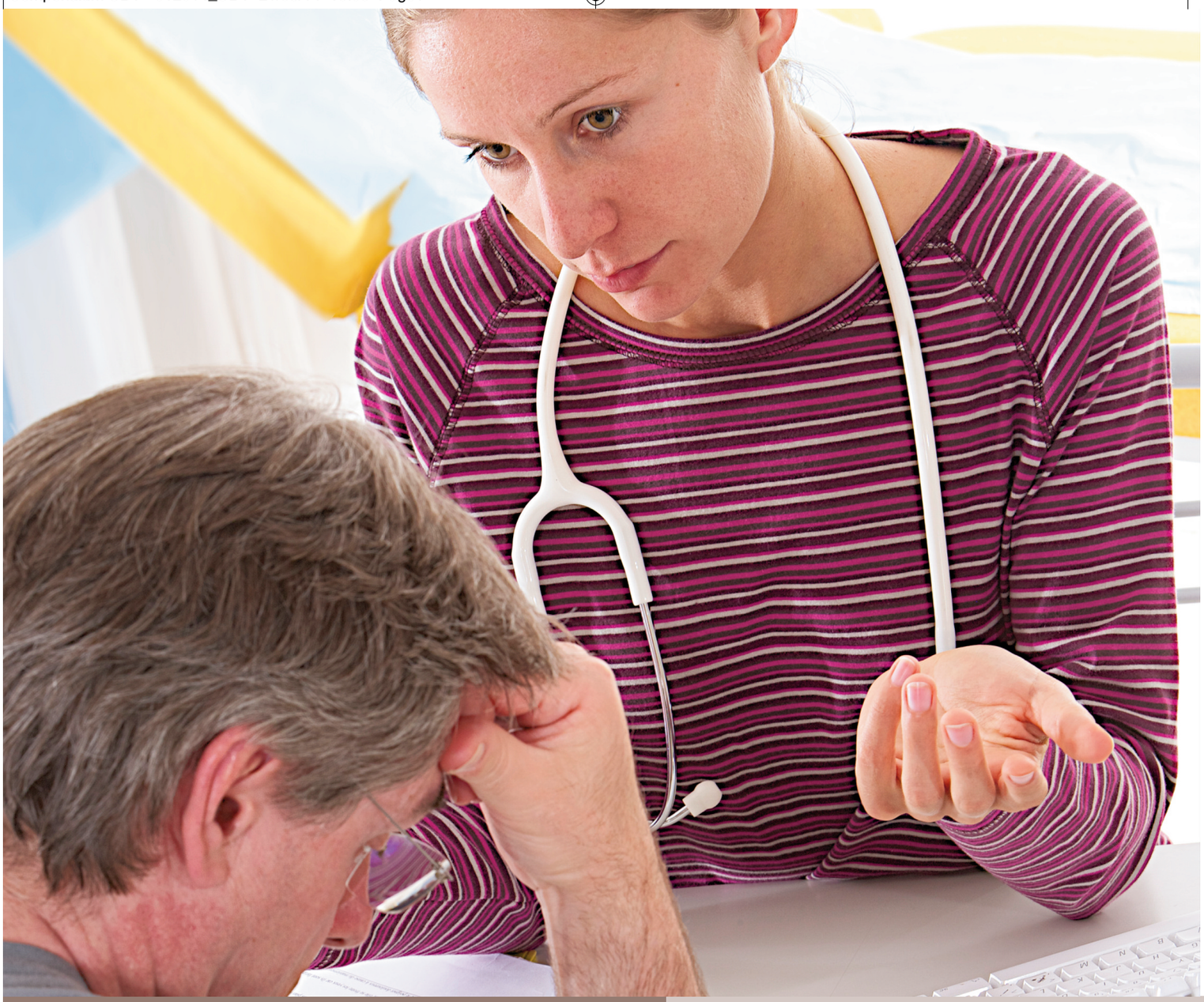

Compendium

Carbohydrate Deficient Transferrin

A specific and sensitive marker of chronic alcohol abuse

Collection of practical experiences

SEBIA Education Library

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Introduction

Key facts[1]

- The harmful use of alcohol results in 2.5 million deaths each year.
- 320 000 young people between the age of 15 and 29 die from alcohol-related causes, resulting in 9% of all deaths in that age group.
- Alcohol is the world's third largest risk factor for disease burden; it is the leading risk factor in the Western Pacific and the Americas and the second largest in Europe.
- Alcohol is associated with many serious social and developmental issues, including violence, child neglect and abuse, and absenteeism in the workplace.

Recommended maximum intake of alcoholic beverages[2]

Regular consumption:

Women:
- not more than 2-3 units* of alcohol on an average day (less than 14/week)
- at least two alcohol-free days a week

Men:
- not more than 3-4 units* of alcohol on an average day (less than 21/week)
- at least two alcohol-free days a week

Consumption on an occasional basis:

- not more than 4 units of alcohol on one occasion

Consumption of alcohol must be avoided in the following circumstances:

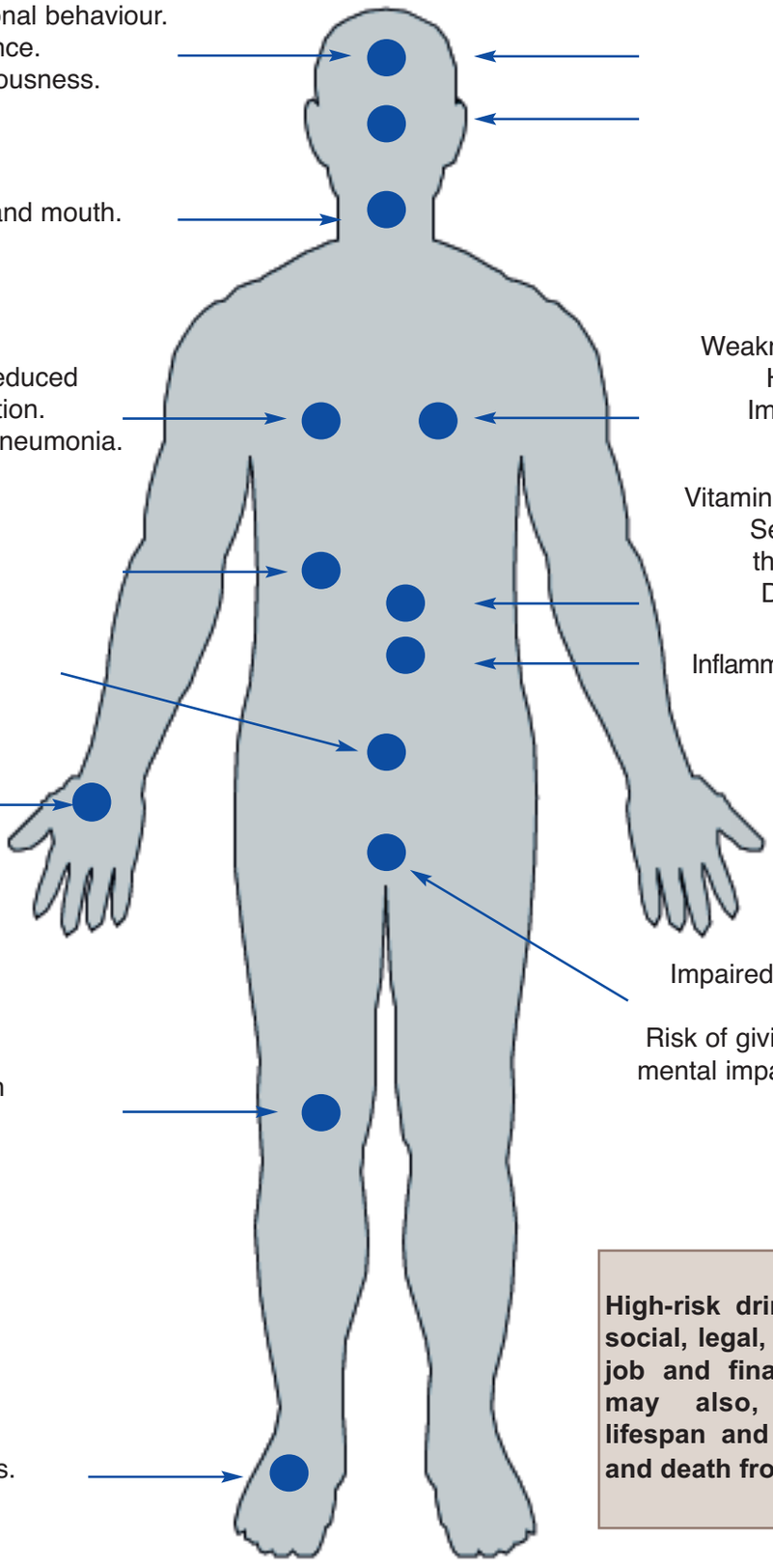
- During pregnancy
- During childhood
- Driving
- Operating dangerous machinery
- When exercising responsibilities which require vigilance
- When taking certain medications
- People with certain chronic or acute diseases (epilepsy, pancreatitis, viral hepatitis, etc.)
- For former alcoholics

* One unit of alcohol is 10 ml (1 cl) by volume, or 8 g by weight of pure alcohol.

[1] WHO. Alcohol Fact Sheet February 2011 (http://www.who.int/mediacentre/factsheets/fs349/en/index.htm)

[2] WHO. Problems related to alcohol consumption. Report of the expert committee. Geneva: World Health Organisation, 1980

Effects of High-Risk Drinking[3]



Aggressive, irrational behaviour. Arguments. Violence. Depression. Nervousness.

Cancer of throat and mouth.

Frequent colds. Reduced resistance to infection. Increased risk of pneumonia.

Liver damage.

Ulcer.

Trembling hands. Tingling fingers. Numbness. Painfull nerves.

Impaired sensation leading to falls.

Numb, tingling toes. Painful nerves.

Alcohol dependence. Memory loss.

Premature aging. Drinker's nose.

Weakness of heart muscle. Heart failure. Anemia. Impaired blood clotting. Breast cancer.

Vitamin deficiency. Bleeding. Severe inflammation of the stomach. Vomiting. Diarrhea. Malnutrition.

