RÄTTSMEDICINALVERKET

Research Work

Published by the Department of Forensic Toxicology
National Board of Forensic Medicine 1956 – 2013

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COMPILED BY PROFESSOR ALAN WAYNE JONES

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Contents

Executive Summary

The subject of forensic toxicology, formerly known as forensic chemistry, has a long history in Sweden and the first government forensic chemist was appointed already in 1872. The occupant of this position was Dr. Nils Peter Hamberg (1815-1902), who was qualified in pharmacy and medicine, and his thesis concerned the extraction of drugs from medicinal plants. For many years, the State Laboratory of Forensic Toxicology was located in Stockholm on the campus of Karolinska Institutet. This gave good opportunities for joint research projects between scientists working at the medical faculty and members of staff at the forensic toxicology laboratory. Examples of joint projects and the resulting scientific publications can be gleaned from the compilation of scientific papers in this report, particularly those published over the years 1956-1979.

In the early 1970s the Swedish Parliament made a strategic decision to re-locate certain government organizations, among them the forensic toxicology laboratory, to smaller Swedish cities as a way to create more job opportunities. In 1979-1980 the toxicology laboratory moved from Stockholm to Linköping, where it occupied rooms at the Faculty of Health Sciences, University of Linköping. An important event occurred in 1991 when the National Board of Forensic Medicine (Rättsmedicinalverket, RMV) was created. This government authority had overall administrative responsibility for forensic medicine, forensic genetics, forensic toxicology and forensic psychiatry, for the whole country. The general director of RMV made it possible for suitably qualified senior staff to participate more actively in research by funding joint appointments as adjunct professors or adjunct lectures at Linköping university. This led to a closer interaction with physicians and students, some of whom embarked on research in toxicology leading to a PhD or MD degree (see compilation of theses).

The workload in forensic toxicology increased appreciably during the 1990s, owing to new government legislation to deal with an increasing abuse of drugs in society. In 1999 a zero-tolerance law for driving under the influence of scheduled drugs was introduced, which meant thousands more blood samples were sent by the police for analysis and laboratory space was no longer adequate. Discussions eventually led to planning of a new purpose-built building, which would accommodate forensic chemistry, forensic medicine and forensic genetics. This state-of-the-art building was erected and opened in 2006.

Forensic toxicology is a good example of a multidisciplinary science combining various aspects of analytical chemistry, physiology, pharmacology and toxicology. Forensic toxicologists are first and foremost trained in analytical chemistry, because they need to extract and identify drugs and toxins in body fluids and tissues from living and deceased persons. Forensic toxicologists are also expected to provide expert testimony in court cases, especially interpretation of the analytical results in relation to signs and symptoms of intoxication or whether a fatal poisoning occurred. Continuous development in analytical chemistry, including computerisation, and highly sensitive and specific methods has meant that drugs and their metabolites can be measured in body fluids in an unequivocal way. Hyphenated techniques, such as computer-aided gas chromatography-mass spectrometry (GC-MS) and more recently liquid chromatography-mass spectrometry (LC-MS) have revolutionized the work done at forensic toxicology laboratories.

On-going or completed research projects include development of new analytical methods, epidemiology of drug abuse in Sweden, alcohol, drugs and driving, toxicity of designer drugs, clinical pharmacology, pharmacokinetics of ethanol and other drugs etc. These projects have resulted in an increasing number of articles published in international scientific journals with 13-28 papers/year appearing over the past 25 years.

Background

Forensic toxicology is a multidisciplinary subject mainly concerned with extraction, detection, identification and quantitative analysis of drugs and their metabolites in biological specimens. Another important task for the forensic toxicology laboratory is to interpret what the analytical results mean in relation to any drug-induced impairment or whether drug intake was responsible for acute toxicity and death. Historically, forensic toxicology is considered the science of poisons and arsenic compounds were once considered the kings of poisons, along with plant alkaloids, exemplified by morphine, nicotine and strychnine. The analysis of sedative-hypnotic drugs, such as barbiturates, became a major concern during the first half of the 20th century, because this type of medication was being increasingly encountered in overdose deaths, both accidental and with suicidal intent.

Close links exist between forensic toxicology and forensic medicine, because many sudden and unnatural deaths are the result of heavy drinking and/or overdosing with drugs. The prescribing of multiple drugs is increasingly common in today's society, especially in the elderly, and this poly-pharmacy has heightened the risk of experiencing an adverse drug-drug or drug-alcohol interaction. Scientific evidence for a drug poisoning death requires making a systematic toxicological analysis of blood, urine and other biological specimens taken from the deceased during a forensic autopsy.

The forensic toxicology laboratory is expected to provide a service to the police and other government agencies when alcohol or drug-related crimes are investigated. Such crimes might involve drunk or drugged driving, use of illicit drugs for recreational purposes, or when drug-facilitated sexual assaults are reported. Furthermore, forensic toxicologists are often required to testify in court as expert witnesses. In this connection they need to explain what the results of their analysis mean in relation to the pharmacological effects of drugs on a person's performance and behaviour. Providing expert testimony

demands a broad knowledge and experience not only from the analysis of drugs, but also from basic pharmacology and toxicology of drug action. The outcome in a criminal trial might depend on the strengths or weaknesses of the scientific evidence presented by an expert witness.

Forensic autopsies in Sweden are performed at the six university teaching hospitals located in Umeå, Uppsala, Stockholm, Göteborg, Linköping and Lund. During an autopsy blood and other specimens (e.g. urine and vitreous humor) are taken from the deceased and shipped for analysis to a dedicated central laboratory in Linköping. A flow diagram illustrating the analytical routines and decisions made during investigation of a drug-related death is shown in figure 1.

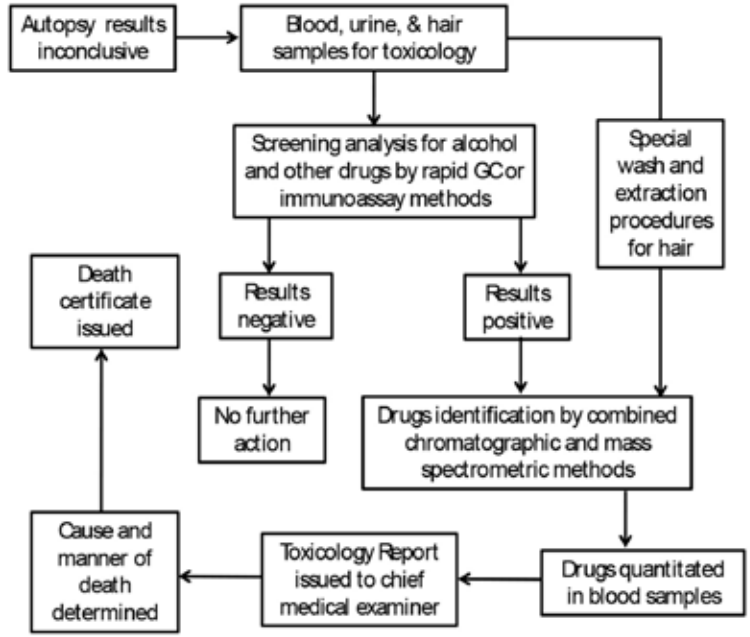


Figure 1. Flow chart of the toxicological routines during unnatural death investigations and suspected poisoning.

Forensic Chemistry Moves to Linköping

During the period 1956 to 1979 the forensic toxicology laboratory was organized into two semi-independent sections. One section specialised in post-mortem toxicology and the other was concerned with the analysis of alcohol and drugs in blood and urine from impaired drivers. In the early 1970s, a decision was made by the Swedish parliament that certain government organizations and laboratories would be re-located away from the capital city Stockholm to smaller towns, with the hope of creating job opportunities.

The toxicology section moved its activities to Linköping in 1979/1980 and office and laboratory space was obtained at the University Hospital in close proximity with other clinical science laboratories. The alcohol section of the laboratory remained in Stockholm until 1985 while awaiting the results of testing and evaluation of evidential breath alcohol instruments. Such breath analyzers were being considered as a possible replacement for blood samples in cases of drunken driving. A new traffic law came into force in 1989 whereby a drunken driver could be prosecuted on the basis of a breath-alcohol test and a new statutory breath-alcohol concentration limit was introduced. The number of blood samples submitted to the laboratory for analysis of alcohol began to decline and after a few years there was a drop from about 25,000 per year to 5,000 per year.

