of the individuals with a high MCV were considered to be consuming excessive amounts of alcohol. Wu and collaborators[230] determined the MCV in 63 alcoholic inpatients of a general hospital and found that 89% had macrocytosis, generally associated with anemia. In this study megaloblastic marrow samples were found in only one third of the patients. Wu and collaborators[230] were able to demonstrate that macrocytosis resolved with alcohol withdrawal but persisted if alcohol intake continued, despite folate supplementation. They concluded that macrocytosis was due to a direct action of alcohol on developing erythroblasts, an opinion held by other workers.[238-240]

In a study of risk factors for cardiovascular disease the hematologic profiles of healthy men aged 48 to 54 years were examined with reference to both their alcohol consumption and their smoking habits.[239] It was found that the correlation of alcohol consumption with erythrocyte count and MCV was more marked in smokers. In contrast, the correlation between alcohol consumption and leukocyte count was more marked in nonsmokers. These findings underscore the need to consider smoking habits with alcohol consumption when interpreting changes, especially in view of the strong association between alcohol abuse and cigarette smoking.

Miscellaneous tests

Changes in the level of uric acid in the serum have been observed in association with heavy drinking.[168] In one large study it was demonstrated that heavy drinkers tended to have higher serum uric acid levels than light drinkers, but this difference was apparent only in men.[167] Changes in serum electrolyte levels, with a decrease in chloride and an increase in lactate concentrations, resulting in acidosis and a decreased excretion of uric acid, may be found in heavy drinkers.[241,242] It has been suggested that if a patient's serum uric acid level is raised on admission to hospital but returns to normal after a few days, then alcohol involvement can be suspected.[2]

Disturbances in acid–base bal-

ance, with ketosis,[243] alterations in porphyrin metabolism[244] and disturbances in carbohydrate metabolism,[245] may occur with chronic alcohol abuse. Alcohol intake may result in an increased excretion of porphobilinogen, aminolevulinic acid and coproporphyrins. In some circumstances there may be a relation between changes in porphyrin excretion and the amount of alcohol consumed.[239-247] Alcohol exerts a complex effect on carbohydrate metabolism. Following heavy alcohol consumption individuals can have low blood glucose levels while fasting,[245] or can exhibit hyperglycemia or glycosuria, especially if they have liver disease.[248-250]

Alcoholic patients have been found to excrete in the urine an increased amount of D-glucaric acid while drinking; this amount decreases after they stop drinking.[251] Urinary glucaric acid excretion increases after the administration of certain drugs and has been used as a marker of microsomal enzyme induction.[252,253] While investigating the role of D-glucaric acid as a marker of alcohol abuse, Spencer-Peet and colleagues[254] found no correlation between serum GGT and urinary glucaric acid levels. This may be due to the fact that an increased GGT level in alcoholics reflects both enzyme induction and structural damage within the liver. If a persistent increase in the amount of D-glucaric acid excreted is directly related to continuous drinking, measurement of the urinary excretion of this substance may be of value in the detection of problem drinking.

Serum levels of bile acids have been found to be abnormally raised in a large number of patients with alcoholic liver disease.[255,256] In a study cited by Overby[256] the serum levels of cholylglycine were found to be raised in 97% of 144 patients with alcoholic liver disease. Milstein and associates[255] detected marginally increased or normal total bile acid levels in the serum of six patients with alcohol-related fatty liver, and significantly raised levels in 93% of a group of 58 patients with more advanced alcoholic liver disease. These findings suggest that an increased concentration of serum bile acids may be a more sensitive indicator of alcoholic liver disease than the results of a number of more standard serologic tests.[256]

A number of studies have drawn attention to abnormalities of mineral and vitamin metabolism in alcoholics. The excretion of magnesium, zinc and calcium is increased by alcohol consumption, so that serum magnesium and zinc concentrations may be low in alcoholic patients.[257] Vitamin and nutrient deficiencies are common in patients who drink heavily. Their cause is determined by a complex interaction of such factors as poor diet and malabsorption, the specific interference of ethanol with the metabolism of vitamins and the presence of liver disease. In a study to detect vitamin B and C deficiency in patients with alcohol-related illnesses Baines[258] found the prevalence of riboflavin deficiency to be 23%, that of thiamin deficiency, assessed by the pyruvate tolerance test, 55% and that of ascorbic acid deficiency 91%. Baines also reported a poor correlation between vitamin deficiency and GGT activity in the serum. In view of the many influences on vitamin status in alcoholic patients, the use of serum or urinary vitamin levels to diagnose alcohol abuse may not be very rewarding.

New biochemical markers

Two possible markers of alcohol abuse have recently been reported: plasma transferrin and salsolinol. Studies by Stibler and coworkers[259] have shown that electrofocusing of plasma proteins and further characterization by immunofixation reveals an abnormal transferrin band with a pH of 5.7 in 81% of alcoholic patients admitting to consumption of more than 60 g of ethanol a day in the previous week. The percentages were 75% and 25% for those reporting a consumption of 20 to 60 g/d and 7 to 20/d respectively, 8% for those reporting abstinence and 1% for control subjects. When ethanol was given to eight controls at a daily dose of 0.6 g/kg an abnormal transferrin appeared after 5 days in one subject at 7 days in a second and at 11 days in a third; the SGOT level was normal in all three. Furthermore, an abnormal transferrin could not be detected in 22 patients with nonalcoholic liver disease, although 84% had abnormally high SGOT levels. The transferrin abnormalities apparently disappeared after the patients stopped drinking alcohol for 10 days.[259,260]

These data indicate that transferrin could be a good indicator of alcohol abuse since it appears not to reflect liver disease and may detect low to moderate alcohol consumption. Unfortunately, the electrofocusing-plus-immunofixation technique is too complex for routine laboratory analysis. Another promising marker appears to be salsolinol, the product of condensation between acetaldehyde and dopamine. (Salsolinol has been found to be 20 times more concentrated in the urine of alcoholic patients admitted for detoxification than in that of controls.[261]) The concentration of salsolinol was reduced to baseline levels following 4 days of withdrawal of alcohol. As with transferrin, the current method for determining salsolinol levels — high-performance liquid chromatography plus mass spectrum analysis — is too elaborate for routine analysis.

Discussion

Excessive alcohol consumption produces measurable physiologic, pathologic, biochemical and morphologic changes in many organs of the body. However, these changes may also be produced by a variety of diseases not related to alcohol abuse. Even the most specific indicators of alcohol abuse may only measure the events resulting from alcohol or its metabolites in a relatively small proportion of alcoholic individuals. Detecting alcohol or a product of its metabolism in body fluids is the only direct way of ascertaining alcohol abuse, but these compounds have a relatively short half-life and cannot provide a measure of alcohol tolerance or of the duration and extent of previous alcohol abuse. The circumstances under which alcohol is detected is important. For example, the presence of alcohol in blood specimens obtained in the morning[153] or following an accident[262] may be a strong indicator that an individual has an alcohol problem.