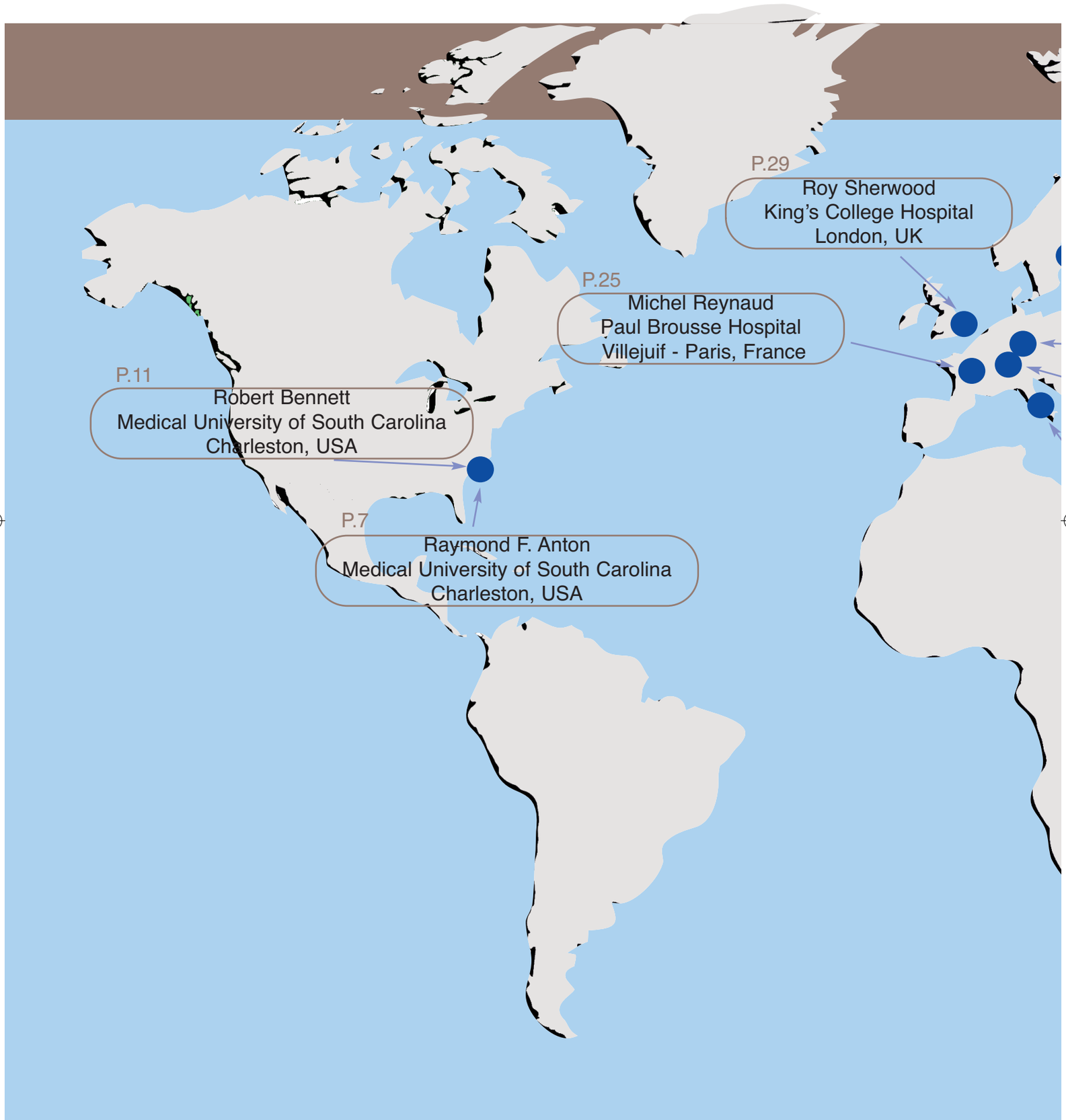
Inflammation of the pancreas.

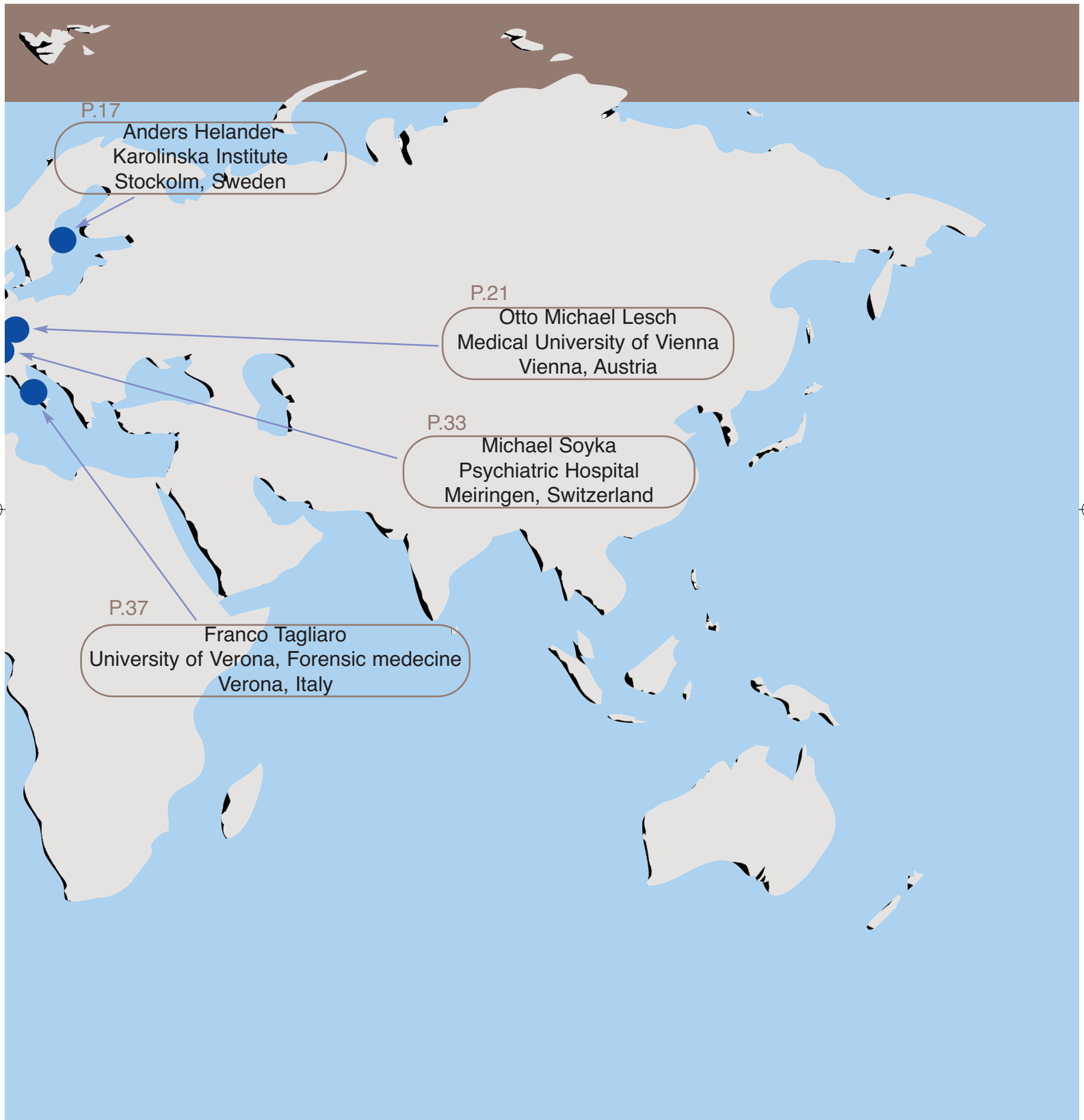
In men: Impaired sexual performance. In women: Risk of giving birth to deformed, mental impairment babies or low birth weight babies.

High-risk drinking may lead to social, legal, medical, domestic, job and financial problems. It may also, cut individuals lifespan and lead to accidents and death from drunken driving.

[3] WHO. AUDIT, The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Care. World Health Organization, Geneva, 2001.

Screen for alcohol use: a worldwide concern

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University of Verona, Forensic medecine
Verona, Italy

"...CDT is useful in monitoring alcohol use during treatment.
It is like monitoring hemoglobin A1c with diabetes."
Raymond F. ANTON

Raymond F. ANTON

Academic background

Raymond F. Anton, M.D., is an Addiction Psychiatrist and Psychopharmacologist. He is a Distinguished University Professor of Psychiatry and Behavioral Science at the Medical University of South Carolina in Charleston, SC, where he is the Director of the Center for Drug and Alcohol Programs; the Clinical Scientific Director of an NIAAA funded Alcohol Research Center, and the Director of the Clinical Laboratory in the Institute of Psychiatry.

General presentation

Raymond Anton is a former President of the Research Society on Alcoholism (RSA) and is currently on the Board of Directors of the International Society for Biomedical Research on Alcoholism (ISBRA) and Vice-Chair of the Board of the Alcohol Beverage Medical Research Foundation (ABMRF). He is an elected Fellow to the American College of Neuropsychopharmacology, he is currently serving as Chair of the ACTIVE workgroup, a consortium of academics, government agencies and the pharmaceutical industry whose task is to define the best methods for clinical trials for alcohol use disorders.
Raymond Anton is also an elected Distinguished Life Fellow of the American Psychiatric Association. He has published over 260 articles and book chapters and has active funding for incorporating neuroimaging and genetics into clinical alcohol trials. He also helped pioneer the clinical utility of the CDT blood test for the detection and monitoring of heavy alcohol use.

The USA experience

How much of a problem is alcohol in the US? What prevention campaigns, and alcohol programs are there, and their effectiveness?

Statistically, in any given year, 3-4 % of the population meets alcohol dependence criteria, and the same number meets alcohol abuse criteria. The official distinction between alcohol abuse and dependence was dropped in the DSM 5, so at least 5-7 % will be classified as suffering from Alcohol Use Disorder. Then there is another group that are heavy drinkers currently estimated to be about 10 %. Overall, the CDT test could be useful to detect heavy drinking in up to 20 % of adults in the US.
There is very little in the way of large government prevention programs, except for drunk driving. There is more funding for public health announcements and combating illicit drug abuse because alcohol is a legal substance. You cannot tell people not to drink in a free society, as it is legal. At least 80 % drink some alcohol.

Have you made a contribution to an alcohol testing policy? What are the implications, which actions have you taken?

There is no testing policy in the US at all. In Europe, CDT is used to monitor drunk drivers in order to get their licenses back, but not in the US. In the US, state laws in most cases take precedence over federal laws, so there is little will or funding to support a change in policy. Also, the Judiciary is not knowledgable in this area which represents an educational challenge and opportunity.
I have worked mainly in biomedical and clinical areas. I am trying to get clinicians to use biomarkers in their assessment, diagnosis and monitoring of people in treatment. I also try to educate pharmaceutical firms and the Food and Drug Administration (FDA) to try to incorporate biomarker monitoring in clinical trials.
Lastly, I work locally with a forensic toxicologist who consults on the use of CDT for family custody cases and criminal cases. As local judges get more educated about CDT and other alcohol drinking markers they are requesting them prior to making judicial decisions. In the US, not many clinicians or laboratory workers know about CDT to even provide the education. Lack of knowledge has been a big stumbling block to acceptance of CDT in the US.

What tools are available to clinicians to assess a patient's alcohol use pattern?

There is a large need for proper screening across the US. Those assessing alcohol use tend to be addiction psychiatrists and internal medicine practitioners. They are more familiar with screening tools and more likely to use biomarkers as they are more educated. Still, it is a tough sell.