Re-location of the forensic toxicology laboratory from Stockholm to Linköping gave a good opportunity to review and upgrade older methods of analysis and to purchase more modern equipment for chemical-toxicological analysis. Major efforts were also made to introduce computer-aided techniques whenever this was possible. Examples of improved methods included enzyme immunoassay technique for rapid screening analysis of drugs of abuse in urine, headspace gas chromatography for blood-ethanol determinations, capillary-column gas chromatography (GC) for the analysis of medicinal drugs in blood and liver samples. The highly sensitive and

specific method of gas chromatography-mass spectrometry (GC-MS) played an important role for verification analysis.

The analytical workload in toxicology depends to a large extent on introduction of new laws regulating the use and abuse of drugs in society. After it was made illegal (in 1988) for illicit drug to be used for recreational purposes, the laboratory saw a dramatic increase in the numbers of blood and urine samples sent by the police for toxicological analysis. These so-called petty drug offences still represent a significant part of the routine analytical work done at the laboratory.

In 1999 a zero-tolerance law for driving with a controlled substance in blood was approved by the government, which meant that impairment evidence was no longer necessary. This stricter type of legislation led to a dramatic increase in the number of blood samples sent by the police for toxicological analysis. Prior to introduction of the zero-tolerance law for driving under the influence of drugs, between 500-1000 cases per year were analyzed compared with 13,000 ten years later.

In 1990 the National Board of Forensic Medicine (Rättsmedicinalverket, RMV) was created and this government authority had overall administrative responsibility for forensic chemistry, forensic pathology, forensic genetics and forensic psychiatry. Another significant event in 2002 was approval by the government to build a new laboratory where forensic medicine, forensic toxicology and forensic genetics would be housed together in the same building. This meant moving away from the university hospital to a new site located in close proximity to the National Laboratory for Forensic Science, the police authorities, the prosecutors and the law courts. In January 2006 this laboratory was opened and three forensic specialities (genetics, medicine and toxicology) were housed together in the same purpose-built building.

The early history of forensic chemistry in Sweden and the creation of an official position as government forensic chemist was reviewed by

Professor Erik Wolff, MD, PhD (1891-1971), who was head of the department during the years 1925-1956 (see appendix 1). Later developments in forensic chemistry mainly covering the period 1956 to 1999 were reviewed by AW Jones (see appendix 2). As background information both these articles are included in this RMV report.

Wolff E. Statens rättskemiska laboratoriums och rättskemistbefattningens historia. In W. Kock (editor) Medicinhistorik Årsbok, Stockholm, 1968 pp 196-207.

Jones AW. Historical developments of forensic toxicology in Sweden. Nordisk Rettsmedisin 2:35-44, 1998.

Research in Forensic Toxicology

The multidisciplinary nature of forensic toxicology is reflected in the various research projects documented in this compilation of published papers. Research aimed at developing and evaluating new analytical methods is fundamentally important because the drugs encountered in routine case work are continually changing. Also well represented are studies of the epidemiological of alcohol and drug abuse in society, especially in relation to impaired driving and drug-related deaths. The clinical pharmacology of medicinal and illicit drugs has been a major focus of our research including both pharmacokinetic and pharmacodynamic studies. Although alcohol is a legal drug, heavy drinking and drunkenness are major problems in society and the analysis of ethanol in biological fluids, as well as absorption, distribution and metabolism of ethanol in the body have been extensively studied.

The need for highly sensitive and specific analytical methods for detection, identification and quantitative analysis of drugs and poisons was recognized already during the 1960s. Some of the first applications of the powerful technique of gas chromatography combined with mass spectrometry (GC-MS) in toxicological casework originated from Sweden. No fewer than 13 articles were published between 1970

and 1975 describing the use of GC-MS for analysis of drugs and poisons in biological fluids. These studies were possible thanks to a good collaboration between Dr. Ragnar Ryhage, who headed the mass spectrometry unit at Karolinska Institutet, and Professor Roger Bonnichsen, who was head of forensic toxicology at the time.

The scientific evidence necessary for prosecuting drunk and drugged drivers is derived from analysis of blood samples at the forensic toxicology laboratory. The current statutory blood alcohol limits for driving in Sweden are 0.20 ‰ (drunken driving) and 1.0 ‰ (aggravated offence), whereas a zero limit exists for driving with a controlled substance in blood. The non-alcohol drugs used by drivers have changed over the years. In the 1960s these were dominated by sedative-hypnotics, such as barbiturates and benzodiazepines, as well as abuse of central stimulant amines (amphetamine) and sniffing of various organic solvents (e.g. toluene).

These early studies showed that the clinical signs and symptoms of drug influence were poorly correlated with the concentrations of drugs determined in the driver's blood. The examination of traffic offenders by a physician did not provide the most reliable scientific evidence of impairment, which instead was furnished by toxicological analysis of blood samples. Scores of papers were subsequently published about the demographics of offenders, the types of drugs they abuse and the concentrations in blood when arrested.

The scientific productivity of the department, both in qualitative and quantitative terms, depends to a large extent on well-trained scientific staff holding an advanced degree (PhD or MD). For many years only the chief toxicologist and the two section heads had formal research training with the academic title of docent (assistant professor). Today many more of the scientific staff have defended a thesis and hold a joint appointment with the University of Linköping as adjunct professors or adjunct university lectures. Collaboration with scientists and students at the university hospital intensified during Professor Johan

Ahlner's tenure as head of the forensic toxicology department (1999-2013) as reflected in an appreciable increase in the number of dissertations for MD/PhD degree.

Recent publications from the department document the upsurge in abuse of designer drugs in society (e.g. spice), often purchased over the internet. The unequivocal identification and quantitative analysis of these substances requires highly sensitive and specific analytical methods. Looking at the instruments in use today, one notes a definite trend away from the well established GC-MS methods towards LC-MS or various combined technologies e.g. GC-MS/MS or LC-MS/MS, which have become the gold standards. The use of liquid chromatography in combination with time of flight mass spectrometry (LC-TOF-MS) has proven highly effective for screening body fluids for a wide range of drugs of abuse.

Some scientists at the forensic toxicology laboratory have developed a special interest and expertise in the analysis of drugs in hair strands, which serves as a useful alternative specimen and a complement to blood and urine specimens. Segmental analysis of hair is particularly useful and this allows establishing an approximate time-line of drug use or drug administration. Identification of drugs in different segments of hair furnishes proof of compliance with medication, which is useful information in certain forensic cases. Moreover, hair is a viable specimen even if the body is decomposed, which often precludes obtaining suitable blood samples for toxicology. Both hair and nails are obtainable from exhumed bodies so drug intake during life can be verified long after death.

After the forensic toxicology laboratory moved from Stockholm to Linköping, opportunities for collaboration with physicians and students at the University Hospital increased appreciably. Clinical research projects with healthy volunteers and hospital patients have resulted in scores of publications and several MD/PhD theses as documented in this RMV report.

During the prosecution of drunk and drugged drivers many arguments are often raised by defense lawyers in an attempt to cast doubt on the reliability of the forensic toxicology evidence. Such challenges are particularly common in drunk-driving trials and might necessitate special research projects to test the validity of the many claims made in such cases. The results of these experiments were later published in peer-review scientific journals and these studies are often cited and used internationally.

The broad spectrum of research projects undertaken over the period 1956-2013 can be gleaned from the titles of the articles in the list of publications. These articles are arranged in chronological order and include names of the authors, title of the work, name of the scientific journal where the article was published as well as volume and page numbers. Besides many projects originating from within the toxicology department, collaboration with scientists at other government agencies, laboratories or universities both in Sweden and internationally are also well documentet.

It is often said that research does not exist until it gets published, which means that writing articles for publication and placing the information they contain in the public domain is the key to success in science. Within academia the quality and quantity of a person's published papers are a mark of distinction and prestige. Accumulating a long list of publications brings credit to the authors of the articles and also the institution or department where the work was done.

The research done for several MD/PhD projects in forensic toxicology took advantage of the rich source of information from routine forensic casework. The demographics of drug abusers, the prevalence and types of drugs used as well as the concentrations in blood and other body fluids in living and deceased persons are available from two national databases, namely TOXBASE and RÄTTSBASE. These databases were used to study the epidemiology of drug abuse

in Sweden and the dangers of various drug combinations as a cause of poisoning and premature death.