The severity of a number of medical sequelae of alcoholism, such as liver disease and ascites, is related to total lifetime consumption of alcohol.[263,264] If one accepts the concept that the severity of liver disease is proportional to the number of abnormal clinical and laboratory findings indicative of this condition,[61,265] then many of the clinical signs and symptoms of liver disease are sensitive only at later stages of alcohol abuse. This situation probably applies to a number of medical concomitants of alcohol abuse that may take 5 to 10 years to develop.[266] Thus, signs of liver disease or neurologic disorders will be present in only a small proportion of younger drinkers or those whose drinking problem is of recent onset.[75]

Clinical and laboratory indicators of alcohol abuse may provide objective information to complement interview data. This is of importance, since reports by the patient and interview data are subject to distortion or denial.[267,268] However, there are problems with the application of biomedical data for the detection of alcohol abuse. Some of the medical and laboratory indicators, such as hepatomegaly and raised serum transaminase levels, are reversible if individuals reduce their alcohol consumption or abstain from drinking. In addition, symptoms and signs and biochemical alterations only represent pathologic responses to excessive alcohol consumption and are relatively nonspecific. There are no specific clinical markers of alcoholism, and "true" biochemical markers of alcohol abuse await development.

Incomplete knowledge of the sensitivity and specificity of many of the laboratory tests used in the detection of chronic excessive alcohol consumption prevents a firm recommendation for the selection of available diagnostic laboratory tests. The diagnostic value of the tests most widely investigated or used is summarized in Table II. Measurement of the MCV and the serum GGT and SGOT levels is likely, taking costs and benefits into consideration, the most appropriate collection of laboratory tests, for increased levels of these variables should provide a strong indication of recent consumption of more than 60 g of ethanol a day.

In conclusion, we are impressed both with the diversity of biomedical and psychosocial disorders related to excessive drinking, and with the real difficulties in isolating specific indicators of the early stages of alcohol abuse. This creates a dilemma. Available evidence suggests that a favourable prognosis is contingent on early identification and treatment. Clearly, a concerted program of research with a multidisciplinary focus is needed if we are to make significant gains in our understanding of the development of alcohol abuse.

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References

1. EDWARDS G, GROSS MM, KELLER M, MOSER J, ROOM R (eds): *Alcohol Related Disabilities*, WHO offset publ no 32, WHO, Geneva, 1977
2. NOBLE EP (ed): *Third Special Report to the U.S. Congress on Alcohol and Health from the Secretary of Health, Education, and Welfare*, National Institute on Alcohol Abuse and Alcoholism, Rockville, Md, 1978
3. O'HOLLAREN P, WELLMAN WM: "Hidden" alcoholics: medical implications of undiscovered addiction. *Calif Med* 1958; 89: 129–131
4. MCCARTHY RG: Alcoholism: attitudes and attacks, 1775–1935. *Ann Am Acad Pol Soc Sci* 1958; 315: 12–21
5. PEARSON WS: The "hidden" alcoholic in the general hospital. A study of "hidden" alcoholism in white male patients admitted for unrelated complaints. *NC Med J* 1962; 3: 6–10
6. NEUSTADT JO: The vise of alcohol. *Maryland Med J* 1966; 15: 25–34
7. RUBINGTON E: The hidden alcoholic. *Q J Stud Alcohol* 1972; 33: 667–683
8. WILKINS RH: *The Hidden Alcoholic in General Practice; A Method of Detection Using a Questionnaire*, Elek Science, London, Engl, 1974
9. MURRAY RH: Screening and early detection instruments for disabilities related to alcohol consumption. In EDWARDS G, GROSS MM, KELLER M, MOSER J, ROOM R (eds): *Alcohol Related Disabilities*, WHO offset publ no 32, WHO, Geneva, 1977, 89–106
10. JACOBSON G: *The Alcoholisms: Detection Diagnosis and Assessment*, Human Sci Pr, New York, 1976
11. MILLER WR: Alcoholism scales and objective assessment methods: a review. *Psychol Bull* 1976; 83: 649–674
12. MOSS MC, BERESFORD DAVIES E: *A Survey of Alcoholism in an English County. A Study of the Prevalence, Distribution and Effects of Alcoholism in Cambridgeshire*, Geigy Sci Publ, London, Engl, 1967
13. CAVALIÉ B: Influence de l'éthylisme chronique sur la morbidité et les accidents du travail (Effect of chronic alcoholism on morbidity and industrial accidents). *Q J Stud Alcohol* 1957; 18: 327
14. PELL S, D'ALONZO CA: The prevalence of chronic disease among problem drinkers. *Arch Environ Health (Chicago)* 1968; 16: 679–684
15. MEDHUS A: Morbidity among female alcoholics. *Scand J Soc Med* 1974; 2: 5–11
16. GOMBERG ES: Prevalence of alcoholism among ward patients in a Veterans Administration hospital. *J Stud Alcohol* 1975; 36: 1458–1467
17. ASHLEY MJ, OLIN JS, LE RICHE WH, KORNACZEWSKI A, SCHMIDT W, COREY RP, RANKIN JG: The physical disease characteristics of inpatient alcoholics. *J Stud Alcohol* (in press)
18. SALUM I: Delirium tremens and certain other acute sequels of alcohol abuse: a comparative clinical, social and prognostic study. *Acta Psychiatr Scand* [*Suppl*] 1972; 235: 15–16
19. SELLERS EM, KALANT H: Alcohol intoxication and withdrawal. *N Engl J Med* 1976; 294: 757–762
20. HOGAN WJ, VIEGAS DE ANDRADE SR, WINSHIP DH: Ethanol-induced acute esophageal motor dysfunction. *J Appl Physiol* 1972; 32: 755–760
21. DREHER KF, FRASER JG: Smoking habits of alcoholic out-patients. II. *Int J Addict* 1968; 3: 65–80
22. DENNIS GW, CASTELL DO: Inhibitory effect of smoking on the lower esophageal sphincter. *N Engl J Med* 1971; 284: 1136–1137
23. CHAPUT J-C, PETITE J-P, GUEROULT N, BUFFET C, REGENSBERG M,