Primary health care providers are less educated and generally are reluctant to deal with alcohol problems, even though this comprises their patient care. Physicians mostly just treat the effects of alcohol abuse. Many physicians misdiagnose it and just supply antidepressants. They do not even know what to do when they identify a heavy drinker, or alcoholic. They just tell them not to drink, or to go to Alcoholics Anonymous. They often wonder why they should spend all the effort to diagnose when they think there is no solution. Also, they often do not believe that the patient will validly represent what they are actually drinking, so why ask!

Most physicians do not know the US federal government has agreed to pay through federal insurance programs for patients' alcohol screening. Some insurance companies also offer to pay for alcohol screening. Many people do not have medical care, insurance, or money to pay for treatment, but that is changing rapidly. A large segment of the US is covered by health insurance, as well as veterans. A few hospitals, state organizations, and outpatient clinics utilize CDT in their testing, but not many primary care practices. I had worked with Drs Peter Millar and Steve Ornstein who were funded by NIH to investigate primary care practices and screening for alcohol, and how alcohol relates to hypertension and diabetes. Heavy alcohol consumption is one of the primary causes of high blood pressure. They have been able to start working with primary care practices to use their electronic data records to start screening hypertension patients by asking a few basic questions about alcohol. The primary screening test called the AUDIT, a 10 question screening questionnaire developed by World Health Organization (WHO) and National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the US, which asks about amount and regularity of heavy alcohol consumption. There is an even shorter version that uses several questions that could be almost as accurate, as long as the patient is honest in their responses (which is not always the case).

What biomarkers are used to measure alcohol abuse, what are their indications of use and what are their positives and negatives?

In the US, though CDT was approved 10 years ago, there is not much uptake. It is slowly growing. The company that bought the rights to the initial product did not understand the market and gave up on it quickly.

CDT testing is available in a few big reference labs to which academic centers send samples. CDT is seen as a reference test rather than a standard lab test. The biggest problems are availability, perceived expense, and proper interpretation. It is most useful in situations where alcohol problems are suspected and you want to confirm whether there is in fact heavy alcohol use. CDT has a 70 % chance of picking up someone drinking 5-6 drinks per day on a continuous basis. One argument for non-adoption is missing 30 % of people, but the counter argument is identifying many people who would be missed, providing long-run cost savings and better treatment. A big positive for CDT is in identifying the heavy drinkers responsible for excessive health care utilization and costs.

Phosphatidylethanol (PEth) is a completely different test, measuring alcohol in red blood cells rather than in the liver. The technology is complicated which increases barriers to implementation. PEth specifically identifies alcohol use, but cannot distinguish between lower and higher level of alcohol use. Results are positive after several drinks a day which might not be harmful drinking. PEth is useful to monitor abstinence over a prolonged period (days to weeks) and is useful in certain settings, e.g. judicial programs and abstinence based treatment programs.

Ethyl glucuronide (EtG) is a very sensitive urine test measuring an alcohol conjugate product excreted through the kidneys. It is only positive for 24-48 hours after last alcohol use. It monitors complete abstinence, e.g. useful in judicial situations, health care professionals, airline pilots, child custody for previous alcoholics, and assessments prior to liver transplants for alcoholics where 6 months abstinence might be required.

What is the definition of CDT? What is CDT?

CDT is an abnormal form of transferrin, a liver protein transporting iron from the gastrointestinal tract to other organs where it is needed. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) workgroup has defined

CDT to be only the disialo-transferrin isoform of CDT.

What are the reasons to order a CDT test? When does it make sense to analyze CDT? What are the clinical settings?

Those are large questions. Clinically, where people personally request alcohol treatment, a test is not needed to identify them. For them, CDT is useful in monitoring alcohol use during treatment. It is similar to monitoring diabetics with hemoglobin A1c. It will go up and down depending on disease status, in this case drinking status. However, it could be useful for screening people in addiction settings who admit to drug use, but minimize alcohol abuse.
In general psychiatry it is used in both screening and monitoring. General psychiatrists are as poor at screening for heavy alcohol use as primary care physicians. Primary care screening is even more important. Patients identified in primary health care settings are often referred for treatment and monitoring by an addiction specialist, although newer models suggest that primary care providers should being doing this as well.
CDT is useful for acute care medicine, e.g. gastrointestinal complaints, where alcohol abuse is suspected. Charite Hospital in Berlin uses screening for pre-surgical evaluations, avoiding alcohol related surgery complications.
Use during pregnancy for fetal alcohol syndromes is not indicated since pregnancy can interfere with proper results interpretation.

What are the existing technologies for CDT testing and why are they easily usable in routine laboratories?

Originally immuno-based assays were commercialized. With the more general use of sophisticated chromatographic assays for CDT, more isoforms were identified. CDT test values were not consistent across methods. There is a feeling that there needs to be standardization of CDT levels. A workgroup has been working on a standardization process. Our lab is the only one in the US participating in this IFCC workgroup on the standardization of CDT using the most specific and accurate High Performance Liquid Chromatography (HPLC) assay with spectrophotometric detection (the one recommended by the IFCC workgroup as the reference assay worldwide). There are other commercial HPLC assay products. Several companies have developed HPLC kits that use

reagents and columns for measurement of CDT. It is still a relatively complicated procedure that uses sophisticated machinery, and highly trained technicians to run them. Then, there is capillary electrophoresis. Though I have never tested it, the isoform detection is similar to HPLC, but not currently calibrated* to the reference HPLC method. Most academic labs have capillary electrophoresis (CE) machines which can be used for CDT testing. Then there is an amino-based assay, the N Latex CDT kit, which uses an antibody based method to measure CDT. It does not correlate that well with the other assays. That one is fairly widely used, and automatable and with the high throughput.

What are the advantages of CDT compared with more traditional markers like Gamma-glutamyltrans-peptidase (GGT)?

The biggest advantage for CDT is, that it is more sensitive: sensitivity of 30-40 % for GGT, compared to 60-70 % for CDT. GGT is less specific ; GGT can be elevated by other forms of liver pathology, hormones, drugs and even obesity. Only severe liver problems may falsely elevate CDT and the chromatograhic assays can detect these false positives. GGT takes more drinking to elevate it again during relapse drinking, while CDT goes up and down more precisely in relationship to relapse drinking.

Can an advantage be gained by combining CDT and GGT?

You can get an advantage by using both CDT and GGT together, especially if you can rule out other causes of GGT elevation. I am sure you can also improve detection and monitoring by also using PEth and EtG together with CDT and GGT. One could envision an Alcohol Lab Panel where all of them are measured.

* Sebia is currently working on the implementation of the IFCC Harmonization of CDT (2014).

“I went to the courts and said we have a CDT test, which is an objective test that will provide strong evidence if a person is abusing alcohol.”

Robert BENNETT

Robert BENNETT

Academic background

Robert Bennett has extensive experience as a forensic toxicologist, expert witness, forensic pharmaceutical scientist, and consultant, and in that capacity has provided case analysis, affidavits*, depositions, trial testimony, cause and effect relationships, and forensic examination, with a major focus on alcohol, drugs and toxicology.

General presentation

Robert Bennett has two degrees from the Medical University of South Carolina: a PhD in Pharmaceutical Sciences and a Pharmacy degree. He is full-time Forensic Scientist and Forensic Pharmaceutical Expert and has testified in many cases in various courts as an Expert Witness. He is also a qualified expert in Forensic Toxicology, drug testing, alcohol testing and Deoxyribonucleic Acid (DNA) testing. He also has extensive experience in testing for toxic substances, chemicals, medicines and abusable substances for criminal, domestic, DSS, and federal cases.

Robert Bennett founded the first drug and alcohol testing company in Charleston, SC, over 20 years ago and has directed, performed, and reviewed over 31,000 drug and alcohol tests. Robert Bennett was the toxicologist overseeing the 5-year construction of the largest cable-stayed bridge in North America. He introduced Carbohydrate Deficient Transferrin (CDT) testing for forensic use to detect heavy alcohol use and is the only forensic provider in the state to do so.

The USA experience

How much of a problem is alcohol in the US? What prevention campaigns, and alcohol programs are in place, and how effective are they?

There are some important statistics that detail the problem of alcohol in the US. Here in the US we have the National Highway Traffic Safety Administration (NHTSA), a governmental agency that monitors the safety of our highways and traffic. The statistic of primary concern is the number of traffic deaths in the US. We have an alarming number of traffic deaths in the US. In previous years, on average 40,000 people died per year on the roads. The most recent statistic is 32,885 people died in traffic crashes in the US in one year. Over 10,000 of those, approximately 1/3, died whilst clinically drunk. Thirty (30) deaths per day involve an alcohol-impaired driver; 1 death every 48 minutes. The cost of this is phenomenal. The annual cost of alcohol-related crashes is USD 51 billion. Among the drivers with a prior conviction for driving under the influence of alcohol, 42 % were involved in a fatal crash and had a blood alcohol level that was over twice the legal limit. In the US, when people do drink and drive, they drink excessively, usually over two times the legal limit. People that drive with an elevated blood alcohol concentration are 9 times more likely to have a prior conviction for driving whilst impaired.

In my view, the problem in this country is repeat offenders. When people are involved in an accident whilst alcohol impaired, you would think that it would be a wake up call and they would not drink and drive again. We are not seeing that. There are a vast number of people who repeatedly drink and drive.

Where we see most deaths is with younger adults. Even though alcohol is a big problem in the US, there are many governmental agencies and private agencies that try to combat the problem. One is called the Substance Abuse and Mental Health Services Administration, which works hard with taxpayers support to educate Americans on the dangers of alcohol. One of the largest organization we have is Mothers Against Drunk Driving (MADD). Members of the group have lost a child due to drunk driving. They are very large, powerful and influential. The latest from MADD is the push to get ignition interlock systems installed in vehicles, an alcohol detection method in the vehicle that requires the driver to blow into with alcohol-free breath to allow the car to start. I have worked with a number of repeat offenders, and my biggest concern is parents driving their kids in their car. They get their children to blow into the lock, so there are ways around the interlock devices. However, CDT testing could play a wider role in that.

Alcohol is the No. 1 drug killing more teenagers than all the other drugs combined. Drinking in college is a massive problem. The latest figure is 1,825 college students between 18 and 24 died from alcohol-related injuries in a year. Each year, approximately 600,000 students are injured due to alcohol, 700,000 students assaulted by others under the influence, and 97,000 are victims of alcohol-related sexual assault. Ninety percent (90 %) of students meet the criteria for alcohol abuse, or alcohol dependency, but only 5 % of these students seek treatment for their alcohol problem. So the problems of alcohol starts young.

In US schools and colleges, there is currently a big push to address the huge problem of alcohol on campus. So there is a relatively new impetus from the government to get colleges to address their alcohol problems and do something about it. I am working with some colleges in my area to provide seminars and education materials and help develop policies that are more strict when alcohol abuse has resulted in severe consequences, such as accidents on campus, property damage, injuries, fighting and sexual assaults.