The graph below (figure 2) plots the annual number of papers published by the department over the years 1956-2013. One notes a significant increase in research activity, as reflected in an increased number of publications, after the laboratory moved to Linköping in 1979/1980. Indeed, over the past 25 years the number of papers published has ranged from about 13-28 per year with a mean of 18 articles per year. Not included in the list of publications, nor plotted on the graph, are the hundreds of abstracts of papers presented in connection with attendance at national and international forensic science and toxicology conferences.

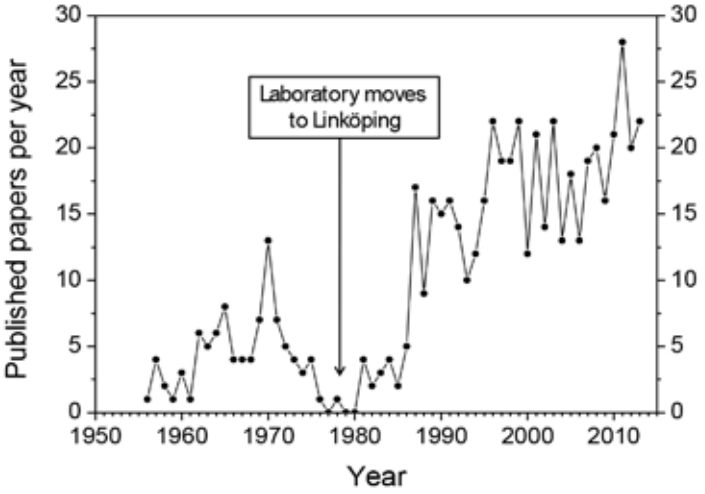
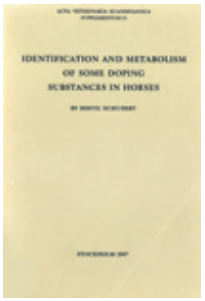


Figure 2. Development in annual number of scientific publications from the National Laboratory of Forensic Toxicology 1956- 2013.

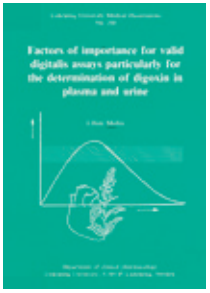
Dissertations presented for higher degree (PhD or MD) by members of staff at RMV's forensic toxicology division or research workers affiliated with the department

Bertil Schubert
Identification and metabolism of some doping substances in horses.
Stockholm (Veterinary University), 1967.

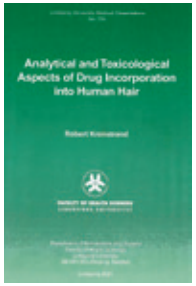


Stergios Kechagias
Clinical pharmacokinetics of small doses of ethanol: role of gastric emptying and other influences in the upper gastrointestinal tract.
Linköping University, 2001.

Lilian Molin
Factors of importance for valid digitalis assays particularly for the determination of digoxin in plasma and urine.
Linköping University, 1986.

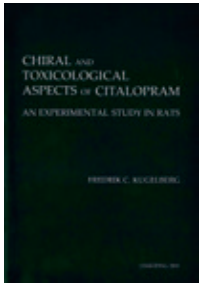


Robert Kronstrand
Analytical and toxicological aspects of drug incorporation into human hair.
Linköping University, 2001.



Åke Norberg
Clinical pharmacokinetics of intravenous ethanol: Relationship between the ethanol space and the total body water.
Stockholm (Karolinska Institutet), 2001.

Fredrik C. Kugelberg
Chiral and toxicological aspects of citalopram: An experimental study in rats.
Linköping University, 2003.

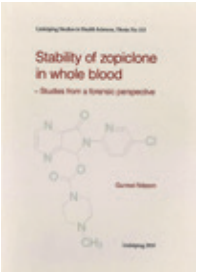


Björn Carlsson
From achiral to chiral analysis of citalopram.
Linköping University, 2003

Anna-Lena Zackrisson
Pharmacogenetics from a forensic perspective: CYP2D6 and CYP2C19 genotype distributions in autopsy cases.
Linköping University, 2009.

Per Holmgren
Postmortem toxicology – aspects on interpretation.
Linköping University, 2004.

Gunnel Nilsson
Stability of zopiclone in whole blood – Studies from a forensic perspective.
Linköping University, 2010.



Anna K. Jönsson
Drug-related morbidity and mortality – pharmaco-epidemiological aspects.
Linköping University, 2007.

Maria Kingbäck
Genetic influence on enantiometric drug disposition: Focus on venlafaxine and citalopram.
Linköping University, 2011.

Maria Dolores Chermá Yeste
Therapeutic drug monitoring in psychiatry – some aspects of utility in clinical practice and research.
Linköpings University, 2009.

Louise Karlsson
P-glycoprotein and chiral antidepressant drugs: Pharmaco-kinetic, pharmaco-genetic and toxico-logical aspects.
Linköping University, 2012.

Svante Vikingsson
Development of new methodology for therapeutic drug monitoring of thiopurine treatment.
Linköping University, 2012.

Salumech Bastami
Practical and clinical use of opioids.
Linköping University, 2013.

Published Papers

1956

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1957

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7. Åberg CJ, Bonnichsen RK. *Några synpunkter på rattfylleri-problemet*. Alkoholfrågan 52;1-4, 1958.

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Appendix 1 Särtryck ur Nordisk Medicinhistorisk Årsbok 1968

Statens rättskemiska laboratoriums och rättskemistbefattningens historia

av Erik Wolff, Föreståndare för statens
rättskemiska laboratorium 1925-1956

Rättskemiska laboratoriet är en ganska ung institution. Som avdelning av statsmedicinska anstalten tillkom det genom statsmakternas beslut 1907, och självständigt laboratorium blev det först 1917. Däremot är rättskemistbefattningen av betydligt äldre datum; den inrättades redan 1872 och rättskemisten skulle då själv hålla sig med laboratorium för sina undersökningar.

Grunderna för en rationell organisation av de rättskemiska undersökningarna i Sverige angavs för omkring 100 år sedan av Nils Peter Hamberg, som några år senare blev landets förste rättskemist. Vid nedläggandet av ordförandeskapet i Svenska Läkaresällskapet 1865 höll han ett föredrag med titeln *Några ord om legala kemiska analyser vid förgiftningar*. Hamberg visar sig här synnerligen framsynt, och de krav han ställer har först sent, och i vissa delar ännu i dag icke helt, uppfyllts. Det torde därför vara av intresse att återge några väsentliga punkter i föredraget.

Hamberg framhåller först betydelsen av att om olika organ vid obduktion tillvaratagits i skilda kärl, organen också undersökas var för sig. ”Det kan nemligen vara af vigt att erfara, huruvida giftet förefanns uti primae viae eller uti organer, som äro mera aflägsna och ej så åtkomliga, t.ex. lefvern, blodkärl, hjernarr etc.” Han understryker vidare vikten av skyndsam undersökning ”alldenstund en del gifter hastigt så förändras, att de icke med säkerhet kunnat framdragas, t.ex. fosfor, blåsyra m.fl.”

Hamberg påpekar vikten av att känna till de förändringar, giftiga ämnen kan undergå i kroppen, och kräver att giftiga ämnen om möjligt skall kvantitativt bestämmas, då fynd av små mängder av

en del gifter ofta nog icke berättigar till antagandet att en förgiftning ägt rum.

Därefter övergår Hamberg till en diskussion av kompetenskraven på undersökaren. Enligt då gällande författningar (Sundhetskollegii af Kungl. Maj:t den 18 nov. 1818 fastställda allmänna stadgande om hvad iakttagas bör vid medicolegala besigtningar å döda kroppar) skulle undersökning av likdelar på gifter utföras på ett apotek av läkaren biträdd av apotekaren eller provisorn.

Hamberg framhåller, att en ansvarsfördelning är olämplig och att såväl läkare som apotekare ofta saknar intresse och erforderliga insikter i toxikologisk-kemisk analys. Han kräver därför, att sådana undersökningar endast bör få utföras av specialutbildad person. Denne maste ocksa ha tillgang till kemikalier och reagenser, vilkas renhet bör underkastas särskild kontroll. Han utdömer ocksa apotekslaboratorier som lokaler för toxikologiskt kemiska analyser, bl.a. därför att för sådana undersökningar krävs, att obehöriga icke äger tillträde till lokalerna. De mindre apoteken har dessutom vanligen icke erforderliga instrument och pålitliga reagenser i tillräcklig mängd.