ETIENNE J-P: La fibroscopie d'urgence dans les hémorrhagies digestives des cirrhoses. A propos de 100 cas. *Nouv Presse Med* 1974; 3: 1227–1230
24. MALLORY GK, WEISS S: Hemorrhages from lacerations of the cardiac orifice of the stomach due to vomiting. *Am J Med Sci* 1929; 178: 506–516
25. PALMER ED: Gastritis: a revaluation. *Medicine (Baltimore)* 1954; 33: 199–290
26. DAVENPORT HW: Gastric mucosal hemorrhage in dogs. Effects of acid, aspirin, and alcohol. *Gastroenterology* 1969; 56: 439–449
27. PITCHUMONI CS, GLASS GBJ: Patterns of gastritis in alcoholics. *Biol Gastroenterol (Paris)* 1976; 9: 11–16
28. JOSKE RA, FINCKH ES, WOOD IJ: Gastric biopsy: study of 1,000 consecutive successful gastric biopsies. *Q J Med* 1955; 24: 269–294
29. WOLFF G: Does alcohol cause chronic gastritis? *Scand J Gastroenterol* 1970; 5: 289–291
30. FERGUSON D: Some characteristics of repeated sickness absence. *Br J Ind Med* 1972; 29: 420–431
31. ENGESET A, LYGREN T, IDSÖE R: The incidence of peptic ulcer among alcohol abusers and non-abusers. *Q J Stud Alcohol* 1963; 24: 622–626
32. BENJAMIN ES, IMRIE CW, BLUMGART LH: Alcohol and the pancreas. In EDWARDS GE, GRANT M (eds): *Alcoholism: New Knowledge and New Responses*, Univ Park, Baltimore, Md, 1977: 328–334
33. MEZEY E, JOW E, SLAVIN RE, TOBON F: Pancreatic function and intestinal absorption in chronic alcoholism. *Gastroenterology* 1970; 59: 657–664
34. COOKE AR: Ethanol and gastric function. *Gastroenterology* 1972; 62: 501–502
35. KAUFMAN SE, KAYE MD: Effect of ethanol upon gastric emptying. *Gut* 1979; 20: 688–692
36. PIROLA RC, DAVIS AE: Effects of intravenous alcohol on motility of the duodenum and of the sphincter of Oddi. *Australas Ann Med* 1970; 19: 24–29
37. ROBLES EA, MEZEY E, HALSTED CH, SCHUSTER MM: Effect of ethanol on motility of the small intestine. *Johns Hopkins Med J* 1974; 135: 17–24
38. KRASNER N, COCHRAN KM, RUSSELL RI, CARMICHAEL HA, THOMPSON GG: Alcohol and absorption from the small intestine. I. Impairment of absorption from the small intestine in alcoholics. *Gut* 1976; 17: 245–248
39. WALD A, BACK C, BAYLESS TM: Effect of caffeine on the human small intestine. *Gastroenterology* 1976; 71: 738–742
40. LINDENBAUM J, LIEBERS CS: Effects of chronic ethanol administration on intestinal absorption in man in the absence of nutritional deficiency. *Ann NY Acad Sci* 1975; 252: 228–234
41. KRAWITT EL: Effect of ethanol ingestion on duodenal calcium transport. *J Lab Clin Med* 1975; 85: 665–671
42. TOMASULO PA, KATER RM, IBER FL: Impairment of thiamine absorption in alcoholism. *Am J Clin Nutr* 1968; 21: 1341–1344
43. WOJCIKI J, SAMOCHOWIEC L, KADYKOW M: Effect of ethanol on iron absorption in the small intestine of rats. *Q J Stud Alcohol* 1972; 33: 958–961
44. ROE DA: Alcohol and alcoholism. In ROE DA (ed): *Drug Induced Nutritional Deficiencies*, Avi, Westport, Conn, 1976: 202–210
45. ASHLEY MJ, OLIN JS, LE RICHE WH, KORNACZEWISKI A, SCHMIDT W, RANKIN JG: Skid row alcoholism. A distinct sociomedical entity. *Arch Intern Med* 1976; 136: 272–278
46. LELBACH WK: Epidemiology of alcoholic liver disease. *Prog Liver Dis* 1976; 5: 494–515
47. BRUNT PW: Alcohol and the liver. *Gut* 1971; 12: 222–229
48. ROWNTREE LG: Considerations in cirrhosis of the liver. *JAMA* 1927; 89: 1590–1597
49. JOLLIFFE N, JELLINEK EM: Vitamin deficiencies and liver cirrhosis in alcoholism: cirrhosis of the liver. *Q J Stud Alcohol* 1941; 2: 544–583
50. SEELEY JR: Death by liver cirrhosis and the price of beverage alcohol. *Can Med Assoc J* 1960; 83: 1361–1366
51. LEDERMANN S: *Alcool, Alcoolisme, Alcoolisation; Données Scientifiques de Caractère Physiologique, Economique et Social*, Presses Univ de France, travaux et documents, cahier no 42, Paris, 1964
52. LINT J DE, SCHMIDT W: The epidemiology of alcoholism. In ISRAEL Y, MARDONES J (eds): *Biological Basis of Alcoholism*, Wiley, New York, 1971: 423–442
53. RANKIN JG, SCHMIDT W, POPHAM RE, LINT J DE: Epidemiology of alcoholic liver disease — insights and problems. In KHANNA JM, ISRAEL Y, KALANT H (eds): *Alcoholic Liver Pathology*, Addiction Research Foundation of Ontario, Toronto, 1975: 31–41
54. SCHMIDT W, LINT J DE: Causes of death of alcoholics. *Q J Stud Alcohol* 1972: 33: 171–185
55. WILKINSON P, KORNACZEWSKI A, RANKIN JG, SANTAMARIA JN: Physical disease in alcoholism. Initial survey of 1,000 patients. *Med J Aust* 1971; 1: 1217–1223
56. LEEVY CM, ZINKE MR, WHITE TJ, GNASSI AM: Clinical observations on the fatty liver. *Arch Intern Med* 1953; 92: 527–541
57. GREEN JR: Subclinical acute liver disease of the alcoholic. *Australas Ann Med* 1965; 14: 111–124
58. KNOTT DM, BEARD JD: Liver function in apparently healthy chronic alcoholic patients. *Am J Med Sci* 1966; 252: 260–264
59. GALAMBAS JT: Alcoholic hepatitis: its therapy and prognosis. In POPPER HP, SCHAFFNER F (eds): *Progress in Liver Diseases*, vol 4, Grune, New York, 1972: 567–588
60. BHATHAL PS, WILKINSON P, CLIFTON S, RANKIN JG, SANTAMARIA JN: The spectrum of liver diseases in alcoholism. *Aust NZ J Med* 1975; 5: 49–57
61. RANKIN JGD, ORREGO-MATTE H, DESCHÊNES J, MEDLINE A, FINDLAY JE, ARMSTRONG AIM: Alcoholic liver disease: the problem of diagnosis. *Alcohol Clin Exp Res* 1978; 2: 327–338
62. SHER PP: Diagnostic effectiveness of biochemical liver-function tests, as evaluated by discriminant function analysis. *Clin Chem* 1977; 23: 627–630
63. ORREGO H, BLENDIS LM, BLAKE JE, KAPUR BM, ISRAEL Y: Reliability of assessment of alcohol intake based on personal interviews in a liver clinic. *Lancet* 1979; 2: 1354–1356
64. BOWMAN KM, JELLINEK EM: Alcoholic mental disorders. In JELLINEK EM (ed): *Effects of Alcohol on the Individual. A Critical Exposition of Present Knowledge. Volume I: Alcohol Addiction and Chronic Alcoholism*, Yale U Pr, New Haven, Conn, 1942: 81–169
65. VICTOR M: Alcohol and nutritional diseases of the nervous system. *JAMA* 1958; 167: 65–71
66. TOMMASI M: Les encéphalopathies des alcooliques. *Rev Lyon Med* 1958; 7: 215
67. COURVILLE CB: *Effects of Alcohol on the Nervous System of Man*, Univ Publ, New York, 1955
68. HORVATH TB: Clinical spectrum and epidemiological features of alcoholic dementia. In RANKIN JG (ed): *Alcohol, Drugs, and Brain Damage. Proceedings of a Symposium: Effects of Chronic Use of Alcohol and Other Psychoactive Drugs on Cerebral Function*, Addiction Research Foundation of Ontario, Toronto, 1975: 1–16
69. FAHLGREN H, HED R, LUNDMARK C: Myonecrosis and myogloblinuria in alcohol and barbiturate intoxication. *Acta Med Scand* 1957; 158: 405–412
70. SONG SK, RUBIN E: Ethanol produces muscle damage in human vo-