Have you made a contribution to an alcohol testing policy? What are the implications, which actions have you taken?

When I learnt what CDT testing could do, I was already working in the legal field. I looked to see whether CDT testing was used in the legal field and discovered it was not used anywhere in the country. About 7 years ago, I took it upon myself to take CDT testing into the legal field and have the courts use it as a tool in dealing with cases involving alcohol. I have developed a chain of custody system so it can be used in court, developed a forensic collection procedure and I provide seminars and training and education programs for judges and lawyers. I also testify in court on CDT testing. Every time I, or another CDT expert, testifies in court on a specific case, it lends credibility to the test. For example, when DNA testing was originally used in court, its credibility was questioned. The more it was used, the more it was accepted. My goal is to do the same with CDT, and have it used in court cases over and over again to the point it is accepted in every court across the country.

Right now, my campaign is to educate attorneys and

judges on the value of CDT testing with repeat offenders. The first time a person is arrested for drunk driving, they go through the booking process, then they go before a judge where they typically promise never to do it again. At this point, I want them to take the CDT test. If they are negative, then they would get leniency and a reduced sentence. However, if they fail the CDT test with a positive result, the judge should not show leniency and they do not get their license back until they pass the CDT test. I am pushing for judges to use CDT as the key element as to whether or not driver's licenses are returned. That should do a great job in eliminating repeat offenders, which is where the biggest problem lies. That is my biggest campaign so far.

In criminal courts, there are many cases of what is known as 'alcohol induced crimes'. These are all types of crimes that people claim are committed when they are under the influence of alcohol. Blaming alcohol, they say, "If I was not drinking, I would not have done that and if I stay sober, I will not commit crimes." The response should be that if you blame alcohol as the cause of you committing these crimes, and if you stay alcohol free for the rest of your life, it will reduce your sentence and you will have to take CDT testing for the rest of your life. I want to implement that into the criminal courts for alcohol related crimes.

Outside criminal court, there is a need for CDT testing in family courts. This is where I am most often using CDT currently. This is where I was able to introduce CDT testing and it has been well accepted. Many divorces occur because of a claim of habitual drunkenness, which is a legal basis for divorce in this country. The courts will grant divorce based on that, but you have to prove your spouse is a habitual drinker. Up until the advent of CDT testing, the only evidence we had were, for example, pictures of the spouse coming out of the bar or pub, or passed out on the sofa, smelling of alcohol. This evidence was very subjective. I went to the courts and introduced CDT testing, which is an objective test that will provide strong evidence if a person is abusing alcohol. The judges overwhelmingly accepted CDT testing.

Even more importantly, the judge has to decide who gets custody of the children. Courts do not want to place children in the home of habitual drinkers. Family courts then order the person accused of habitual drinking to go through CDT testing with me to determine whether or not they are abusing alcohol. If they pass, they can get partial or full custody of their children. If they fail, then they can, at most, get supervised visitation, but no custody until they can prove they can pass the CDT test.

What tools are available to clinicians to assess a patient's alcohol use pattern?

It is very limited. Clinicians that I work with look at the patients' physical appearance and behavior. There is an interview about how alcohol is affecting their personal life and work, relationships etc, but they rely on the subjective answers of the person they are interviewing. Research, and there is published scientific studies in medical literature on this, proves though scientific study that people will consistently underrate their alcohol consumption patterns. So when a physician asks what degree of alcohol consumption is in their life, they will underrate that by a significant amount. Relying on an interview, makes it impossible to know a true alcohol use pattern.

What biomarkers are used to measure alcohol abuse, what are their indications of use and what are their positives and negatives?

We have had some old tests in the past: Gamma Glutamyl Transferase (GGT), Aspartate Transaminase (AST) Alamine Transaminase (ALT) liver enzyme ratios, Ethylglucuronide (EtG), even simple blood alcohol testing, but those tests really do not give us a view of alcohol dependence. That is the value of the CDT test. The other tests have significant limitations. The GGT liver enzyme test had been used for decades to detect if someone is an alcohol abuser. However, other substances and medications can elevate GGT, as well as factors such as liver disease. CDT is much more alcohol specific. EtG does not measure heavy alcohol use, it measures any alcohol use, and it only does that within a short time of alcohol use, a couple of days at most.

What is the definition of CDT? What is CDT?

CDT is a protein that allows for the movement of oxygen and transport to cells. When the body is

exposed to alcohol on a consistent basis, the alcohol will chemically cleave the carbohydrate groups off the transferrin molecule, the protein then becomes carbohydrate deficient. In the US, the FDA has approved the use of CDT testing as a biological marker for heavy alcohol consumption. I get asked frequently "what does heavy mean?" It is hard to define. The clinical definition based on clinical evaluations is, for most people, the consumption of multiple drinks typically (3 or 4) on a daily basis, as part of their ongoing lifestyle. A bottle of beer, a mixed drink, or a glass of wine will have roughly the same amount of alcohol – about 0.6 ounces (14g) of ethanol. Each individual beverage has the same amount of alcohol. So scientists took people that consumed 3-4 alcoholic beverages daily, measured their CDT levels, and established that baseline.

What are the reasons to order a CDT test? When does it make sense to analyze CDT? What are the clinical settings?

CDT detects heavy alcohol use on typically a daily basis, but does not determine alcoholism. That is a clinical definition based on a variety of factors. CDT also does not determine episodes of heavy drinking, intoxication or binge drinking. Binge drinkers could pass the CDT test. Someone sober during the week, totally drunk all weekend and doing that on a regular basis could still pass the CDT test, because their body has a chance to heal or recover during the week.

The reasons for me to order a CDT test, is any time there is a situation where there is a concern about heavy alcohol use. Assessment could include counseling sessions, whether personal, marriage or financial counseling. This should be addressed by the counselor, saying "lets talk about alcohol in your life and see if that has any impact on why you are here in counseling." In our research, we found that alcohol can be a very strong component in a person's need for counseling. Currently, counselors typically will not address that. Every counselor should include discussing the impact of alcohol use within the counseling, and CDT should be used to determine whether heavy drinking is an influencing factor.

As one example, I have talked with financial counselors helping people that are not doing well with their finances or in investments because of their alcohol intake. The problem with poor financial investments often causes them to get upset and turn to alcohol, which perpetuates the problem. Alcohol is relied upon as a crutch, which alleviates the problem only temporarily.

I have had many people in my office who have failed a CDT test and it really shocks them. They often say that they refused to believe people telling them they have an alcohol problem, but seeing the test results in black and white confirms this, and helps them assess their own personal lifestyle.

It would be my goal to have every family aware of the CDT test, and that it can be taken on an individual basis if needed. Drugs are a big problem in this country. You can buy drug testing kits in food stores or pharmacies where you can confidentially test yourself, spouse, or children. This gives you an idea, on a personal level, whether drugs are involved. In the future, in my view, there needs to be some sort of method where everyone is aware of CDT testing and can have a test done confidentially. This will be easier once we have overcome the blood draw requirement.

Physicians essentially treat people because they are sick for a variety of reasons. They prescribe medication for that illness. There are a staggering number of medications that are influenced by alcohol, as stated on warning labels. However, I am finding many people in the US are not heeding those warnings. They are taking the medications whilst still drinking alcohol and they are having bad reactions to the combination, sometimes deadly. Physicians should be aware that for any medications with which alcohol should not be utilized, they should require a CDT test from the patient to show they are not using alcohol heavily.

Though CDT is used to a certain extent, there are many other areas CDT could play a much bigger part.

What are the existing technologies for CDT testing and why are they easily usable in routine laboratories?

There is capillary electrophoresis. Some of the labs are using latex agglutination which in my opinion is inferior for CDT testing. A lab I work closely with is using HPLC, which is a highly specific type of assay to detect CDT quantity. There are a variety of technologies. However, capillary electrophoresis and HPLC are the premier technologies for CDT testing. Nowadays, capillary electrophoresis can easily be used with a desktop analyzer, the same analyzer that could be used for other routine lab procedures, so the CDT test could be used relatively easily and inexpensively.

As a result, even in doctor's offices, as well as labs, the capillary electrophoresis CDT test can and should be included in routine procedures.

What are the advantages of CDT compared with more traditional markers like GGT?

We have already discussed that GGT has its limitations, affected by a variety of non-alcoholic conditions, so with an elevated GGT we cannot automatically assume it is alcohol. However, we can with CDT. We can quickly rule out any other causes of elevated CDT levels other than alcohol. So the specificity for alcohol is there.

What are the conditions that may affect the diagnosis?

Because individuals vary genetically, we have experience with the phenomenon that some people can drink more than others. There is a genetic and biological basis for that. There are some generalities. Males can handle alcohol better than females. One reason being females have less total liquid body volume than males so alcohol is more concentrated in females. We can adapt that to people's sizes as well. A 100 lb man (45 kg) is not going to handle as much alcohol as a 200 lb man (90 kg).

This comes back to my question I am asked often – "What is the definition of heavy alcohol abuse?"

Heavy use is very individualistic to the person and can vary widely. On average, however, there needs to be 3-4 drinks per day to be positive, even if extremes may occur.

Can an advantage be gained by combining CDT and GGT?

Yes, all the CDT testing I do has GGT testing with it as well. CDT allows me to determine whether there has been at least 1-4 weeks of heavy drinking. However, if a person abstains for 1-4 weeks, they can pass the CDT test. GGT takes longer to return to normal. Another reason to combine GGT and CDT is that they test two different biomarkers. A previous study** tested both together, which reported the sensitivity of the CDT test was around 0.52, which I believe was 50 % of the people tested. The GGT was 0.54. However, when combined, the sensitivity jumped to 0.76. We are able to raise the sensitivity of each test by combining the tests. The study used an older CDT method. With new CDT testing methods, combined with GGT, we are raising specificity for alcohol to near 95 %.

In summary, the CDT test has such wide spread application that it should be used more often than DNA testing, and in dealing with the toll alcohol causes worldwide, CDT testing could save countless lives.

**Allen, Litten, Anton, and Cross, Alcohol Clin Exp Res. 1994 Aug;18(4):799-812.

**Litten, *et.al.*, Alcohol Clin Exp Res. 1995 Dec;19(6):1541-6.

*Affidavit is a formal sworn statement of fact, signed by the declarant (who is called the affiant or deponent) and witnessed (as to the veracity of the affiant's signature) by a taker of oaths, such as a notary public.

“Traditional liver function tests like GGT are often used, though GGT is not very sensitive or specific for alcohol related effects. CDT in serum is frequently used in Sweden, and also in some other European countries. Most Swedish laboratories analyse CDT on a routine basis.”

Anders HELANDER

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Academic background

Anders Helander is Adjunct Professor in Dependence Research at the Department of Laboratory Medicine at the Karolinska Institute (Sweden). He is a researcher in alcohol biomarkers and has done a lot of teaching and education in these matters.