Ännu några år förflöt emellertid innan någon myndighet vidtog åtgärder för att förverkliga dessa synpunkter. Den 14 dec. 1871 avgav Sundhetskollegium en underdånig skrivelse till Kungl. Maj:t, vari begärdes, att en rättskemistbefattning skulle inrättas. Rättskemisten skulle övertaga den kemiska undersökningen beträffande gifter av vid obduktion tillvaratagna organ. I skrivelsen framhålles den kemiska toxikologiens framsteg under de senaste årtiondena, men också de krav som måste ställas på undersökaren. Denne borde vara ”förtrogen med alla olika undersökningsmetoder och deras inbördes företräden” samt besitta ”stor vana vid kemiskt-analytiska operationers utförande.”

Sundhetskollegium framhåller, att de i ovannämnda obduktionsstadga intagna föreskrifterna för den rättskemiska undersökningen på sin tid utarbetats av ingen mindre än kollegiets dåvarande ledamot

Jöns Jacob Berzelius och ”särdeles hvad angick undersökning på arsenik grundade sig på de af denne ryktbare kemist enkom anställda försök” och att de utan tvivel förtjänade att anses som de för sin tid mest tillförlitliga, men att redan efter tvenne decenniers förlopp metoderna för påvisande av gift i blandningar av organiska ämnen utvecklats i så hög grad att nya anvisningar erfordrades, varför kollegiet uppdrog åt en dåvarande lärare vid Karolinska Medico-Chirurgiska Institutet sedermera professorn Nils Johan Berlin att författa en sådan. Denna utkom också 1845, men då den innehöll flera olika metoder för pavisande av samma gift, ansåg kollegiet att den icke kunde ”till ovillkorlig efterföljd anbefallas.”

Som motivering för behovet av en verkligt kompetent rättskemist anförde kollegiet svårigheten att i annat fall bedöma graden av omsorg och skicklighet, varmed undersökningen utförts. Kollegiet hänvisade speciellt till att det mer än en gång hänt, att arsenik icke påvisats vid undersökningen, trots att symtomen före döden och obduktionsfynden, ja till och med den brottsliges egen bekännelse klart talat för arsenikförgiftning, medan i andra fall arsenik anträffats, som eventuellt kunnat härröra från arsenikhaltiga reagenser. Dessa förhållanden hade under flera år vållat kollegiet bekymmer, men två nyligen timade fall hade varit närmaste anledningen till framställningen.

Som följd av denna skrivelse beslöt Kungl. Maj:t den 24 maj 1872, att en rättskemistbefattning skulle inrättas, varjämte härav föranledda ändrade bestämmelser om undersökning av likdelar på gifter utfärdades (Kungl. Maj:ts stadganden 1872 och Sundhetskollegii cirkulär 1872-76).

Sundhetskollegiet förordnade ovannämnde medicine doktor Nils Peter Hamberg som rättskemist från den 1 november 1872.

I proposition till 1874 års riksdag begärdes professors lön åt rättskemisten (4.500 kr) i enlighet med Sundhetskollegiets hemställan. Kollegiet hade dock alternativt begärt, att om icke tillräcklig erfarenhet om göromålens mängd och beskaffenhet ansågs föreligga efter endast

ett år, arvodet åtminstone skulle höjas från 2.000 till 3.000 kr. Statsutskottet gick naturligtvis på sparsamhetslinjen. Efter livliga debatter stannade kamrarna för olika beslut: andra kammaren följde statsutskottet, medan första kammaren gick på Kungl. Maj:ts förslag.

I andra kammaren yttrade en ledamot, hr Törnfelt, bl.a. "Efter att för en stund sedan ha sålt själens lif och helsa för 3.000 kr (andra kammaren hade avslagit en motion av Adolf Hedin om införande av censorer vid avgångsexamina från folkskollärarseminarierna [beräknad kostnad 3.000 kr]), skall man nu troligen sälja kroppens lif och helsa för halfva summan." Vid gemensam votering segrade statsutskottets förslag.

Följden av riksdagens sparsamhet blev att den tillförordnade rättskemisten doktor N. P. Hamberg redan den l juli 1874 avgick från sin befattning, varefter de rättskemiska undersökningarna en tid verkställdes av adjunkten i kemi vid Karolinska mediko-kirurgiska institutet.

Sundhetskollegiet ansåg denna tillfälliga anordning otillfredsställande och förnyade sin hemställan till Kungl. Maj:t att rättskemistbefattningen måtte uppföras på kollegiets stat med professors namn och lön. Kungl. Maj:t framlade ånyo proposition härom 1875 och denna gång biföll riksdagen. Befattningen uppfördes alltså i 1876 års stat. Rättskemisten måste emellertid själv hålla sig med laboratorium och fick ersättning för varje särskild undersökning, vari inberäknades kostnaderna för lokal, reagenser m.m. Genom kungl. brev den 29 oktober 1875 fastställdes ordningen för befattningens tillsättande och instruktion för rättskemisten.

Till befattningen utnämndes från den l jan. 1876 doktor Nils Peter Hamberg, vilken alltså, utom under nyssnämnda interregnum, var rättskemist från l nov. 1872 till utgången av 1883.

Hamberg, som vi redan inledningsvis lärt känna genom hans föredrag i Svenska Läkaresällskapet om rättskemiska analyser vid förgiftningar, var en mångsidig man. Han var född 1815. Han började

sin bana som apotekare, övergick därefter till medicinska studier och disputerade 1848 för medicine doktorsgraden på en avhandling om vegetabiliska drogers insamling och förvaring. Han har utgivit ett stort antal skrifter om analys av hälsobrunnars vatten, om arsenik, karbolsyra, kloroform etc. Droger tycks ha varit hans speciella intresse att döma av de talrika demonstrationer av sådana han företog vid Läkaresällskapets sammankomster. Han var ledamot av Vetenskapsakademien och hedersledamot bl.a. av Pharmacological Society of Great Britain. Han uppnådde den höga åldern av 87 år.

Hamberg efterträddes av fil. och med. doktorn Axel Johan Wimmerstedt, som var rättskemist från 1883 till 1894 (han hade också uppehållit befattningen under ovannämnda interregnum). Hans doktorsavhandling handlade om analys av Medevi hälsobrunn. Belysande för den tidens klassiska bildning är att Wimmerstedt som ung student en kortare tid undervisade i grekiska vid Kalmar högre elementarläroverk.

Näste innehavare av rättskemistbefattningen var Hjalmar Dillner. Denne uppehöll tjänsten på förordnande från 1893, blev ordinarie 1895 och dog redan i dec. 1898 (han ramlade på natten i Nybroviken och drunknade). Dillners gradualavhandling hette ”Några rättskemiska studier” och utgjordes av metodologiska anmärkningar och erfarenheter beträffande påvisande av fosfor och arsenik samt i någon mån metallgifter i likdelar.

Rättskemistens arbete bestod i påvisande av (1) giftiga ämnen i likdelar vid misstanke på förgiftning (2) blodfläckar och deras art på klädespersedlar, vapen etc samt (3) sädesfläckar på kläder eller andra föremål.

Fram till slutet av 1890-talet synes inga väsentliga förändringar ha ägt rum i fråga om den rättskemiska verksamheten eller organisationen. I januari 1897 tog medicinalstyrelsen genom en skrivelse till Kungl. Maj:t initiativ till upprättandet av en statsmedicinsk anstalt. Kungl. Maj:t tillsatte i oktober samma år en kommitte för att utreda behovet av en statsanstalt för diagnostiskt-bakteriologiska

undersökningar, tillverkning av terapeutiskt bakteriologiska medel och vacciner samt för rättsmedicinska och medicinskt statistiska undersökningar.

Kommittén, vars ordförande var medicinalrådet Richard Wavrinsky och där bland andra medicinalstyrelsens chef generaldirektör Klas Linroth var medlem, avgav sitt utlåtande den 30 november 1899. Kommittén föreslog inrättande av en statsmedicinsk anstalt med ett bakteriologiskt laboratorium (enligt en reservant två bakteriologiska laboratorier, ett humanmedicinskt och ett veterinärmedicinskt), ett rättsmedicinskt laboratorium huvudsakligen för rättskemiska undersökningar och ett laboratorium för hygien och farmaci. Det sistnämnda skulle ha mycket omfattande uppgifter: prövning av desinfektionsmedel, undersökning av närings- och njutningsmedel, undersökning av luft, vatten och avloppsförhållanden, fabriks- och bostadshygien samt läkemedelskontroll. Denna avdelnings tilltänkta uppgifter motsvarade alltså ungefär de som åvilar nuvarande statens institut för folkhälsan + statens farmacevtiska laboratorium.