lunteers. *Science* 1972; 175: 327–328
71. RUBIN E: Alcoholic myopathy in heart and skeletal muscles. *N Engl J Med* 1977; 301: 28–33
72. JACOBS MS, SELLERS EM: Emergency management of alcohol withdrawal. *Drug Ther (Hosp)* 1977; 28–34
73. VICTOR M: Polyneuropathy due to nutritional deficiency and alcoholism. In DYCK PJ, THOMAS PK, LAMBERT EM (eds): *Peripheral Neuropathy*, Saunders, Philadelphia, 1975: 1030–1066
74. MARSDEN CD: Neurological disorders induced by alcohol. In EDWARDS G, GRANT M (eds): *Alcoholism: New Knowledge and New Responses*, Univ Park, Baltimore, Md, 1977: 189–197
75. SKINNER HA, HOLT S, ALLEN BA, HAAKONSON NH: Correlation between medical and behavioral data in the assessment of alcoholism. *Alcohol Clin Exp Res* 1980; 4: 371–377
76. GOODWIN DW, HILL SY: Chronic effects of alcohol and other psychoactive drugs on intellect, learning and memory. In RANKIN JG (ed): *Alcohol, Drugs and Brain Damage. Proceedings of a Symposium: Effects of Chronic Use of Alcohol and Other Psychoactive Drugs on Cerebral Function*, Addiction Research Foundation of Ontario, Toronto, 1975; 55–69
77. TARTER RE: Psychological deficit in chronic alcoholics: a review. *Int J Addict* 1975; 10: 327–368
78. PARSONS OA: Brain damage in alcoholics: altered states of unconsciousness. In GROSS MM (ed): *Alcohol Intoxication and Withdrawal, Experimental Studies II*, Plenum Pub, New York, 1975; 569–584
79. WILKINSON DA, CARLEN PL: Relationship of neuropsychological test performance to brain morphology in amnesic and non-amnesic chronic alcoholics. *Acta Psychiatr Scand* 1980; 62 (suppl 286): 89–101
80. Idem: Neuropsychological and neurological assessment of chronic alcoholism. Discrimination between groups of alcoholics. *J Stud Alcohol* 1980; 41: 129–139
81. LEE K, MOLLER L, HARDT F, HAUBEK A, JENSEN E: Alcohol-induced brain damage and liver damage in young males. *Lancet* 1979; 2: 759–761
82. JELLINEK EM: What does alcoholism cost? *Health* 1947; 14
83. OBSERVER (pseudonym), MAXWELL MA: A study of absenteeism, accidents and sickness payments in problem drinkers in one industry. *Q J Stud Alcohol* 1959; 20: 302–312
84. ZYLMAN R, BACON SD: Police records and accidents involving alcohol. *Q J Stud Alcohol* 1968; (suppl 4): 178–211
85. KENDELL RE: Alcoholism: a medical or a political problem? *Br Med J* 1979; 1: 367–371
86. ASHLEY MJ, OLIN JS, LE RICHE WH, KORNACZEWSKI A, SCHMIDT W, RANKIN JG: Social class and morbidity in clinically treated alcoholics. *Drug Alcohol Depend* 1976; 1: 263–276
87. ASHLEY MJ, OLIN JS, LE RICHE WH: Continuous and intermittent alcoholics: a comparison of demographic, sociological and physical disease characteristics in relation to the pattern of drinking. *Addict Dis* 1976; 2: 515–532
88. BRENNER B, SELZER ML: Risk of causing a fatal accident associated with alcoholism, psychopathology, and stress: further analysis of previous data. *Behav Sci* 1969; 14: 490–495
89. HOLT S, STEWART IC, DIXON JMJ, ELTON RA, TAYLOR TV, LITTLE K: Alcohol and the emergency service patient. *Br Med J* 1980; 281: 638-640
90. NILSSON BE: Conditions contributing to fracture of the femoral neck. *Acta Chir Scand* 1970; 136: 383–384
91. SAVILLE PD: Alcohol-related skeletal disorders. *Ann NY Acad Sci* 1975; 252: 287–291
92. ISRAEL Y, ORREGO H, HOLT S, MACDONALD DW, MEEMA HE: Identification of alcohol abuse: thoracic fractures on routine chest x-rays as indicators of alcoholism. *Alcohol Clin Exp Res* 1980; 4: 420–422
93. MENDELSON JH, CHAFETZ ME: Alcoholism as an emergency ward problem. *Q J Stud Alcohol* 1959; 20: 270–275
94. ROWBOTHAM GF, MACIVER IM, DICKSON J, BOUSFIELD ME: Analysis of 1,400 cases of acute injury to the head. *Br Med J* 1954; 1: 726–730
95. BARR JB, RALSTON GJ: Head injuries in a peripheral hospital. *Lancet* 1964; 2: 519–522
96. KERR TA, KAY DW, LASSMAN LP: Characteristics of patients, type of accident, and mortality in a consecutive series of head injuries admitted to a neurosurgical unit. *Br J Prev Soc Med* 1971; 25: 179–185
97. GALBRAITH S, MURRAY WR, PATEL AR, KNILL-JONES R: The relationship between alcohol and head injury and its effect on the conscious level. *Br J Surg* 1976; 63: 128–130
98. RUTHERFORD WH: Diagnosis of alcohol ingestion in mild head injuries. *Lancet* 1977; 7: 1021–1023
99. SPODICK DH, PIGOTT VM, CHIRIFE R: Preclinical cardiac malfunction in chronic alcoholism. Comparison with matched normal controls and with alcoholic cardiomyopathy. *N Engl J Med* 1972; 287: 677–680
100. GYNTELBERG F, MEYER J: Relationship between blood pressure and physical fitness, smoking and alcohol consumption in Copenhagen males aged 40–59. *Acta Med Scand* 1974; 195: 375–380
101. KANNEL WB, SORLIE P: Hypertension in Framingham. In PAUL O (ed): *Epidemiology and Control of Hypertension*, Stratton Intercon, New York, 1975: 553–592
102. KLATSKY AL, FRIEDMAN GD, SIEGELAUB AB, GÉRARD MJ: Alcohol consumption and blood pressure. Kaiser-Permanente mutiphasic health examination data. *N Engl J Med* 1977; 296: 1194–1200
103. SCHMIDT W, POPHAM RE: Heavy alcohol consumption and physical health problems: a review of the epidemiological evidence. *Drug Alcohol Depend* 1975/76; 1: 27–50
104. ASHLEY MJ, RANKIN JG: Alcohol consumption and hypertension — the evidence from hazardous drinking and alcoholic populations. *Aust NZ J Med* 1979; 9: 201–206
105. DEMAKIS JG, PROSKEY A, RAHIMTOOLA SH, JAMIL M, SUTTON GC, ROSEN KM, GUNNAR RM, TOBIN JR JR: The natural course of alcoholic cardiomyopathy. *Ann Intern Med* 1974; 80: 293–297
106. ALEXANDER CS: Idiopathic heart disease. I. Analysis of 100 cases with special reference to chronic alcoholism. *Am J Med* 1966; 41: 213–228
107. BRIGDEN W, ROBINSON J: Alcoholic heart disease. *Br Med J* 1964; 2: 1283–1289
108. BURCH GE, DEPASQUALE N: Alcoholic lung disease — an hypothesis. *Am Heart J* 1966; 73: 147–148
109. RANKIN JG, HALE GS, WILKINSON P, O'DAY DM, SANTAMARIA JN, BABARCZY G: Relationship between smoking and pulmonary disease in alcoholism. *Med J Aust* 1969; 1: 730–733
110. EMERGIL C, SOBOL BJ, HEYMANN B, SHIBUTANI K, REED A, VARBLE A, WALDIE J: Pulmonary function in alcoholics. *Am J Med* 1974; 57: 69–77
111. YULES RB, LIPPMAN ME, FREEDMAN DX: Alcohol administration prior to sleep. The effect on EEG sleep stages. *Arch Gen Psychiatry* 1967; 16: 94–97
112. JOHNSON LC, BURDICK JA, SMITH J: Sleep during alcohol intake and withdrawal in the chronic alcoholic. *Arch Gen Psychiatry* 1970; 22: 406–418
113. GROSS MM, GOODENOUGH D, TOBIN M, HALPERT E, LEPORE D, PERLSTEIN A, SIROTA M, DIBIANCO