General presentation

Anders Helander's work aims to identify, evaluate and introduce a panel of more sensitive and accurate markers for the hazardous drinking and alcohol abuse diagnosis. With his group, he also aims to determine optimal clinical applications for these markers in detection, prevention, and rehabilitation of persons with alcohol-related problems. Finally, he aims to find bio-analytical methods for these markers being suitable for routine application in routine laboratories, to allow for a widespread use. He has published many peer reviewed papers related to this matter in International journals.

The Swedish experience

How much of a problem is alcohol in Sweden? What prevention campaigns, and alcohol programs are there, and their effectiveness?

Overall alcohol is a major health problem. Swedes have a tradition to binge drink at weekends, but nowadays continental habits have increased the popularity of drinking wine and beer during weekdays as well. Overall, the alcohol consumption in Sweden, which used to be low in comparison to the rest of Europe, increased about 10 years ago resulting from changes in both tax regulation and limits of alcohol imports. Average intake rose to 10 liters per person per year.

This level has now started to go down slightly partly because teenage people tend to drink less. There seems to be more reduction amongst young men than women. One theory is that as young boys play computer games more, they cannot be drunk because if they are, they lose. However, another problem is that they instead drink lots of energy drinks, and are far less physically active.

In Sweden there is a state monopoly for alcohol, and there are legal limits for providing alcohol to young people. Those together with a relatively high tax level are the standard ways (i.e. availability and cost) of alcohol prevention. There have been national campaigns to reduce smoking, but nothing similar for alcohol, although the temperance organizations have regular activities aiming for abstinence.

Have you made a contribution to an alcohol testing policy? What are the implications, which actions have you taken?

In my research, we have developed, evaluated and introduced in routine clinical use a number of new and improved alcohol biomarkers. I also do a lot of teaching and education in these issues.

For example, I was engaged by the government to make company healthcare workers understand the value of screening for risky alcohol consumption and how this can be introduced in daily work, using biomarkers and questionnaires in combination and giving feedback to employees. I have also written instructional papers published in the Swedish Medical Journal with proposed recommendations for routine testing of alcohol use and abuse and early detection of risky drinking. At the Karolinska Institute we continuously give courses to doctors and nurses working in company healthcare and to laboratory personnel on how to test, which tests to use in which circumstances, and how to deal with the results.

What tools are available to clinicians to assess a patient's alcohol use pattern?

Clinicians use questionnaires, like the AUDIT developed by the WHO, either on paper or computer, and take blood and urine for biomarker testing. Traditional liver function tests like GGT are often used, though GGT is not very sensitive or specific for alcohol related effects. CDT in serum is frequently used in Sweden, and also in some other European countries. Most Swedish laboratories analyse CDT on a routine basis. People working with alcohol related problems are well aware of the CDT test. More recently we have introduced EtG in urine and PEth in blood as short, medium to long-term tests. So today there are a number of routine tests that cover different drinking amounts and different time windows. We regularly teach people how to use them and what improvements have been done in terms of analytical methods, sensitivity and specificity, etc. I recently published a review of these biomarkers in the Swedish Medical Journal.

What biomarkers are used to measure alcohol abuse, what are their indications of use and what are their positives and negatives?

Liver function tests like GGT are frequently used as tests for alcohol abuse but they suffer from being insensitive and unspecific for recent risky drinking. CDT has a much higher specificity for alcohol, so you know a markedly elevated test result is due to alcohol. However, CDT doesn't catch all the people that are drinking highly.

PEth is a new blood test that has become very popular in Sweden. PEth is a metabolite of a phospholipid and ethanol. No alcohol means no PEth in the blood. We now need to do a lot of the same background research on PEth that we had done years ago for CDT. In comparison with CDT, PEth can detect regular moderate or low drinking and can distinguish heavy drinkers.

We also routinely use the urine EtG test, usually in combination with Ethyl Sulfate (EtS), which is a short-term alcohol biomarker. Analyzing urine for EtG and EtS can detect drinking up to 3 days after ethanol is no longer detectable. It is a specific and sensitive test, but sometimes too sensitive. Even "alcohol free" drinks (in Sweden beverages containing less than 0.5% ethanol can be sold as alcohol free) can produce a low but positive EtG and EtS test. It is therefore important to use a sufficiently high cut-off to eliminate unintentional alcohol consumption.

There are many clinical and medical-legal applications for alcohol biomarkers. In traffic medicine, for example, when re-applying for driving license that has been lost due to drunk driving, you must take a number of tests, like GGT and CDT, to exclude excessive drinking. There is also the possibility to install an alcohol breath test device (alcohol interlock) in the car, which will not start when alcohol has been consumed.

What is the definition of CDT? What is CDT?

CDT is the alcohol-induced change in the profile of transferrin, a common plasma protein. As an alcohol biomarker CDT most importantly covers a well-defined drinking quantity and time window and, compared with liver function tests, has a much higher specificity for alcohol. Today we know a lot about risks for analytical interferences by genetic transferrin variants, etc.

What are the reasons to order a CDT test? When does it make sense to analyze CDT? What are the clinical settings?

CDT is used in many different clinical settings. People treated in hospital care often have undetected alcohol related problems, which could influence their treatment, e.g. in surgery there is a much higher risk for post-operative complications with alcohol. This is the same with smoking. Then we can identify risk patients with biomarkers like CDT. Furthermore it is very important to use CDT and other biomarkers in outpatient treatment of alcohol and drug addicts. Also it is a good healthcare test for companies. We know that eating the wrong food, taking too little exercise and drinking too much is less good for health. Many companies now use CDT as a healthcare test, though it is important to distinguish this use from workplace drug testing programmes.

What are the existing technologies for CDT testing and why are they easily usable in routine laboratories?

In our laboratory we routinely use high-performance liquid chromatography (HPLC) for CDT testing because we are experienced using it and because it gives a visible result of the transferrin pattern. We have developed an HPLC candidate reference method that is used also for research projects. Other methods for CDT testing include capillary electrophoresis and immunoassay, and you may combine the different techniques. For example, we published a study on the combined use of capillary electrophoresis for CDT screening and with HPLC as a verification method. This is in analogy with the routines for testing of illicit drugs, where we use immunological screening and then confirm positive screening results using mass spectrometry, which is more selective.

What are the advantages of CDT compared with more traditional markers like GGT?

Given the way alcohol biomarkers are often used as “drug tests”, it’s essential to only use specific tests.

A major advantage of CDT over liver function tests is its much higher specificity for alcohol, implying a much lower risk for generating false-positive indications of alcohol abuse.

What are the conditions that may affect the diagnosis?

We know of several genetic variants of transferrin that may cause analytical interference in CDT testing, but we can detect those using the HPLC or capillary electrophoresis methods, so there is no risk for false positives which is a good thing. In most cases we can still estimate the CDT level into “positive/negative”, but if this is impossible we recommend PEth as an alternative test. In our laboratory we routinely list all patients, so if they had already been classified with a genetic variant, we can adjust accordingly.

Can an advantage be gained by combining CDT and GGT?

I usually recommend combining alcohol biomarkers (CDT) and liver function tests (GGT), for many of the reasons listed above. There is seemingly no direct health issue having a high CDT, but there is having a high GGT, because this indicates your liver is not working properly. Some treatments such as Antabuse may induce liver damage so then GGT testing is necessary. And it is the same serum sample, you do not need to take different samples.

"We also use CDT, especially helpful for long-term patients and purposes. If we have been controlling a patient's sobriety a long time, CDT can tell he is drinking."

Otto Michael LESCH

Otto Michael LESCH

Academic background

Otto Michael Lesch is currently president of the Austrian Society of Addiction Medicine, Head of the Addiction Medicine Research Group at the Medical University of Vienna.

General presentation

Otto Lesch has been responsible for long-term studies in alcohol dependence since 1972 and has organized a large number of international clinical trials and basic research studies in alcohol and tobacco dependence. He developed clinical assessment tools to define sub-groups of addiction for better treatment approaches and the Lesch Typology, devised by Otto Lesch himself, is used to categorize patients with alcohol dependence into four subgroups. Otto Lesch was the secretary of the European Society for Biomedical Research on Alcoholism (ESBRA) for 12 years.

The Austrian experience

How much of a problem is alcohol in Austria? What prevention campaigns, and alcohol programs are there, and their effectiveness?

Thirty per cent (30 %) of males and 15 % of females abuse alcohol. There is a relationship between alcohol and tobacco. However, 7 % of the global population are susceptible to any kind of addiction, including alcohol dependence. Our main drug is alcohol. At internal treatment centers, nearly 30 % have higher CDT, a specific marker of excessive alcohol consumption, levels at admission. This means they are drinking more than 80 g pure alcohol per day for over three weeks before their admission.

There are a lot of prevention programs. Information in schools, centers for little children and other programs. A lot of money is spent on the problem. In my opinion they are not well organized, very low quality and do not really touch the problem, just information - leaflets, and some TV and radio. There is nothing for young people. The problem is you need not just alcohol prevention but solutions for young people. This includes positivity of education and work. An increased unemployment rate for young people (between 18 and 25) means a lot of problems. A decrease of that would be a good start. A good example is Finland, which is the best country in Europe for prevention, what is to be done in schools if a young person has problems, and to get help as fast as possible. They think the life of a young person in Finland is so important because there do not have many young people.

Have you made a contribution to an alcohol testing policy? What are the implications, which actions have you taken?

I have been working in this area since 1972. I am now the president of the Austrian Society for Addiction Medicine (AUSAM). We work on detecting and planning treatment. It is essential to decrease the perception that alcoholics are bad guys. We have a lot of trials. As an example, we investigated 8,000 18 year old girls and boys and we looked at the parents, what happens during birth, behavior, disturbances in childhood, and then drinking, smoking and drug use. These factors are critical. Our work has been published in a lot of journals. However, we are also working on heterogeneity of this disease. There are many reasons people drink. Because they have withdrawal symptoms, anxiety states, depression, or compulsive behavior. We then work out subgroups, and different treatments and medicines.

What tools are available to clinicians to assess a patient's alcohol use pattern?

We have developed our own diagnostic instrument, www.lat-online.at a free alcoholism test and treatment program. It is in 14 languages, and divides the subject into a sub group giving a tailored treatment program for that person. There has been a lot of research on this from US, Europe and Brazil. We are also working on biological markers to detect alcoholism. I have been closely involved in the development of CDT linked with 2 different methods, which are still on the market.

We are also seeing the differences of patients in different situations. I.e. those in a homeless shelter or psychiatry are significantly different kinds of patients. We completed one study, where just 1.4 % sought specified treatment, 98.6 % did not go to specialized treatment, they went to their general practitioner (GP), social shelters, and so on. So it is very important for specialists to reach the GP's. There is too much ideology in this area, and less evidence based medicine. Therefore we are working hard to develop who can stop completely, and who can just reduce their drinking intake in a 'step down' drinking program. This has really worked in Finland and also accepted by FDA 1994. It is a mistake just to switch patients from one addiction to another, like alcohol to tobacco, they will all just die of lung cancer. Tobacco is more poisonous than alcohol.