Om dittillsvarande anordningar beträffande rättskemistens laboratorium framhöll kommittén det olämpliga i att det var inrymt i rättskemistens privatvåning, vilket bland annat lett till klagomål från övriga hyresgäster i fastigheten. Ventilationssvårigheterna underströks, speciellt avsaknaden av ett särskilt rum för svavelväteutveckling. Vid ombyte av tjänsteinnehavare kunde rättskemisten stå helt utan laboratorium, vilket just för tillfället vore fallet på grund av förre rättskemistens död.

Det skulle föra för långt att gå in på alla faserna i statsmedicinska anstaltens tillkomsthistoria. Här må blott i korthet anföras följande. De medicinska fakulteterna i Uppsala och Lund liksom Karolinska institutet ansåg alla, att det hygieniskt-farmacevtiska laboratoriet skulle få alltför omfattande uppgifter. Medicinalstyrelsen förordade ett hygieniskt-farmacevtiskt laboratorium, men om det ansåges att båda dessa uppgifter icke kunde anförtros åt ett gemensamt laboratorium,

föredrog den att tillsvidare åtminstone ett hygieniskt laboratorium inrättades vid anstalten. Föredraganden professor J. Lundgren instämde med reservanten i kommittén angående behovet av två särskilda bakteriologiska laboratorier. Medicinalstyrelsen avgav på begäran förnyade utlåtanden 1902 och 1906 och anslöt sig slutligen till kravet på två bakteriologiska laboratorier.

Proposition till riksdagen avgavs 1907 och gick ut på inrättande av en statsmedicinsk anstalt bestående av två bakteriologiska laboratorier (ett humanmedicinskt och ett veterinärmedicinskt), ett teknisk-hygieniskt och ett rättskemiskt laboratorium. Statsutskottet förordade dock, att anstalten tillsvidare endast skulle bestå av ett bakteriologiskt och ett rättskemiskt laboratorium. Riksdagen beslöt också i enlighet härmed. Beträffande den teknisk-hygieniska avdelningen hade utskottet ansett behovet mindre trängande, varjämte genom uteslutande av läkemedelskontrollen från dess uppgifter en av de väsentligare grunderna för dess inrättande ansågs ha bortfallit.

Riksdagsdebatten rörde sig i huvudsak om behovet av nyssnämnda avdelning, varvid från regeringshåll särskilt frågan om vattenförorening underströks. Man diskuterade också livligt, om två särskilda bakteriologiska laboratorier behövdes. Om det rättskemiska laboratoriets nödvändighet rådde enighet. Statsutskottet framhöll särskilt, att människors ära, frihet och liv kunde bero på de rättskemiska undersökningarnas resultat och att allt därför måste göras för att undanröja de rådande svårigheterna.

Med hänsyn till senare erfarenheter kan det ha sitt intresse att notera, att enligt hr Starbäcks yttrande i andra kammaren rättskemisten icke blivit hörd i frågan utan själv måst göra sig påmind.

Statsutskottet ansåg, att behovet av den teknisk-hygieniska avdelningen var mindre trängande och att genom uteslutning av läkemedelskontrollen från dess uppgifter en av de väsentliga grunderna för dess inrättande hade bortfallit. Utskottet förordade,

att anstalten tillsvidare skulle bestå av ett bakteriologiskt och ett rättskemiskt laboratorium. Riksdagen beslöt också i enlighet härmed.

För den nyinrättade statsmedicinska anstaltens båda avdelningar, den bakteriologiska och den rättskemiska, jämte vaktmästarbostäder, förhyrdes från den 1 oktober 1908 lokaler i ett privathus, Regeringsgatan 18. Rättskemiska avdelningens lokaler utgjordes av 5 rum om tillsammans 100 m^2 i en vanlig bostadsvåning, som givetvis försetts med gas, vatten och avlopp, kapell och effektiv ventilation samt tillgång till elektrisk kraft.

Rättskemist var vid statsmedicinska anstaltens tillkomst Valter Lindberger, vilken uppehållit befattningen under vakans efter Dillners död och utnämnts till professor och rättskemist i december 1901. Han blev 1908 föreståndare för statsmedicinska anstaltens rättskemiska avdelning och kvarstod som sådan (resp. efter omorganisationen som föreståndare för statens rättskemiska laboratorium) till 1924. Lindberger hade disputerat i Uppsala 1893 på ett arbete om dödliga förgiftningar i Sverige 1873-1892.

I statsverkspropositionen 1917 föreslogs uppdelning av statsmedicinska anstalten i tre fristående laboratorier, statens bakteriologiska, rättskemiska och farmacevtiska laboratorier. En farmacevtisk avdelning hade tillkommit 1914 och stod till att börja med under rättskemistens ledning (till 1924). Vid samma riksdag motionerade hr Ingvarson i andra kammaren om utredning rörande nybyggnad för statsmedicinska anstalten i dess helhet eller åtminstone för dess bakteriologiska avdelning jämte djurstallar. Efter en mycket animerad debatt avslogs motionen, som dock hade tillstyrkts av andra kammarens andra tillfälliga utskott. Propositionen om tre självständiga laboratorier antogs däremot.

Statsmedicinska anstaltens lokaler i Regeringsgatan 18 blev snart otillräckliga. Detta gällde särskilt den bakteriologiska avdelningen, som redan avflyttade därifrån 1915. Här är icke platsen att redogöra för bakteriologiska laboratoriets törnbeströdda väg till en

slutlig lycklig lösning av lokalfrågan. Rättskemiska laboratoriet kvarstannade emellertid i de gamla lokalerna ända till 1923.

Redan till 1916 års riksdag hade dock Kungl. Maj:t i proposition nr 108 föreslagit att fastigheten nr 5 i kvarteret Grönlandet norra, tillhörig Vetenskapsakademien, skulle inköpas för 650,000 kr och ombyggas. Där skulle då medicinalstyrelsen, statsmedicinska anstaltens samtliga avdelningar och tandläkarinstitutet kunna inrymmas. Riksdagen beslöt om inköp av fastigheten, men också om förnyad utredning angående dess användning. Ett omarbetat förslag, enligt vilket efter en mindre ombyggnad endast medicinalstyrelsen och statens rättskemiska och farmacevtiska laboratorier, men ej statens bakteriologiska laboratorium eller tandläkarinstitutet skulle beredas plats och en del befintliga institutioner skulle kvarbli, framlades för riksdagen 1918 (prop. 294). Statsutskottet ansåg emellertid, att det mera omfattande ombyggnadsförslaget vore mera ekonomiskt och att tandläkarinstitutet borde inrymmas inom fastigheten. Riksdagen beslöt också en ombyggnad i huvudsaklig överensstämmelse med det större alternativet. I fråga om bakteriologiska laboratoriets lokaler skulle dock vidare utredning avvaktas.

I augusti 1923 kunde rättskemiska laboratoriet äntligen inflytta i mera tidsenliga lokaler, c:a 300 m^2, i Vetenskapsakademiens gamla byggnad tillsammans med medicinalstyrelsen, statens farmacevtiska laboratorium och tandläkarinstitutet.

Laboratoriets föreståndare Valter Lindberger var tjänstledig på grund av sjukdom alltsedan 1918 och blev enligt gällande reglemente förtidspensionerad 1924. Under hans tjänstledighet och under påföljande vakans uppehöll hans brorson Bertil Julius Lindberger, som varit assistent vid laboratoriet sedan 1913, föreståndartjänsten 1918-1923. Sistnämnda år utnämndes Erik Wolff till föreståndare och kvarstod i tjänsten till uppnådd pensionsålder 1956.

Verksamheten vid laboratoriet, som tidigare huvudsakligen bestått i undersökning av likdelar på förekomsten av giftiga ämnen, ävensom

påvisning av blod- eller spermafläckar i brottmål, utvidgades väsentligt på 1930-talet.