J, FULLER R, KISHNER I: Sleep disturbances and hallucinations in the acute alcoholic psychoses. *J Nerv Ment Dis* 1966; 142: 493–514
114. MASTERS WH, JOHNSON VE: *Human Sexual Response*, 1st ed, Little, Boston, 1966
115. LEMERE F, SMITH JW: Alcohol induced sexual impotence. *Am J Psychiatry* 1973; 130: 212–213
116. SMITH JW, LEMERE F, DUNN RB: Impotence in alcoholism. *NW Med* 1972; 71: 523–524
117. WILSON GT: Alcohol and human sexual behavior. *Behav Res Ther* 1977; 15: 239–252
118. MARGOLIS J, ROBERTS DM: Frequency of skin lesions in chronic drinkers. *Arch Dermatol* 1976; 112: 1326
119. WOEBER K: The skin in the diagnosis of alcoholism. *Ann NY Acad Sci* 1975; 252: 292–295
120. LOWENFELS AB: *The Alcoholic Patient in Surgery*, Williams & Wilkins, Baltimore, Md, 1971: 1–12
121. ROSSET M, OKI G: Skin diseases in alcoholics. *Q J Stud Alcohol* 1971; 32: 1017–1024
122. YOUNG AW: Cutaneous stigmata of alcoholism. *Alcohol Health Res World* 1974; summer: 24–28
123. MARKS R: Concepts in the pathogenesis of rosacea. *Br J Dermatol* 1968; 80: 170–177
124. ASHER R, SMITH R: It is worth looking at clothes. *Arch Intern Med* 1964; 114: 33–35
125. SMITH JD, SMITH EB: Multiple fire ant stings. A complication of alcoholism. *Arch Dermatol* 1971; 103: 438-441
126. RUKSTINAT GJ: Tattoos: a survey with special reference to tattoos and scars as indicators of syphilis. *Arch Pathol* 1941; 31: 640–655
127. TANYOL H: The contribution of excessive consumption of alcohol to the development of varicose veins. A re-evaluation of the role of valvular incompetence and suggestions concerning the possible role of increased blood flow in the genesis of varicose veins. *Surgery* 1960; 48: 1061–1067
128. BARBORIAK JJ: Drug reactions after ingestion of alcohol. *Wis Med J* 1964; 63: 213–214
129. YOUNG AW JR, ROSENBERG FR: Cutaneous stigmas of heroin addiction. *Arch Dermatol* 1971; 104: 80–86
130. ROBERTS KE: Mechanism of dehydration following alcohol ingestion. *Arch Intern Med* 1963; 112: 154–157
131. BEARD JD, KNOTT DH: Fluid and electrolyte balance during acute withdrawal in chronic alcoholic patients. *JAMA* 1968; 204: 133–139
132. JOSKE RA, TURNER CN: Studies in chronic alcoholism: the clinical findings in 78 cases of chronic alcoholism. *Med J Aust* 1952; 1: 729–734
133. BEAN WB: *Vascular Spiders and Related Lesions of the Skin*, Blackwell Sci Publ, Oxford, Engl, 1959
134. BRAVERMAN IM: *Skin Signs of Systematic Disease*, Saunders, Philadelphia, 1970: 339–344
135. SHERLOCK S: *Diseases of the Liver and Biliary System*, 5th ed, Blackwell Sci Publ, Oxford, Engl, 1975
136. VAN THEIL DH, LESTER R: Alcoholism: its effect on hypothalamic pituitary gonadal function. *Gastroenterology* 1976; 71: 318–327
137. SU C-K, PATEK AJ JR: Dupuytren's contracture. Its association with alcoholism and cirrhosis. *Arch Intern Med* 1970; 126: 278–281
138. TERRY R: White nails in hepatic cirrhosis. *Lancet* 1954; 1: 757–759
139. MUEHRECKE RC: The finger-nails in chronic hypoalbuminaemia. A new physical sign. *Br Med J* 1956; 1: 1327–1328
140. LEWIN K: The finger nail in general disease. A macroscopic and microscopic study of 87 consecutive autopsies. *Br J Dermatol* 1965; 77: 431-438
141. MACKAY IR: The effects of alcohol on the gastro-intestinal tract. *Med J Aust* 1966; 2: 372–376
142. MANDEL L, BAURMASH H: Parotid enlargement due to alcoholism. *J Am Dent Assoc* 1971; 82: 369–373
143. DUGGAN JJ, ROTHBELL EN: Asymptomatic enlargement of the parotid glands. *N Engl J Med* 1957; 257: 1262–1267
144. WOLFE SJ, SUMMERSKIL WHJ, DAVIDSON CS: Parotid swelling, alcoholism and cirrhosis. *N Engl J Med* 1957; 256: 491–495
145. KALTREIDER HB, TALAL N: Bilateral parotid gland enlargement and hyperlipoproteinaemia. *JAMA* 1969; 210: 2067–2070
146. SHAW GK, THOMSON A: A joint psychiatric and medical outpatient clinic for alcoholics. In EDWARDS G, GRANT M (eds): *Alcoholism: New Knowledge and New Responses*, Croom Helm, London, Engl, 1977: 328–334
147. ALAPPATT JL, ANANTHACHARI MD: A preliminary study of the structure and function of enlarged parotid glands in chronic relapsing pancreatitis by sialography and biopsy methods. *Gut* 1967; 8: 42–45
148. ISENBERG J, BOYLE JD: Recurrent parotid swelling, arterial hypertension, and pancreatitis. *Gastroenterology* 1968; 55: 277–281
149. DAVIDSON D, LEIBEL BS, BERRIS B: Asymptomatic parotid gland enlargement in diabetes mellitus. *Ann Intern Med* 1969; 70: 31–38
150. BORSANYI S, BLANCHARD CL: Asymptomatic enlargement of the parotid gland. Its diagnostic significance and particular relation to Laennec's cirrhosis. *JAMA* 1960; 174: 20–25
151. National Council on Alcoholism, criteria committee: Criteria for the diagnosis of alcoholism. *Am J Psychiatry* 1972; 129: 127–135
125. RENTOUL E, SMITH H: *Glaister's Medical Jurisprudence and Toxicology*, 13th ed, Churchill, Edinburgh, 1973
153. HAMLYN AN, BROWN AJ, SHERLOCK S, BARON DN: Causal blood-ethanol estimations in patients with chronic liver disease. *Lancet* 1975; 2: 345–347
154. ORREGO H, BLENDIS LM, BLAKE JE, KAPUR BM, ISRAEL Y: Reliability of assessment of alcohol intake based on personal interviews in a liver clinic. *Lancet* 1979; 2: 1354–1356
155. TENNANT FS JR, DAY CM, UNGERLEIDER T: Screening for drug and alcohol abuse in a general medical population. *JAMA* 1979; 242: 533–535
156. WECHSLER H, KASEY EH, THUM D, DEMONE WH JR: Alcohol level and home accidents. A study of emergency service patients. *Public Health Rep* 1969; 84: 1043–1050
157. MCCOLL KEL, WHITING B, MOORE MR, GOLDBERG A: Correlation of ethanol concentrations in blood and saliva. *Clin Sci* 1979; 56: 283–286
158. PHILLIPS M, VANDERVOORT RE, BECKER CE: A sweat test for alcohol consumption. In SEIXAS FA (ed): *Currents in Alcoholism*, vol 3, Grune, New York, 1978: 505–514
159. AUGUSTINE JR: Laboratory studies in alcoholics. *Can Med Assoc J* 1967; 96: 1367–1370
160. REECE RJ, WEGNER ME: Chemical patterns of 500 alcoholics. *Minn Med* 1970; 53: 575–585
161. KONTTINEN A, HÄRTEL G, LOUHIJA A: Multiple serum enzyme analyses in chronic alcoholics. *Acta Med Scand* 1970; 188: 257–264
162. POLLACK B, BUCKELL M: Abnormal laboratory tests in the alcoholic patient. *J Alcohol* 1974; 9: 135–143
163. HILL SY, GOODWIN DW, CADORET R, OSTERLAND CK, DONER SA: Association and linkage between alcoholism and eleven serological markers. *J Stud Alcohol* 1975; 36: 981–992
164. GELLENS HK, GOTTHEIL E, ARAYATA L, ALTERMAN AI: Blood chemistry changes in drinking alcoholics. *Br J Addict* 1976; 71: 103–108
165. LEVI AJ, CHALMERS DM: Recognition of alcoholic liver disease in a district general hospital. *Gut* 1978; 19: 521–525
166. GALIZZI J, MORGAN MY, CHITRANUKROH A, SHERLOCK S: The detection of minimal alcoholic liver disease by three methods. *Scand J Gastroenterol* 1978; 13: 827–832