You just talked about biomarkers. What are the main biomarkers used to measure alcohol abuse, what are their indications of use and what are their positives and negatives?

Biomarkers are most helpful when linked to questioning and with talking to the patients. You need to ask the right questions first. Not about drinking, but disturbances encountered by the patient, which most have had. Then ask does alcohol help or worsen the troubles and how much alcohol they need to help. If a patient drinks half a

bottle of vodka to deal with problems or anxiety, then both of you start to understand the problems and effects of the alcohol. Another critical set of questions is how much a patient drinks before they get drunk and the drinking pattern. What did they do in the last week and then ask how much they drink for each situation, at home, playing tennis, etc.

The most important biological marker is alcohol in breath. Then we measure blood alcohol and liver enzymes. Some patients do not like to talk about drinking at first, and we use an alcohol-screening program.

We also use CDT, especially helpful for long-term patients and purposes. If we have been controlling a patient's sobriety a long time, CDT can tell he is drinking.

We cannot use CDT as marker with severe end stage liver disease (Child-Pugh Score C) since in these conditions liver metabolism is too disturbed. I wrote about that as far back as 2001. We use CDT to control patients after liver transplantation. There is a large center for liver transplants in our hospital.

What are the reasons to order a CDT test? When does it make sense to analyze CDT? What are the clinical settings?

CDT is important especially with liver disease patients (Child-Pugh Score A and B). CDT will detect a lot of drinking. CDT is important if a patient is going for surgery, to check whether they will encounter side effects and the withdrawal effects, as there is a lot more side effects after surgery for alcohol dependent patients. Ten percent (10 %) of schizophrenic patients abuse alcohol. CDT detects this fact and then they need a significant different treatment. Other psychological disorders, epilepsy, diabetics and a range of other chronic conditions are influenced by alcohol abuse. It is essential to identify these alcohol-abusing patients with different chronic somatic diseases, because they have a different biological vulnerability. Use of alcohol stops many drugs for these conditions from working properly. Screening methods just to control patients are not so important in my opinion.

What are the advantages of CDT compared with more traditional markers like GGT?

GGT is too unspecific for alcohol, with too much false positive data. One third of alcohol dependent patients are not sensitive to alcohol and show normal liver enzymes and also normal Mean Corpuscular Volume (MCV), but also alcohol dependent patients admitted to alcohol treatment have only in 63 % increased CDT levels.

There are a lot of improvements that still need to be done. We need to understand CDT more from a genetic point of view. We need markers with more sensitivity. A combination of markers, which has been known for many years now, increases this sensitivity (alcohol breath, AST, ALT, GGT, MCV and % CDT), DeRitis Factor (AST/ ALT) together with % CDT are at the moment the best markers to detect clinically relevant chronic alcohol abuse. GGT alone is too unspecific and not sensitive enough.

"To follow chronic use, CDT and GGT combined are truly the best markers indicated. They change relative to consumption and can serve as monitoring tools. CDT is more sensitive and specific while GGT may be positive in the absence of CDT."

Michel REYNAUD

Michel REYNAUD

Academic background

Michel Reynaud is a Professor of Medecine and a Psychiatrist and is currently Head of Psychiatry and Addictology Department at the Paul-Brousse Universitary Hospital (Villejuif, Paris, France).

General presentation

Michel Reynaud is the author of numerous books including « Les pratiques addictives » (Odile Jacob, 2000), « L'amour est une drogue douce… en général » (Robert Laffont, 2005), « Traité d'Addictologie » (Flammarion, 2008), « Addiction au cannabis » (Flammarion, 2010), « Addictions à la cocaïne » (Flammarion, 2011).

The French experience

What is the situation with alcohol in France?

Overall in the past 30 years there has been a downward trend in alcohol consumption. Alcohol consumption has declined by three-quarters, decreasing from 30 liters/person/year to 10 liters/person/year. France which topped the list of heaviest drinking countries is now third in Europe.

The significant change is that daily wine consumption has slightly decreased.

However, beer and spirits consumption is stable or increasing. Young men (30-35 years) and women are the most at-risk populations. In these groups, there is a developing of anglo-saxon type behaviours, like *binge drinking*, that are rapidly very harmful.

This is encouraged by a change in the legislation and by an authorization of internet advertising.

What prevention campaigns, and alcohol programs are there, and what is their effectiveness?

For prevention campaigns, France could do better. It recently ranked 27th/30 for alcohol prevention campaigns. Drink driving prevention is the only field where it is not too bad.

There is no change in sight in this field because of a strong alcohol lobby, in particular winegrowers.

They are always up in arms against new laws and they also have the support of political decision-makers.

How is a patient managed? Are the resources available today sufficient? How can we improve patient care?

There has been a change over the last ten years. We went from a moral struggle to the medical care. Alcoholism was recognized as a disease, which resulted in the establishment of health care structures dedicated to fight against alcohol and others addictions. However France could do better in this area too.

This would include increasing the identification in hospitals. Many hospital stays are due to alcohol. More than half of the crimes in France are committed under the influence of alcohol. At the Emergency department, many injuries are directly related to alcohol.

In addition, there are not enough means of support and they do not meet the major social costs caused by alcoholism.

It should also be noted that there is very little scientific research on this issue and that the subject in hardly addressed during doctors training.

How should a patient who has an alcohol problem be approached, what are the means available to the clinician? How can we diagnose excessive alcohol consumption?

In specialized care structures, diagnosis is not difficult as we are used to doing it. What is more difficult is to determine the level of addiction and to implement a program of care and treatment.

For front-line players (Emergency Medical Services, family physicians, occupational health doctors), the strategy to address and diagnose a patient is less obvious.

There are questionnaires such as the CAGE or the AUDIT. There is also a strategy validated by the WHO for early detection and short-term intervention. However, there is a severe lack of training and only a few physicians benefit from it. They cannot rely on a competent network and lack of knowledge to make the diagnosis.

Beyond diagnosis, how are these patients monitored?

This is a complicated disease, which takes time and requires a real personal investment from the caregiver.

Monitoring is based both on clinical means, such as monitoring of consumption and its consequences, and on non-clinical means, such as the biomarkers.

What is new today for the care and treatment of these patients? Is abstinence still the objective?

Today, the objective is not necessarily abstinence. The aim is rather to reduce the consumption to gain patient acceptance.

What is complicated is that there is no biological criterion for identifying patterns of addiction. Who will be able to stay sober, who won't be?

There are brain addiction markers, which are determined by Magnetic Resonance Imaging (MRI), but we are only at the research stage in the area.

What is the role of biomarkers, especially CDT in this new approach?

In our practice, biomarkers are important because they are objective witnesses to the state of consumption.
The most effective markers are CDT and GGT and the combination of these two markers is more efficient than the isolated use.
However, in general or occupational medicine, CDT is less used because general awareness is not very good. GGT is more used as a marker but it is less specific.

CDT is a marker of chronic alcohol abuse that reflects the consumption of previous weeks. Can it be helpful to control a “reasonable” consumption?

To follow chronic use, CDT and GGT combined are truly the best markers indicated. They change relative to consumption and can serve as monitoring tools.
CDT is more sensitive and specific while GGT may be positive in the absence of CDT.
The CDT is not an on/off marker. We are talking about a pathological area. Any increase is proportional to alcohol consumption. We can therefore determine a threshold and monitor consumption.
With a regular measurement of GGT and CDT, you can follow-up the consumption compared to a baseline, although the base may differ from one individual to another.
Communication work around these markers should be done. This would help to change the unscientific and blind look taken on alcohol problems in France.

"CDT is slowly coming of age as the best marker of chronic excess alcohol intake.
Unlike GGT, CDT is not abnormal in fatty liver, obesity, diabetes or hepatitis. CDT reflects alcohol intake not liver disease."
Roy SHERWOOD

Roy SHERWOOD

Academic background

Roy Sherwood is Consultant Clinical Scientist in the Department of Clinical Biochemistry at King's College Hospital, London, a post he has held for the last 24 years. He is also Scientific Director of KingsPath and Professor of Clinical Biochemistry at King's College London. He has been involved with CDT testing for the last 15 years. He has been an advisor to both the Department of Transport and the Driver and Vehicle Licensing Authority (DVLA) on the use of CDT testing and is the co-author of the textbook Liver Disease and Laboratory Medicine, published by the Association for Clinical Biochemistry. He has published over 180 peer reviewed papers and 20 reviews/book chapters.

General presentation

About King's College Hospital

King's College Hospital is a major teaching hospital located in South London with over 5000 staff, providing a full range of hospital services for local people and specialist services to patients from further afield. King's is recognised internationally for its work in liver disease and transplantation, heart and brain surgery, blood cancers (such as leukaemia), stoke and major trauma.

The British experience

How much of a problem is alcohol in the UK? What prevention campaigns and alcohol programs are there and how effective are they?

That is an interesting question. From assorted figures from 2005-2012 there are 1.6 million alcohol dependent individuals. Nearly 90 % of the UK population consumes some alcohol and the cost is GBP 25 billion a year. It is quite frightening. Overall, 20 % of hospital admissions (1.2 million in 2011/12) are alcohol related and that rises to 25-40 % on weekends. Most admissions represent chronic alcohol issues, but also accidents, falls and fights caused by alcohol; about 50 % of all violent incidents are committed by intoxicated people.

There has been recent debate about changing the drink-drive breathalyzer limit from 80 mg/dL to 50 mg/dL to fall in line with many European countries. This could save a large number of both fatal and general accidents.

In the last 10 years drink related deaths and alcoholic liver disease have been rising with a 20 % increase in a decade in the UK. This contradicts the European Union where the general trend is a slow and steady fall. Absolute alcohol consumption in the UK was 4.5 litres per person in 1961, peaked at 9.5 litres in 2003 but has fallen slightly in 2011.

In the UK alcohol related liver disease or other conditions are increasing, with no signs of a change. However, little action will be taken in the foreseeable future. The UK government has made it clear in 2013 it has no wish to follow Scotland on a minimum pricing policy for alcohol or to change current drink-drive limits. So the way the government seems to be viewing it is "Oh dear, that's a shame, oh well, there's not a lot we can do about it".

One of the big changes we are seeing is supermarkets pushing cheap priced alcohol, especially 'alco-pops' with a higher alcohol content over wine or beer. The result is people get tempted. Alcohol has also become relatively cheaper per unit over the last 10-20 years.

We are working with our Scottish colleagues on alcohol consumption during pregnancy that can result in foetal alcohol syndrome. Currently, some evidence suggests lesser degrees of impairment can occur with alcohol consumption during pregnancy without the full-blown syndrome. There is significant variation in the incidence of foetal alcohol exposure with the geographical area. A pilot study in Glasgow using CDT to identify problem drinking in pregnancy was published in 2013.