Först upptogs på undertecknads initiativ blodgruppsbestämningar i faderskapsärenden (1930). Ar 1932 övertog laboratoriet alkoholanalyserna i blod från motorfordonsförare. Sedan Widmark i Lund utfört sina grundläggande undersökningar över sambandet mellan alkoholkoncentrationen i blodet och alkoholpåverkan och därefter som försöksverksamhet utfört alkoholanalyser i rattfylleriärenden, ansågs det riktigt att dessa undersökningar skulle förläggas till rättskemiska laboratoriet.

I bägge fallen fick laboratoriet under ett antal år använda de inflytande avgifterna för blodproven till bestridande av såväl avlöning av personal som övriga kostnader för verksamheten.

Det blodgruppsserologiska arbetet svällde alltmera, dels därigenom att ”nya” blodgrupper upptäcktes, dels genom att domstolarna alltmer började tillmäta dessa undersökningar juridisk beviskraft. En särskild roll kom Rh-faktorn att spela. Sedan Birger Broman vid laboratoriet (och vid Kronprinsessan Lovisas Barnsjukhus) skrivit sin avhandling om Rh-faktorn (1944), kom laboratoriet snart att tjänstgöra som ett referenslaboratorium för hela landet beträffande Rh.

Laboratoriet försåg också nyssnämnda institutioner med testserum för Rh-bestämningar. Likaså framställde laboratoriet, särskilt under krigsåren, men även långt senare, ABO-testserum för försvaret.

På grund av den efter kriget våldsamt stegrade motortrafiken ökades också antalet blodalkoholanalyser starkt.

Rättskemiska laboratoriets lokalfråga kom vid denna tidpunkt i ett brydsamt läge. För de avdelningar som sysslade med blodgruppsserologi och blodalkoholanalys hade man i slutet på 30-talet fått ökade utrymmen inom fastigheten Grönlandet norra. Genom statsmakternas beslut 1944 skulle emellertid tandläkarinstitutet få starkt utvidgade lokaler inom fastigheten, delvis på medicinalstyrelsens bekostnad. Styrelsen krävde då att få övertaga rättskemiska

laboratoriets lokaler. Då andra lämpliga lokaler icke stod till buds, tvangs statens farmacevtiska laboratorium, som hade ganska rymliga lokaler i en industribyggnad vid Lindhagensgatan, att ”provisoriskt” dela med sig av dessa, och de båda laboratorierna levde sedan där i nio år i symbios. Trots trångboddheten var sämjan i allmänhet god.

Redan vid överflyttningen till Lindhagensgatan hemställde medicinalstyrelsen om utredning angående nybygge för båda laboratorierna, och Kungl. Maj:t uppdrog i november 1945 åt byggnadsstyrelsen att verkställa sådan utredning. Denna slutfördes 1947, och Kungl. Maj:t framlade proposition till 1949 års riksdag om nybyggnad för båda laboratorierna på Norrbackaområdet. Emellertid väcktes i båda kamrarna motioner om avslag å propositionen och utredning om överflyttning av rättskemiska laboratoriets uppgifter på andra statliga institutioner.

Enligt motionärerna kunde den toxikologiska avdelningen inklusive alkoholavdelningen anslutas till statens kriminaltekniska anstalt medan blodgruppsseralogien kunde förläggas till statens bakteriologiska laboratorium (eller till Karolinska institutets rättsmedicinska avdelning). På så sätt kunde nybyggnads- eller hyreskostnader helt elimineras och endast vissa mindre, lokala omändringar inom kriminaltekniska anstalten och statens bakteriologiska laboratorium skulle erfordras, varjämte sannolikt personalbehovet kunde väsentligt reduceras (!).

Statstttskottet tog starkt intryck av motionerna och hemställde enhälligt om avslag på propositionen och bifall till motionerna.

I första kammaren vidtog en livlig debatt, varvid statsrådet Mossberg med kraft försvarade propositionen. Kammaren beslöt med 63 röster mot 33 (5 avstod) återremiss till utskottet. Även andra kammaren beslöt återremiss. Det torde vara ganska sällsynt att kamrarna går emot ett enhälligt statsutskott.

Efter förnyad behandling av ärendet tillstyrkte statsutskottet Kungl. Maj:ts förslag om ett anslag av l miljon kronor till utbyggnad

för statens rättskemiska och farmacevtiska laboratorier, men föreslog, att bygget icke skulle få igångsättas innan förnyad utredning ägt rum om rättskemiska laboratoriets arbetsuppgifter och om eventuell inskränkning av lokalutrymmena. Båda kamrarna biföll detta salomoniska förslag.

I anledning av riksdagens beslut tillkallades i juni 1949 fem sakkunniga att inom inrikesdepartementet biträda med den begärda utredningen. Denna bedrevs med berömvärd snabbhet, och redan i december samma år avgav de sakkunniga sitt utlåtande.

De sakkunniga hade inhämtat yttranden från ett antal berörda institutioner. Kriminaltekniska anstalten önskade övertaga undersökningar av blod- och spermafläckar. På grund av personal- och lokalbrist kunde den icke övertaga de toxikologiska undersökningarna.

Statens bakteriologiska laboratorium förklarade, att det icke kunde åtaga sig de serologiska undersökningarna utan väsentlig ökning av lokaler och personal.

Medicinska fakulteten i Lund önskade att i brådskande fall få utföra blodalkoholanalyser och toxikologiska undersökningar av likdelar.

Karolinska institutet ansåg att det skulle vara menligt för forskningen, om dess institutioner skulle åläggas att övertaga rutinundersökningar från statens rättskemiska laboratorium.

De sakkunniga själva ansåg, att om vissa av rättskemiska laboratoriets uppgifter överfördes till universitetsinstitutioner i Lund, krävde konsekvensen motsvarande ordning beträffande Karolinska institutet och medicinska fakulteten i Göteborg, men detta skulle i själva verket innebära ett upphörande av statens rättskemiska laboratorium.

Nackdelarna härav vore i första rummet förlusten av en central institution, för vilken dessa undersökningar utgjorde ett huvudintresse. Det ringare antalet undersökningar på de perifera institutionerna skulle försvåra samlandet av vetenskaplig erfarenhet, och fakultets-

institutionernas vetenskapliga forskning skulle hämmas genom rutinarbetet.

Någon personalbesparing skulle icke heller uppnås genom decentraliseringen. Lokalutrymmena för rättskemiska och farmacevtiska laboratorierna enligt det föreliggande förslaget ansåg de sakkunniga icke för stort tilltagna, men den nödvändiga återhållsamheten med investeringar krävde dock åtminstone tillsvidare en viss begränsning ”även om vissa olägenheter för laboratorierna därigenom skulle uppstå.”

De sakkunniga föreslog sålunda att ingen ändring skulle ske i arten eller omfattningen av rättskemiska laboratoriets arbetsuppgifter samt att nybyggnaden för de båda laboratorierna skulle uppföras i huvudsak enligt föreliggande ritningsförslag varvid i byggnaden utrymmen till en yta av 375 m² tillsvidare skulle användas för något annat statens ändamål. Det blev tandläkarhögskolan som utöver sina lokaler på annat håll fick disponera ifrågavarande utrymmen.

Rättskemiska laboratoriet fick i den nya byggnaden disponera c:a 950 m², farmacevtiska laboratoriet c:a 1630 m², varjämte c:a 680 m² avsågs för gemensamt bruk, djuravdelning, operationsrum, bibliotek och matsal m.m. Lokalerna var ändamålsenliga och vid inflyttningen tillräckliga men på grund av nedskärningen saknades utvecklingsmöjligheter för den snabbt expanderande verksamheten.

Den blodgruppsserologiska avdelningen, som ursprungligen endast utförde undersökningar i faderskapsärenden, fick genom Rh-avdelningen en viktig uppgift som central för Rh-undersökningar i hela landet med kontroll, testserumframställning för sjukhus och mödravårdscentraler, utbildning av elever och icke minst genom samarbetet med Karolinska sjukhusets kvinnoklinik beträffande vården av Rh-immuniserade mödrar och deras barn, lidande av morbus hämolyticus neonatorum. Dödligheten bland dessa barn uppgick före 1944 till 62% men har genom blodgruppsserologiens framsteg och blodutbytesterapien sjunkit till omkring 3%. Också i

övrigt har mångfalden av nyupptäckta blodgruppsfaktorer medfört en betydande utvidgning av arbetet på denna avdelning och starkt förbättrade möjligheter till faderskapsbevisning.