167. WHITFIELD JB, HENSLEY WJ, BRYDEN D, GALLAGHER H: Effects of age and sex on biochemical responses to drinking habits. *Med J Aust* 1978; 2: 629–632
168. Idem: Some laboratory correlates of drinking habits. *Ann Clin Biochem* 1978; 15: 297-303
169. WHITEHEAD TP, CLARKE CA, WHITEFIELD AGW: Biochemical and haematological markers of alcohol intake. *Lancet* 1978; 1: 978–981
170. WHITFIELD JB, HENSLEY WJ, BRYDEN D, GALLAGHER H: Estimation of alcohol intake from laboratory results. *Ann Clin Biochem* 1978; 15: 304–306
171. WAERN U, BOBERG J, HELLSING K: Evaluation of indices of alcohol intake in a population of 60-year-old men in Uppsala, Sweden. *Acta Med Scand* 1979; 205: 353–360
172. ZIEVE L: Jaundice, hyperlipemia and hemolytic anemia: a heretofore unrecognized syndrome associated with alcoholic fatty liver and cirrhosis. *Ann Intern Med* 1958; 48: 471–496
173. LIEBER CS, SPRITZ N, DECARLI LM: Role of dietary adipose, and endogenously synthesized fatty acids in pathogenesis of alcoholic fatty liver. *J Clin Invest* 1966; 45: 51–62
174. CHAIT A, MANCINI M, FEBRUARY AW, LEWIS B: Clinical and metabolic study of alcoholic hyperlipidaemia. *Lancet* 1972; 2: 62–64
175. LIEBER CS: Liver adaptation and injury in alcoholism. *N Engl J Med* 1973; 288: 356–362
176. AVOGARO P, CAZZOLATO G: Changes in the composition and physicochemical characteristics of serum lipoproteins during ethanol-induced lipemia in alcoholic subjects. *Metabolism* 1975; 24: 1231–1242
177. CASTELLI WP, DOYLE JT, GORDON T, HAMES CG, HJORTLAND MC, HULLEY SB, KAGAN A, ZUKEL WJ: Alcohol and blood lipids. The Cooperative Lipoprotein Phenotyping Study. *Lancet* 1977; 2: 153–160
178. NIKKILÄ EA, TASKINEN M-R: Relation between H.D.L.-cholesterol levels and triglyceride metabolism (C). *Lancet* 1978; 2: 892
179. BARBORIAK JJ, RIMM AA, ANDERSON AJ, SCHMIDHOFFER M, TRISTANI FE: Coronary artery occlusion and alcohol intake. *Br Heart J* 1977; 39: 289–293
180. YANO K, RHOADS GG, KAGEN A: Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. *N Engl J Med* 1977; 297: 405–409
181. HULLEY SB, COHEN R, WIDDOWSON G: Plasma high-density lipoprotein cholesterol level. Influence of risk factor intervention. *JAMA* 1977; 238: 2269–2271
182. WILLIAMS P, ROBINSON D, BAILEY A: High-density lipoprotein and coronary risk factors in normal men. *Lancet* 1979; 1: 72–75
183. BERG B, JOHANSSON BG: Effects on parameters of liver function, plasma lipid concentrations and lipoprotein patterns. *Acta Med Scand [Suppl]* 1973; 194 (552): 13–18
184. BELFRAGE P, BERG B, HÄGERSTRAND I, NILSSON-EHLE P, TORNQVIST H, WIEBE T: Alterations of lipid metabolism in healthy volunteers during long-term ethanol intake. *Eur J Clin Invest* 1977; 7: 127–131
185. JOHANSSON BG, MEDHUS A: Increase in plasma α-lipoproteins in chronic alcoholics after acute abuse. *Acute Med Scand* 1974; 195: 273–277
186. DANIELSSON B, EKMAN R, FEX G, JOHANSSON BG, KRISTENSSON H, NILSSON-EHLE B, WADSTEIN J: Changes in plasma high-density lipoproteins in chronic male alcoholics during and after abuse. *Scand J Clin Lab Invest* 1978; 38: 113–119
187. KAPUR BM, HOLT S, BLAKE J, ORREGO H: HDL-cholesterol in alcoholics with liver disease. Presented at Joint Meeting of the American Association for Clinical Chemistry and the Canadian Society of Clinical Chemists, Boston, July 20–25, 1980 (in press)
188. SKUDE G, WADSTEIN J: Amylase, hepatic enzymes and bilirubin in serum of chronic alcoholics. *Acta Med Scand* 1977; 201: 53–58
189. ROSALKI SB, RAU D: Serum-γ-glutamyl transpeptidase activity in alcoholism. *Clin Chim Acta* 1972; 39: 41–47
190. COHEN JA, KAPLAN MM: The SGOT/SGPT ratio — an indicator of alcoholic liver disease. *Dig Dis Sci* 1979; 24: 835–838
191. ZEIN M, DISCOMBE G: Serum gamma-glutamyl transpeptidase as a diagnostic aid. *Lancet* 1970; 2: 748–750
192. SZEWCZUK A: A soluble form of gamma-glutamyl transpeptidase in human tissues. *Clin Chim Acta* 1966; 14: 608–614
193. WU A, CHANARIN I, SLAVIN G, LEVI AJ: Folate deficiency in the alcoholic — its relationship to clinical and haematological abnormalities, liver disease and folate stores. *Br J Haematol* 1975; 29: 469–478
194. VAN WAES L, LIEBER CS: Glutamate dehydrogenase: a reliable marker of liver cell necrosis in the alcoholic. *Br Med J* 1977; 2: 1508–1510
195. ROLLASON JG, PINCHERLE G, ROBINSON D: Serum gamma glutamyl transpeptidase in relation to alcohol consumption. *Clin Chim Acta* 1972; 39: 75–80
196. POMERLEAU O, PERTSCHUK M, ADKINS D, BRADY JP: A comparison of behavioural and traditional treatment for middle-income problem drinkers. *J Behav Med* 1978; 1: 187–200
197. MIYAZAKI S, OKUMURA M: Change of serum γ-glutamyl transpeptidase level and isoenzyme pattern in heptobiliary pancreatic disease. *Clin Chim Acta* 1972; 40: 193–197
198. LUM G, GAMBINO SR: Serum gamma-glutamyl transpeptidase activity as an indicator of disease of liver, pancreas, or bone. *Clin Chem* 1972; 18: 358–362
199. LAMY J, BAGLIN MC, FERRANT JP, WEILL J: Diminution de la γ-glutamyltranspeptidase sérique des éthyliques à la suite du sevrage. *Clin Chim Acta* 1974; 56: 169–173
200. TESCHKE R, BRAND A, STROHMEYER G: Induction of hepatic microsomal gamma-glutamyl transferase activity following chronic alcohol consumption. *Biochem Biophys Res Commun* 1977; 75: 718–724
201. MARTIN-BOYCE A, SCHWARTZ D, DREYFUS J, SCHNEEGANS P: Biochemical and haematological markers of alcohol intake (C). *Lancet* 1978; 2: 529
202. WESTWOOD M, COHEN MI, MCNAMARA H: Serum gamma-glutamyl transpeptidase activity: a chemical determinant of alcohol consumption during adolescence. *Pediatrics* 1978; 62: 560–562
203. REYES E, MILLER WR, TAYLOR CA, SPALDING CT: The activity of gamma-glutamyl transpeptidase in the serum of problem drinkers. *Proc West Pharmacol Soc* 1978; 21: 289–297
204. KOKOT F, KUSKA J: Üuber die Bedeutung der Isoenzyme der γ-glutamyl-transpeptidase in der Klinischen diagnostik. *Clin Chim Acta* 1965; 11: 118–121
205. ROBINSON D, MONK C, BAILEY A: The relationship between serum gamma-glutamyl transpeptidase level and reported alcohol consumption in healthy men. *J Stud Alcohol* 1979; 40: 896–901
206. KONTTINEN A, HÄRTEL G, LOUHIJA A: Multiple serum enzyme analyses in chronic alcoholics. *Acta Med Scand* 1970; 188: 257–264
207. NYGREN A, SUNDBLAD L: Lactate dehydrogenase isoenzyme patterns in serum and skeletal muscle in intoxicated alcoholics. *Acta Med Scand* 1971; 189: 303–307
208. JENKINS WJ, ROSALKI S, FOO Y, SCHEUER PJ, SHERLOCK S: Is serum glutamate dehydrogenase a reliable marker of liver cell necrosis in the alcoholic? The effect of recent alcohol excess (abstr). *Drug Alcohol Depend* 1980; 6: 16–17
209. WORNER TM, LIEBER CS: Plasma glutamate dehydrogenase (GDH) as a marker of alcoholic liver injury (abstr). Ibid: 36–37