Have you made a contribution to an alcohol testing policy? What are the implications, what actions have you taken?

We carried out a study funded by the UK Department of Transport on the use of biochemical markers for identification of continuing alcohol misuse in 'High-Risk' drink-drive Offenders (HRO) seeking return of their driving licence. These are defined as those on their 2nd offence or more than 2 times the limit of the breath test; there are over 25 000 such cases per annum.

The historic policy was to use GGT and MCV as biochemical markers along with clinical assessment. However, GGT increases in any case where fat is deposited in the liver including diabetes and obesity. The typical profile of a high-risk offender (HRO) is male, 40-60 years old, overweight and potentially diabetic so it is not surprising many have a raised GGT regardless of their alcohol intake. MCV is a very non-specific marker and many chronic diseases or nutritional deficiencies can cause it to be abnormally high.

The Department of Transport sought advice on how to improve this testing policy. We found CDT is not affected by obesity, diabetes or chronic non-alcohol related liver disease. As a result of that study, the national policy has changed to use CDT as the only biochemical marker for the return of driving licences in HROs. A pilot study was carried out in 2012 to demonstrate the feasibility of this and from March 2013 the policy was implemented in England.

What tools are available to clinicians to assess a patient's alcohol use pattern?

There are tests covering three different timescales of alcohol consumption. Breath, blood or urine ethanol measurement are positive for only 12-36 hours so are only useful in the acute setting. For chronic alcohol misuse, serum CDT is preferred as it represents an objective measurement of intake over the preceding 7-14 day period. Neither ethanol nor CDT are good markers of 'binge' drinking. EtG, a very specific metabolite of alcohol excreted in urine, appears to remain positive for up to 72 hours in our hands; other claims of 90 hours are not convincing. We published a review on EtG in 2012. There are case reports in the literature of both false positive and false negative EtG tests in the presence of urinary tract infections as certain bacteria contain enzymes that can add or remove the glucuronide group. Combining EtG measurement with EtS using mass spectrometry obviates this problem. We hope that EtG will be the best detector for 'binge' drinking, whereas CDT is more suited for long-term abuse. Someone who drinks only at the weekend can test negative on a Monday for urine/blood ethanol and CDT because five days a week they are not drinking. The hope is that combining EtG and EtS will pick these up as positive.

What is the definition of CDT? What is CDT?

I refer to CDT as the HbA1c of alcoholism as it is used in diagnosing and monitoring long-term alcohol dependence similar to the use of HbA1c in monitoring glycaemic controls in diabetics. CDT represents less sialylated (asialo or disialo) forms of transferrin that increase in the blood circulation due to defective transferrin glycosylation, increased desialylation and reduced degradation during chronic daily excess alcohol intake. A high CDT concentration, expressed as a percentage of total transferrin, indicates a minimum alcohol intake of 50-80 g/day for 7-14 days

prior to sample collection. The advantage of CDT compared to more traditional biomarkers such as GGT is that CDT directly reflects alcohol consumption and is independent of any liver disease whether caused by alcohol or not. When cirrhosis develops GGT will remain abnormal even if the subject is abstinent.

What are the reasons to order a CDT test? When does it make sense to analyze CDT? What are the clinical settings?

Many CDT requests are not clinically related – they are for employment or family law, transport workers, and for many other reasons. In clinical terms we do less CDT testing than other groups. A clinical example of a good use of CDT would be a patient at a GP surgery or hospital clinic with a raised GGT, a degree of obesity and possibly diabetic, but denies drinking to excess. CDT will reveal the truth. In my opinion, an area that CDT has not proved particularly useful is in psychiatric detoxification units where the subjects have admitted drinking, in some cases up to the door of the unit! However, we have found it useful in subjects attending a drug detoxification unit who admit to abusing drugs but not alcohol. CDT is seldom useful in patients on liver transplant waiting lists either because of reduced overall synthesis of transferrin or in obstructive liver disease due to reduced clearance.

What are the existing technologies for CDT testing and why are they easily usable in routine laboratories?

There are three methodologies: CE, HPLC and immunoassay.
Immunoassay is capable of being run on an automated analyser, but as a disadvantage can be affected by the presence of benign transferrin variants. Capillary electrophoresis and HPLC require more dedicated technology than a basic analyser, but are becoming more common in routine laboratories. CDT is not an urgent test as a 1-2 hour turnaround time is difficult to achieve. It is more appropriate as a batched test, possibly run weekly.

Can an advantage be gained by combining GGT and CDT?

Some papers have suggested there is, but in our studies, and particularly those done for the Department of Transport, we did not find any advantage, so I am not convinced.

Conclusion

CDT is slowly coming of age as the best marker of chronic excess alcohol intake. Unlike GGT, CDT is not abnormal in fatty liver, obesity, diabetes or hepatitis. CDT reflects alcohol intake not liver disease.

*"If a subject is abstinent for 3 weeks,
then the CDT levels will be normal.
It is now a routine test for the retrieval of driving licenses and other forensic questioning."*

Michael SOYKA

Michael SOYKA

Academic background

Michael Soyka has been the medical director at the Psychiatric Hospital Meiringen, in Switzerland, since 2006. Previously, he was a professor of psychiatry at the University of Munich for 20 years. He was also been co-speaker of the Bavarian-Saxonian Research Network “ASAT”, supported by the German Ministry of Science and Technology.

General presentation

Michael Soyka founded the journal ‘Suchtmedizin’ from 1996, and was the first editor. He has published over 500 scientific publications and several text books on alcoholism and related disorders. He has also received numerous awards; in 2007 from the Bayerische Landesbank for project guidelines in alcohol dependence, in 2005 a Research award from the North German Research Association for Substance Use, and in 2000 from the German Society for Psychiatry, Psychotherapy and Neurology. He also received the Wilhelm-Griesinger-Award from the Berlin Society for Neurology and Psychiatry in 1994.

The Swiss and the German experiences

How much of a problem is alcohol in Germany and Switzerland? What prevention campaigns, and alcohol programs are there, and their effectiveness?

That there is a significant problem with alcohol is not a mystery. In Germany and Switzerland, per capita consumption of pure alcohol is 9-10 liters on average per annum from cradle to grave. However, only roughly 5-6 % of the population consumes about 50 % of all alcoholic beverages. The result is the number of people admitted to hospital with alcohol related problems is high.

Those that do seek treatment often seek it late. Most have drunk for approximately 10-15 years before they seek treatment, often in their 40’s. It is very important to reduce the time before people seek treatment.

In both Germany and Switzerland, there are not many publicity campaigns, and there is not a lot of activity to change behavior and opinions in this area, with the exception of youth alcoholism. This is different from smoking, where there are many prevention campaigns. There certainly should be more prevention campaigns for alcohol.

However, once people reach the stage they need treatment, the systems are elaborate, with rehab centers, and outpatient treatment. The result is treatment abstinence rates are acceptable. Some studies suggest a 40-45 % successful abstinence rate, with some even suggesting a 50 % success rate. However, relapse to drinking is still the rule, rather than the exception. Nevertheless, this still compares very favorably to smoking cessation, where the success figures are disastrous at around 20 %.

Have you made a contribution to an alcohol testing policy? What are the implications, which actions have you taken?

As a psychiatrist, and not predominantly in the public health arena. However, I have done a lot of treatment studies, and the result has been new treatment models, but my scientific involvement has less of a direct public impact. What I have established and tested in Germany is research on detox treatment with a special focus on outpatient treatment. The research was funded by health insurances, and have had some public impact. This is different to the genetics of alcoholism that we are also looking at, and has no impact on the patients at the moment.

What tools are available to clinicians to assess a patient's alcohol use pattern?

This is a good question. There can be a broad spectrum of clinical symptoms. There are questionnaires for the GP that facilitate diagnosis, and these come from WHO such as the AUDIT. Blood alcohol also is a good test, often used on drunk drivers that have an accident.

What biomarkers are used to measure alcohol abuse, what are their indications of use and what are their positives and negatives?

Most conventional biomarkers are GGT, Glutamate Oxalalocetate Transaminase (GOT) and Glutamate Pyruvate Transaminase (GPT), also known as AST and ALT liver blood tests. The problem with severe alcohol is GGT is often elevated by other factors that include drugs such as contraceptive pills and hepatitis. Whilst elevated GGT is suggestive of alcoholism, it does not prove it. Whilst GGT is nice in longitudinal studies, it is unspecific.
Another test we use is MCV. That is a direct effect of alcohol on those cells that produce blood, but are impaired by alcohol.
The third is CDT. One of the advantages of CDT is, it is very specific of alcoholism. CDT is now an established marker. What is coming up is EtG, that can be measured in urine and hair. However, it is currently very expensive and only a short-term marker. False positives for EtG are also currently caused by products that include hand sanitizers and mouthwash.

What is the definition of CDT? What is CDT?

This is a protein. Frequently used, CDT has a half-life of about 3 weeks. If a subject is abstinent for 3 weeks, then the CDT levels will be normal. It is now a routine test for the retrieval of driving licenses and other forensic questioning.

What are the reasons to order a CDT test? When does it make sense to analyze CDT? What are the clinical settings?

If there are elevated liver enzymes, CDT can be helpful in forensic settings, for example homicide linked to alcoholism. It is also good for treatment supervision where it is necessary to measure the alcohol intake of patients. There are jobs where alcohol abuse is a problem, including physicians, where there is a question of 'can they work', 'are they reliable'. The number of alcoholic doctors is quite high, CDT is helpful for that.

What are the existing technologies for CDT testing and why are they easily usable in routine laboratories?

There are different kinds of testing systems for CDT. Most labs have the necessary equipment for CDT testing, and offer that. I know different labs have different CDT tests.

What are the advantages of CDT compared with more traditional markers like GGT.

CDT is very specific (much more than GGT for example), and there are few liver disorders that may affect CDT elevations, whereas there are multiple reasons for elevated liver enzymes. There is much room for improvement on all tests, however.

Can an advantage be gained by combining CDT and GGT?

Yes, a diagnosis can never be made on only one value. There are also different time frames involved – CDT takes 3 weeks, EtG is short-term marker in urine, and is 2-3 days. MCV is accurate within 2-3 months. MCV is not as frequently elevated in alcoholics than CDT or liver enzymes.

"The main advantage is the specificity of CDT compared to GGT which is not specific at all. GGT is a commonly used marker that is included in standard tests for liver function. Increased GGT concentrations are caused, for example, by non-alcoholic liver disease, most hepatobiliary disorders, obesity, diabetes mellitus, hypertriglyceridemia, smoking and the use of liver microsome-inducing drugs."