Den intensiva utvecklingen inom alla grenar av kemien, särskilt organisk kemi, läkemedelskemi och biokemi, har medfört helt nya problemställningar, men också mycket vidgade möjligheter för det toxikologisk-kemiska arbetet. Mängden av nya syntetiska läkemedel, besprutningsmedel mot växtohyra, betningsmedel, organiska lösningsmedel och andra tekniska preparat erfordrar nya påvisningsmetoder, men de moderna spektrofotometriska, papperskromatografiska, polaragrafiska och enzymatiska metoderna medger också såväl kvalitativ som kvantitativ analys av ofta ytterst små mängder av de giftiga ämnena.

Antalet undersökningar hade stigit ofantligt under 10-årsperioden 1945-54. Under åren närmast före min avgång gjorde jag ett par gånger framställningar till medicinalstyrelsen, att åtgärder skulle vidtagas för att ordna föreståndarens successionsfråga. Den väldiga utvecklingen på laboratoriets båda huvudområden, det kemiska och det blodgruppsserologiska, gjorde ju att det icke längre kunde vara möjligt för en person att på tillfredsställande sätt behärska båda. I maj 1955 hemställde medicinalstyrelsen med anledning härav, att Kungl. Maj:t ville utse särskilda experter att tillsammans med styrelsen utreda rättskemiska laboratoriets omorganisation.

I augusti samma år tillkallade Kungl. Maj:t sakkunniga (justitieombudsmannen Alfred Bexelius, professorn Hugo Theorell och byrådirektören i statens sakrevision Hans Wihlborg) att inom inrikesdepartementet biträda med utredning om erforderlig omorganisation av rättskemiska laboratoriet. I ett preliminärt betänkande i dec. 1955 föreslog de sakkunniga, att vid dåvarande föreståndarens avgång vid utgången av mars 1956 en provisorisk uppdelning av laboratoriet i en kemisk och en blodgruppsserologisk avdelning skulle ske. Detta blev också statsmakternas beslut.

Även denna gång diskuterades överflyttning av vissa av rättskemiska laboratoriets arbetsuppgifter till andra institutioner. Föreståndaren för statens bakteriologiska laboratorium professor Gunnar Olin ansåg det principiellt riktigt att förlägga de blodgruppsserologiska undersökningarna till nämnda institution men laboratoriets stora arbetsbelastning och bristen på lokaler talade emot en sådan anordning.

Professor Axel Westman vid Karolinska sjukhusets kvinnoklinik förordade en överflyttning enbart av Rh-undersökningarna till denna klinik, men också han ansåg, att lokalfrågan skulle vålla svårigheter.

Utredningen fann, att övervägande skäl talade mot en överflyttning av den blodgruppsserologiska verksamheten till statens bakteriologiska laboratorium. En förläggning av densamma till Karolinska sjukhusets kvinnoklinik skulle väl kunna medföra vissa fördelar ur vetenskaplig synpunkt, men den övervägande delen av Rh-arbetet och hela faderskapsverksamheten ansågs dock falla alldeles utanför sjukhusets arbetsområde.

I sitt slutbetänkande, som avgavs den 1 juli 1956, framhöll utredningen, att den kemiska och den blodgruppsserologiska avdelningen icke hade så nära beröring med varandra att sambandet dem emellan av vetenskapliga skäl behövde bibehållas och att sammankopplingen egentligen var historiskt betingad.

Då den hittillsvarande ordningen icke medfört några väsentliga olägenheter och man icke i onödan borde skapa nya administrativa enheter, förordade utredningen likväl att samarbetet mellan avdelningarna tillsvidare skulle bibehållas, men dessa skulle tillförsäkras ”en sinsemellan fullt självständig ställning.” Utredningen ansäg, att beroendet av medicinalstyrelsen varit till nackdel för laboratoriet, som betungats med för mycket administrativa och kamerala göromål. Härigenom och genom otillräckliga personella och materiella resurser hade det vetenskapliga arbetet i hög grad hämmats.

Utredningen föreslog, att laboratoriet skulle stå under ledning av en särskild styrelse. Båda avdelningarna skulle ha en kvalificerad vetenskapsman som chef, benämnd professor. Den kemiska avdel-

ningen skulle bestå av en toxikologisk-kemisk och en alkoholsektion, den blodgruppsserologiska avdelningen av en Rh-sektion och en faderskapssektion. Dessutom skulle en administrativ sektion inrättas.

I Kungl. Maj:ts proposition till 1957 års riksdag bibehölls emellertid i huvudsak det föregående år införda provisoriet. Viss kameral personal ställdes dock till laboratoriets förfogande.

Till föreståndare och professorer för de båda i realiteten självständiga avdelningarna utsågs Birger Broman för den blodgruppsserologiska och Roger Bonnichsen för den kemiska avdelningen.

Såsom var att vänta visade sig lokalutrymmena snart otillräckliga. För att åtminstone partiellt avhjälpa lokalbristen medgavs 1959 att vissa dittills oinredda källarutrymmen finge inredas. (De av tandläkarhögskolan ” tillsvidare” disponerade lokalerna ansågs nämligen icke kunna friställas).

Ar 1965 uppfördes dessutom en provisorisk barackbyggnad för den blodgruppsserologiska avdelningen. Vid denna avdelning hade man upptagit rutinmässig undersökning av haptoglobinerna i faderskapsärenden och avsåg att göra detta även med andra serumgrupper såsom det av Grubb upptäckta Gm-systemet och det av Jan Hirschfeld vid rättskemiska laboratoriet upptäckta Gc-systemet.

Hösten 1964 anmälde emellertid avdelningsföreståndaren, att man på grund av personalbrist tillsvidare måste inställa undersökningarna såväl av S-och Duffy-faktorerna i de röda blodkropparna som av Gc-systemet i serum, vilka dittills utförts vid den s.k. ”utvidgade undersökningen i faderskapsärenden” (bl.a. i fall med flera eventuella fäder). Uteslutningsmöjligheterna för en med orätt utpekad ”fader” skulle härigenom minskas från 73% till 64%.

I mars 1966 tillkallades av socialdepartementet ekonomidirektören hos väg- och vattenbyggnadsstyrelsen K.J. Walck som särskild utredningsman beträffande rättskemiska laboratoriets verksamhet, och denne avgav sitt betänkande i juni 1966.

Detta utmynnade i förslag om såväl personalförstärkning (fyra nya

tjänster å kemiska avdelningen och åtta å blodgruppsserologiska avdelningen) desuttom en väsentlig ökning av båda avdelningarnas lokalutrymmen. På samma gång framfördes i betänkandet förslag om viss decentralisering av verksamheten vid den blodgruppsserologiska avdelningen. Statsverkspropositionen till 1968 års riksdag ansluter sig i fråga om den serologiska avdelningen i huvudsak till nyssnämnda betänkande. Den upptar några nya tjänster och uttalar den förhoppningen, att de teoretiska uteslutningsmöjligheterna vid med orätt uppgivet faderskap (80-85%) genom utökningen av de personella resurserna skall kunna helt utnyttjas.

För den kemiska avdelningen föreslås inga nya tjänster, men ett belopp anvisas för eventuellt erforderlig extra personal för undersökningar i samband med narkotikaproblemet.

Vidare omtalas, att Kungl. Maj:t uppdragit åt byggnadsstyrelsen att utarbeta förslag till om- och nybyggnad för rättskemiska laboratoriet.

Man kan därför hoppas, att laboratoriet snart får bättre möjligheter till forskning och praktiskt arbete på sina skilda verksamhetsfält.

Appendix 2: Edited version of an article published in Nordisk Rettsmedisin nr 2, 35-44, 1998.