210. SHAW S, LIEBER CS: Characteristic plasma amino acid abnormalities in the alcoholic; respective roles of alcoholism, nutrition and liver injury (abstr). *Clin Res* 1976; 24: 291A
211. SHAW S, STIMMEL B, LIEBER CS: Plasma alpha amino-*n*-butyric acid to leucine ratio: an empirical biochemical marker of alcoholism. *Science* 1976; 194: 1057–1058
212. SHAW S, LUE S-L, LIEBER CS: Biochemical tests for the detection of alcoholism: comparison of plasma alpha amino-n-butyric acid with other valuable tests. *Alcohol Clin Exp Res* 1978; 2: 3–8
213. SHAW S, WORNER TM, BORYSOW MF, SCHMITZ RE, LIEBER CS: Detection of alcoholism relapse — comparative diagnostic value of MCV, GGTP, and AANB. *Alcohol Clin Exp Res* 1979; 3: 297–301
214. MORGAN MY, MILSOM JP, SHERLOCK S: Ratio of plasma alpha amino-*n*-butyric acid to leucine as an empirical marker of alcoholism: diagnostic value. *Science* 1977; 197: 1183–1185
215. DIENSTAG JL, CARTER EA, WANDS JR, ISSELBACHER KJ, FISHER JE: Plasma alpha amino-*n*-butyric acid to leucine (A/L) ratio; nonspecificity as a marker for alcoholism. *Gastroenterology* 1978; 75: 561–565
216. ELLINGBOE J, MENDELSON JH, VARANELLI CC, NEUBERGER O, BORYSOW M: Plasma alpha amino-*n*-butyric acid:leucine ratio. Normal values in alcoholics. *J Stud Alcohol* 1978; 39: 1467–1476
217. HILDERBRAND RL, HERVIG LK, CONWAY TL, WARD HW, MARKLAND FS: Alcohol intake, ratio of plasma alpha-amino-*n*-butyric acid to leucine, and gamma-glutamyl transpeptidase in nonalcoholics. *J Stud Alcohol* 1979; 40: 902–905
218. JANDL JH: The anemia of liver disease: observations on its mechanism. *J Clin Invest* 1955; 34: 390–404
219. WATERS AH, MORLEY AA, RANKIN JG: Effects of alcohol on haemopoiesis. *Br Med J* 1966; 2: 1565–1568
220. JARROLD T, WILL JJ, DAVIES AR, DUFFEY PH, BRAMSCHREIBER JL: Bone marrow–erythroid morphology in alcoholic patients. *Am J Clin Nutr* 1967; 20: 716–722
221. HERBERT V, ZALUSKY R, DAVIDSON CS: Correlation of folate deficiency with alcoholism and associated macrocytosis, anemia, and liver disease. *Ann Intern Med* 1963; 58: 977–988
222. WESTERMAN MP, BALCERZAK SP, HEINLE EW JR: Red cell lipids in Zieve's syndrome: their relation to hemolysis and to red cell osmotic fragility. *J Lab Clin Med* 1968; 72: 663–669
223. HINES JD: Reversible megaloblastic and sideroblastic marrow abnormalities in alcoholic patients. *Br J Haematol* 1969; 16: 87–101
224. MCFARLAND W, LIBRE EP: Abnormal leucocyte response in alcoholism. *Ann Intern Med* 1963; 59: 865–877
225. BRAYTON RG, STOKES PE, SCHWARTZ MS, LOURIA DB: Effect of alcohol and various diseases on leukocyte mobilization, phagocytosis and intracellular bacterial killing. *N Engl J Med* 1970; 282: 123–128
226. LINDENBAUM J, HARGROVE RL: Thrombocytopenia in alcoholics. *Ann Intern Med* 1968; 68: 526–532
227. COWAN DH, HINES JD: Thrombocytopenia of severe alcoholism. *Ann Intern Med* 1971; 74: 37–43
228. WALLS WD, LOSOWSKY MS: The hemostatic defect of liver disease. Gastroenterology 1971; 60: 108–119
229. VELTKAMP JJ, KREUNING J: The diagnostic value of coagulation studies in chronic liver disease. *Scand J Gastroenterol [Suppl]* 1973; 19: 93–95
230. WU A, CHANARIN I, LEVI AJ: Macrocytosis of chronic alcoholism. *Lancet* 1974; 1: 829–830
231. UNGER KW, JOHNSON D JR: Red blood cell mean corpuscular volume: a potential indicator of alcohol usage in a working population. *Am J Med Sci* 1974; 267: 281–289
232. SMITH JA, LONERGAN ET, STERLING K: Spur-cell anemia. Hemolytic anemia with red cells resembling acanthocytes in alcoholic cirrhosis. *N Engl J Med* 1964; 271: 396–398
233. GRAHN EP, DIETZ AA, STEFANI SS, DONNELLY WJ: Burr cells, hemolytic anemia and cirrhosis. *Am J Med* 1968; 45: 78–87
234. DOUGLASS CC, TWOMEY JJ: Transient stomatocytosis with hemolysis: a previously unrecognized complication of alcoholism. *Ann Intern Med* 1970; 72: 159–164
235. Alcohol and the blood (E). *Br Med J* 1978; 1: 1504–1505
236. BUFFET C, CHAPUT JC, ALBUISSON F, SUBTIL E, ETIENNE J-P: La macrocytose dans l'hépatite alcoolique chronique histologiquement prouvée. *Arch Fr Mal App Dig* 1975; 64: 309–315
237. DRUM DE, JANKOWSKI C: Diagnostic algorithms for detection of alcoholism in general hospitals. In SEIXAS FA, BONNER J, PECK SL (eds): *Currents in Alcoholism. Biological, Biochemical and Clinical Studies*, vol 1, Grune, New York, 1977: 361–379
238. CARNEY MWP, SHEFFIELD B: Serum folate and B12 and haemotological status of in-patient alcoholics. *Br J Addict* 1978; 73: 3–7
239. ESCHWEGE E, PAPOZ L, LELLOUCH J, CLAUDE JR, CUBEAU J, PEQUIGNOT G, RICHARD JL, SCHWARTZ D: Blood cells and alcohol consumption with special reference to smoking habits. *J Clin Pathol* 1978; 31: 654–658
240. MYRHED M, BERGLUND L, BÖTTIGER LE: Alcohol consumption and hematology. *Acta Med Scand* 1977; 202: 11–15
241. LIEBER CS, JONES DP, LOSOWSKY MS, DAVIDSON CS: Interrelation of uric acid and ethanol metabolism in man. *J Clin Invest* 1962; 41: 1863–1870
242. LEVY LJ, DUGA J, GIRGIS M, GORDON EE: Ketoacidosis associated with alcoholism in nondiabetic subjects. *Ann Intern Med* 1973; 78: 213–219
243. LEFÈVRE A, ADLER H, LIEBER CS: Effect of ethanol on ketone metabolism. *J Clin Invest* 1970; 49: 1775–1782
244. ORTEN JM, DOEHR SA, BOND C, JOHNSON H, PAPPA A: Urinary excretion of porphyrins and porphyrin intermediates in human alcoholics. *Q J Stud Alcohol* 1963; 24: 598–609
245. HED R, LINDBLAD LE, NYGREN A, SUNDBLAD L: Forearm glucose uptake during glucose tolerance tests in chronic alcoholics. *Scand J Clin Lab Invest* 1977; 37: 229–233
246. ORTEN JM, SARDESAI VM: Protein, nucleotide and porphyrin metabolism. In KISSIN B, BEGLEITER H (eds): *The Biology of Alcoholism*, vol 1: *Biochemistry*, Plenum Pub, New York, 1971: 229–261
247. SHRIVASTARA KC, ORTEN JM: Urinary excretion of coproporphyrin in alcoholics. Studies on "single-voiding" samples. *Q J Stud Alcohol* 1972; 33: 962–965
248. LEEVY CM, FINEBERG JC, WHITE TJ, GNASSI AM: Hyperglycemia and glycosuria in the chronic alcoholic with hepatic insufficiency. Clinical observations in 10 patients. *Am J Med Sci* 1952; 223: 88–95
249. PHILLIPS GB, SAFRIT HF: Alcoholic diabetes. Induction of glucose intolerance with alcohol. *JAMA* 1971; 217: 1513–1519
250. SINGH SP, PATEL DG: Effects of ethanol on carbohydrate metabolism: I. Influence on oral glucose tolerance test. *Metabolism* 1976; 25: 239–243
251. MEZEY E: Increased urinary excretion of D-glucaric acid in alcoholism. *Res Commun Chem Pathol Pharmacol* 1976; 15: 735–742
252. HUNTER J, MAXWELL JD, CARELLA M, STEWART DA, WILLIAMS R: Urinary D-glucaric-acid excretion as a test of hepatic enzyme induction in man. *Lancet* 1971; 1: 572–575
253. SOTANIEMI EA, MEDZIHRADSKY F, ELIASSON G: Glucaric acid as an indicator of use of enzyme-inducing drugs. *Clin Pharmacol Ther* 1974; 15: 417–423
254. SPENCER-PEET J, WOOD DC, GLATT MM, WISEMAN SM: Urinary D-glu-