Franco TAGLIARO

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Academic background

Franco Tagliaro, graduated in Medicine in 1978 with full marks and honours from the University of Padua, Italy. Franco Tagliaro later received post-doctoral diplomas of specialist in biochemistry and clinical chemistry and in forensic medicine. He is currently full professor of Forensic Medicine at the University of Verona, Verona, Italy and serves as director for the Unit of Forensic Medicine, Department of Public Health and Community Medicine. He is also the chairman of an international PhD program in Nanosciences and new Technologies including a curriculum in Forensic Sciences, at the University of Verona.

General presentation

Franco Tagliaro is a member of the Italian Society of Legal Medicine, of the Group of Italian Forensic Toxicologists, of The International Association of Forensic Toxicologists (TIAFT), and of the Academy of Forensic Medical Sciences. He is also consulting editor of the journal Medicine, Science and the Law and member of the editorial board of Forensic Science International*.

The Italian experience

What tools are available to clinicians to assess a patient's alcohol use pattern?

It is well known that the first stage of dealing with a problem is admitting there is a problem. This is most relevant to alcohol abuse. The abuse can take the form of dependence, or physical illness and can represent a severe social problem for the individual. This condition can remain hidden for a considerable period of time.

The clinician's main tool for diagnosis is still the clinical visit and the interview with the subject. If there is evidence of a problem the first task for the clinician is to discover whether there is recognition by the subject and if help is required.

Clinicians think, in the first instance, interviews are preferable to biomarkers. However, this is only the case when the answers from the subject can be trusted. This trust is severely tested when the subject is facing risks. For example, losing a position, care of children or a driving license. Though biomarkers can be reliable on their own, with regard to alcohol abuse, they are considerably more reliable if combined with clinical interview and visit, giving objective support to a clinical diagnosis.

What biomarkers are used to measure alcohol abuse, what are their indications of use and what are their positives and negatives?

The blood tests used traditionally as markers of excessive drinking are the liver enzymes, gamma glutamyl transferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and the red blood cell volume (mean corpuscular volume, MCV). This can help identify damage to organs caused by alcohol. However, this sort of damage is not specific and could be caused by other diseases or factors.

Ethanol in biological fluids

Measuring ethanol concentration in blood, breath or urine can indicate recent alcohol consumption, as ethanol is a direct marker of acute alcohol consumption. Though the diagnostic window is very short, it can be useful to determine the psychological, neurological and biological

performance at the moment of blood sampling (or breath testing). Under particular conditions, blood ethanol concentration can also be used to indicate longer term drinking patterns. For example, a subject that does not appear drunk, but has 1.5-2 mg/mL of ethanol in his/her blood indicates a high tolerance, and thus longer-term abuse.

Nowadays, there are other more sophisticated biomarkers of past/chronic abuse of alcohol that include phosphatidylethanol, 5-hydroxytryptophol, fatty acid ethyl esters, salsolinol, acetylated hemoglobin etc, but CDT and EtG, are most widely recognized for practical application.

Carbohydrate Deficient Transferrin (CDT)

CDT refers to a group of minor glycoforms of transferrin which are deficient in sialic acid residues. CDT as a biomarker is sensitive to chronic alcohol abuse. If a subject only occasionally drinks too much, in general CDT cannot detect this. CDT is sensitive to relatively long periods of sustained alcohol intake. If the subject drinks beverages containing more than 60 to 80 g of alcohol per day (for example 2/3-1 bottle of wine) CDT increases in the blood serum. It takes two weeks for CDT levels to rise, but also takes two weeks for CDT levels to fall again after the abuse is quit. As a result, CDT is useful to monitor the chronic behavior of a subject. For this reason CDT is particularly suitable for identifying alcohol dependence which forces subjects to drink too much too often and they cannot stay sober long enough for the CDT level to fall.

Ethyl glucuronide

A very small amount of alcohol consumed is converted into EtG.

Detectable in urine up to 60 hours after drinking, this marker can be useful to detect a recent intake of alcohol. As a result, this is a different option to CDT. However, there are many variables affecting EtG concentration in urine, including urine dilution (depending on the intake of water of the subject).

An interesting perspective application for EtG might be its determination in hair. We can detect in the hair traces of endogenous or exogenous compounds present in the blood in the months when hair has grown. This has widely been proved in the field of drug abuse, where hair analysis has become an accepted testing. Accordingly, elevated concentrations of EtG are present in the hair of chronic alcohol abusers. However, in my opinion, there has not currently been enough research on EtG in this area to achieve the degree of reliability required in forensic diagnostics. Arguably, a correlation between alcohol intake and concentration of this biomarker in the hair exists, but it is also extremely variable.

Also, the stability of EtG is currently contested, as it can be artificially altered in the environment by bacteria.

In summary, different biomarkers of alcohol abuse can be used for different purposes. Blood alcohol levels test a present state of intoxication. CDT is most useful to measure alcohol in lifestyle, and EtG in urine can test the alcohol intake of a weekend. EtG in hair, when methods will be thoroughly validated also in terms of interpretation, will be most useful to test very long term chronic abuse. CDT is currently the most specific and widely accepted biomarker of chronic abuse of alcohol; the other more traditional biomarkers (i.e. liver enzymes and MCV) are less specific, since they can be elevated by other diseases or factors. Applications where CDT is most useful include diagnosis in general medicine, forensic medicine, psychiatry and analysis to test fitness-to-work, as well as control during withdrawal periods.

What are the methods for CDT tests, and when are they most useful?

There are currently several different existing technologies for determining CDT.

CDT is not a single protein but a group of isoforms of a protein called transferrin. The main detection challenge is that a very small group of isoforms (i.e. CDT) has to be highly accurately measured in a mixture containing prevalent concentrations of other isoforms of the same protein.

Technologies based on immunoassays are based on the specificity of antibodies to detect the forms of transferrin having a lower degree of glycosylation amidst a great excess of others isoforms having a higher degree of glycosylation.

If the percentage of CDT is low, it is currently

challenging to detect CDT with great accuracy, even for a specific antibody with very low cross-reactions, but if CDT is high, the challenges are reduced.
Liquid chromatography (known also with the acronym HPLC) is based on the physical separation of the different isoforms. The CDT molecules can be detected following separation, and this makes the system more specific. Liquid chromatography is based on specific columns that separate the proteins by the number of negative charges. The detection is based on the absorbance of light. In HPLC methods for CDT determination, however, the detection is not focused on the protein structure, but on the iron ions linked to the transferrin molecule. Thus, CDT is indirectly detected from its iron content. Since in the blood we have a lot of different proteins but only two major proteins transporting iron, haemoglobin and transferrin (ferritin is a minor component), this analytical approach is very very selective.
A further approach to the analysis of CDT is the use of Capillary Electrophoresis (CE) which is a traditional and universally used technique for separating proteins. CE separates the proteins under an electric field, based on their different electrophoretic mobility, which depends on the size of the molecule and on the number of charges of each molecule. Using CE we can separate the transferrin glycoforms to isolate the CDT components; detection is carried out by UV light absorption, so that the protein structure and not the iron is detected. For this reason, even if at the detection side the selectivity is lower than the HPLC, CE offers the advantage of a more efficient separation of the proteins present in the sample.
In practical applications, and particularly in a forensic context, more than one method is needed to achieve a sufficient degree of reliability. A screening method, often based on immunoassays or high throughput capillary electrophoresis or liquid chromatography, is best followed by a confirmation step, with one or more sophisticated techniques. In general, both techniques, liquid chromatography and CE, are used. However, CE is generally thought to be cheaper, faster, more efficient and more productive. The results between the two processes in our experience are highly comparable.

What are the advantages of CDT compared with more traditional markers like GGT?

The main advantage is the specificity of CDT compared to GGT which is not specific at all. It is a commonly used marker that is included in standard tests for liver function. Increased GGT concentrations are caused, for example, by non-alcoholic liver disease, most hepatobiliary disorders, obesity, diabetes mellitus, hypertriglyceridemia, smoking and the use of liver microsome-inducing drugs. However, testing for alcohol abuse, GGT has a good sensitivity although with a low specificity. In relation to alcohol abuse, GGT could really only be useful to suggest that the subject should be tested for CDT.

Can an advantage be gained by combining CDT and GGT?

In my opinion, the best way is to use a screening level with the highest sensitivity and then all the positives are crosschecked with a combination of other biomarkers with the aim of optimising the diagnostic specificity, without sacrificing sensitivity. This is the correct approach and excludes false positives as well as false negatives.
However, this is sound literature showing that combining CDT and GGT is a good strategy to improve the reliability of the diagnosis of chronic alcohol abuses. On this point we should stress that CDT has a much higher specificity than GGT, and therefore should be used in combination to verify if an elevated GGT is to be referred to abuse of alcohol or to other conditions, and to avoid missing cases of patients suffering from alcohol abuse with negative GGT.

*Member of Editorial Boards of the following scientific journals:
“Forensic Science International” (since 1996),
“Journal of Chromatography B” (1998-2008),
“Forensic Science Journal” (since 2010),
“Rivista Italiana di Medicina Legale e del Diritto in Campo Sanitario” (since 2013).
- Since 2009 is co-editor of “Bollettino per le Farmacodipendenze e Alcolismo”.
- Since 2010 is International Consulting Editor of “Medicine Science and the Law”.

Glossary

ABMRF	Alcohol Beverage Medical Research Foundation
ACTIVE	Alcohol Clinical Trials Initiative
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUDIT	Alcohol Use Disorders Identification
AUSAM	Austrian Society For Addiction Medicine
CAGE	CAGE questionnaire, named by the acronym of its four questions. Widely used method of screening for alcoholism (Have you ever felt you needed to **C**ut down on your drinking? Have people **A**nnoyed you by criticizing your drinking? Have you ever felt **G**uilty about drinking? Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover? Two "yes" responses indicate that the possibility of alcoholism should be investigated further.
CDT	Carbohydrate-Deficient Transferrin
CE	Capillary Electrophoresis
DMS-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DNA	Deoxyribonucleic Acid
DSS	Department of Social Services
DVLA	Driver and Vehicle Licensing Agency
ESBRA	European Society for Biomedical Research on Alcoholism
EtG	Ethyl Glucuronide
EtS	Ethyl Sulfate
FDA	Food and Drug Administration
GGT	Gamma-glutamyltranspeptidase
GOT	Glutamate Oxaloacetate Transaminase (also known as AST)
GP	General Practitioner
GPT	Glutamate Pyruvate Transaminase (also known as ALT)
HPLC	High-Performance Liquid Chromatography
HRO	High-Risk Offenders
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
ISBRA	International Society for Biomedical Research on Alcoholism
MADD	Mothers Against Drunk Driving
MCV	Mean Corpuscular Volume
NHTSA	National Highway Traffic Safety Administration
NIAAA	National Institute on Alcohol Abuse and Alcoholism
PEth	Phosphatidylethanol
RSA	Research Society on Alcoholism
TIAFT	The International Association of Forensic Toxicologists
WHO	World Health Organization

Patient's questionnaires

AUDIT: http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf

CAGE questionnaire: http://psychology-tools.com/cage-alcohol-questionnaire

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