caric acid excretion and serum gamma-glutamyl transpeptidase activity in alcoholism. *Br J Addict* 1975; 70: 359–364
255. MILSTEIN HJ, BLOOMER JR, KLATSKIN G: Serum bile acids in alcoholic liver disease. Comparison with histological features of the disease. *Am J Dig Dis* 1976; 21: 281–285
256. OVERBY LR: The new serology of alcoholic liver disease. In GITNICK GL (ed): *Current Gastroenterology and Hepatology*, vol 1, H-M Pro Pubs, Boston, 1979: 299–300
257. SULLIVAN JF, HEANEY RP: Zinc metabolism in alcoholic liver disease. *Am J Clin Nutr* 1970; 23: 170–177
258. BAINES M: Detection and incidence of B and C vitamin deficiency in alcohol-related illness. *Ann Clin Biochem* 1978; 15: 307–312
259. STIBLER H, SYDOW O, BORG S: Quantitation of a qualitative change of transferrin heterogeneity in alcoholics. *Drug Alcohol Depend* 1980; 6: 11–12
260. STIBLER H, BORG S, ALLGULANDER C: Clinical significance of abnormal heterogeneity of transferrin in relation to alcohol consumption. *Acta Med Scand* 1979; 206: 275–282
261. COLLINS MA, NIJM WP, BORGE GF, TEAS G, GOLDFARB C: Dopamine-related tetrahydroisoquinolines; significant urinary excretion by alcoholics after alcohol consumption. *Science* 1979; 206: 1184–1186
262. CHAFETZ ME: Alcoholism prevention and reality. *Q J Stud Alcohol* 1967; 28: 345–348
263. LELBACH WK: Organic pathology related to volume and pattern of alcohol use. In GIBBINS RJ, ISRAEL Y, KALANT H, POPHAM RE, SCHMIDT W, SMART RC (eds): *Research Advances in Alcohol and Drug Problems*, vol 1, Plenum Pub, New York, 1974: 93–198
264. PEQUIGNOT G, TUYNS AJ, BERTA JL: Ascitic cirrhosis in relation to alcohol consumption. *Int J Epidemiol* 1978; 7: 113–120
265. ORREGO H, KALANT H, ISRAEL Y, BLAKE J, MEDLINE A, RANKIN JG, ARMSTRONG A, KAPUR B: Effects of short-term therapy with propylthiouracil in patients with alcoholic liver disease. *Gastroenterology* 1979; 76: 105–115
266. LELBACH WK: Quantitative aspects of drinking in alcoholic liver cirrhosis. In KHANNA JM, ISRAEL Y, KALANT H (eds): *Alcoholic Liver Pathology*, Addiction Research Foundation of Ontario, Toronto, 1975: 1–18
267. FISHER JC, MASON RL, FISHER JV: A diagnostic formula for alcoholism. *J Stud Alcohol* 1976; 37: 1247–1255
268. SKINNER HA: Assessment of clients with alcohol problems: basic principles, critical issues and future trends. In ISRAEL Y, GLASER FB, KALANT H, POPHAM RE, SCHMIDT W, SMART RG (eds): *Research Advances in Alcohol and Drug Problems* (in press)