Historical Development of Forensic Toxicology in Sweden

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Summary

This article traces developments in forensic toxicology in Sweden over the past 200 years. Information about the organization and structure of the Swedish National Laboratory of Forensic Chemistry is presented as well as the senior scientists and their contributions to research and development in analytical toxicology. The story starts in the early nineteenth century with the efforts of the great chemist Jöns Jacob Berzelius, who was Sweden's first unofficial forensic toxicologist and, among other things, improved on the Marsh test for arsenic. A professorship in forensic chemistry was established in 1874 and Nils Peter Hamberg MD, PhD, was the first to hold this appointment. However, it took many more years until 1908 before a suitable building and laboratory facilities were made available for forensic chemical analysis. Until 1955, the Department of Forensic Chemistry was mainly concerned with the isolation and identification of poisons in autopsy materials, the analysis of alcohol in blood from drunk drivers and blood-group serology in cases of disputed paternity. An independent department of forensic chemistry-toxicology was created in 1957 when Roger Bonnichsen MD, PhD was appointed as the first head of this unit. The toxicology department was subdivided into two main sections, one dealing with the analysis of alcohol in blood and urine from drunk drivers and the other with postmortem toxicology. Rapid developments in physicochemical methods and in-

strumental analysis took place during the 1950s and many original contributions were made by Swedish scientists, including the alcohol dehydrogenase (ADH) method for blood-alcohol analysis. The ADH-method offered higher selectivity and sensitivity for analysis of ethanol in blood compared with Widmark's micro-diffusion and chemical oxidation method using potassium dichromate and sulphuric acid. Furthermore, some of the first ever applications of the powerful technique of gas chromatography-mass spectrometry (GC-MS) in forensic toxicology came from research done in Sweden. The gradual switch from prescribing barbiturates as the major tranquilizer of the 1950ies toward more selective therapeutic agents such as the benzodiazepines created a need for more reliable chromatographic separation methods. One of the first capillary GC methods used for screening analysis of acidic and basic drugs in whole blood was published by scientists at the department of forensic chemistry. The abuse of illicit drugs in society increased during the 1970-1980ies and use of fully automated immunoassay methods of analysis and computer-aided technology were introduced. The Swedish National Laboratory of Forensic Toxicology was accredited in 1996 (EN 45001) and a large part of the workload today involves analysis of alcohol and drugs in blood from impaired drivers, identification of drugs and poisons in postmortem specimens, and drug-abuse screening in urine specimens from prison inmates and street-addicts, as well as the determination of doping agents such as anabolic steroids.

Early Developments

The development of forensic toxicology as a scientific discipline has its roots in the practice of pharmacy, which advanced considerably during the latter part of the eighteenth century. Sweden can proudly boast one of the greatest analytical chemists of all time, namely Jöns Jacob Berzelius (1779-1848). It was Berzelius who realized that physicians needed a better training in chemistry and he helped to establish the first official position as government forensic chemist.

The starting point was a bungled autopsy performed on the crown prince of Sweden, Karl August (1768-1810). During inspection of his troops in the South of the country (Kvidinge hed, Skåne), the Prince fell from his horse and died aged just 41 years. Almost immediately rumors began to circulate that Karl August had been poisoned.

The political climate for European Monarchy was uncertain at the time because of the ongoing French Revolution. The Swedish government commissioned Berzelius, who was already internationally famous as an analytical chemist, to attend the autopsy of Prince Karl August and make any necessary chemical analysis to confirm or exclude poisoning [1]. After making the long journey from Stockholm to the South of Sweden, which took several days, Berzelius was dismayed to find that an autopsy had already been completed by the Prince's private physician in the presence of three Professors from the University of Lund. The body had been eviscerated and the inner organs washed and treated with spices. Even worse, the contents of the stomach and intestine, of major interest when poisoning deaths were investigated, had been discarded. Embalming fluids and spices were added to body organs and cavities making any chemical analysis for the presence of poisons meaningless [1,2]. In a report to the government, Berzelius complained about the lack of understanding for his efforts to detect poisons and called for an official investigation into the way medico-legal autopsies were conduced and the need for chemical analysis in poisoning deaths.

In 1819, the first statutory regulations for medico-legal autopsies appeared in print and these gave detailed instructions about how the body should be prepared and examined, the need to collect appropriate specimens for chemical analysis and the importance of time after death when an autopsy should be performed [3]. If poisoning was suspected as the cause of death, then the appearance of the stomach including its color, smell, and general appearance of the contents were of major interest. Hitherto, the common practice was to feed the

stomach and intestines to a starved animal, such as a cat or dog. Death of the animal after eating this "meal" was considered a necessary proof of poisoning. Autopsies were only to be done by a qualified physician assisted if necessary by a person skilled in chemistry or pharmacy, with the necessary expertise in analytical chemistry [3].

Arsenic poisoning was widespread during the nineteenth century because of the ready availability and ease of purchase of many arsenic compounds, but definite proof of poisoning was not always easy to obtain [4]. A scientific breakthrough in the identification of arsenic in biological specimens came in 1836 when the British scientist James Marsh (1794-1846) published his arsenic mirror test [5]. Arsenic and its compounds were often encountered in household products in the form of arsenous oxide, which was used to provide white coloring to paint and also in wallpaper (Scheele's green). Arsenic salts were widely available in manufactured goods and accidental as well as deliberate poisoning needed to be considered.


Fig 1. Jöns Jacob Berzelius.

Berzelius supported use of the Marsh test for arsenic analysis and made several improvements to the design and construction of the apparatus thus achieving a higher sensitivity and specificity of the method [6]. This modified procedure for forensic analysis of arsenic in biological specimens became known as the Marsh-Berzelius method [7,8]. With this background, Jöns Jacob Berzelius (figure 1) can be embraced as Sweden's first unofficial forensic toxicologist. But as all scientists know, forensic toxicology was only a tiny part of Berzelius's enormous contribution to analytical chemistry. In the annals of science the name of Berzelius ranks alongside those of Davy, Faraday, Lavoisier, Wöhler and Liebig [9,10].

Many years passed after Berzelius's death in 1848 before money was

earmarked by the Swedish government to fund a position as State forensic toxicologist. This was prompted, at least in part, by a rise in alleged poisonings from newly discovered industrial chemicals such as yellow phosphorous, which was used in the manufacture of safety matches, a well known Swedish invention [11,12]. In 1875, Nils Peter Hamberg (1815-1902) became Sweden's first official forensic toxicologist and this appointment carried the academic title and rank of Professor.

Nils Peter Hamberg

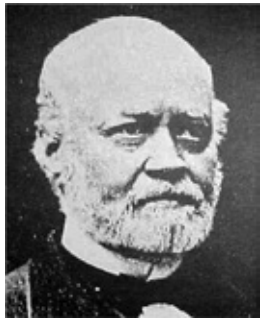

Fig 2. Nils Peter Hamberg.

In 1872 the Swedish Government voted to create a position as forensic chemist with the main task to perform the necessary analysis of poisons during post-mortem examination of corpses. The first holder of this position was Nils Peter Hamberg (1815-1902). Few men were more qualified to uphold this first appointment as Nils Peter Hamberg who was first qualified in pharmacy and for some years owned an apotek (a pharmacy store) in Stockholm. However he was advised to embark on a medical degree and toward this goal he enrolled at Uppsala University. He also took advanced courses in chemistry eventually holding degrees in pharmacy, chemistry, and medicine. His doctoral thesis dealt with the collection, extraction and preservation of medicinal drugs from plants.

Nils Peter Hamberg (figure 2) was a well educated and much traveled man. He had made several study visits to Germany, France, Italy, and Great Britain, which were centers of excellence in the natural sciences during the nineteenth century. M.J.B. Orfila (1787-1853) was the undisputed leader and founder of forensic and analytical toxicology [13,14]. Orfila was born on the Spanish island of Minorca but spent his professional career working in Paris, France when he wrote his famous treatise on the nature and analysis of poisons in biological

materials [15]. Another great European specialist in toxicology and psychoactive drugs was the German Louis Lewin (1850-1929). Lewin managed to produce more than 250 papers and also several classic text books dealing with adverse drug reactions and the disposition and fate of drugs and poisons in the body during his long career as a toxicologist [16,17].

Although Hamberg's contributions to forensic toxicology cannot be compared with those of Mathieu Orfila (1787-1853) or Louis Lewin (1850-1929), he was a prolific writer and experimenter and published scores of papers not only in Swedish journals but also in German and English periodicals. These dealt with the effects of drugs on the body, such as cannabis and the newly discovered salts of morphine and other alkaloids (nicotine and strychnine). Hamberg also investigated the mode of action of poisons and the efficacy of antidotes with major focus on chloroform, prussic acid, carbolic acid (phenol), arsenic, phosphorous, and heavy metals and their salts. It seems that Hamberg was also one of the first to recommend analyzing other organs and tissues besides stomach contents when unnatural deaths were investigated and poisoning was suspected. He also discussed the possibility of identifying metabolites of these substances as additional proof of poisoning.

Unfortunately, the analytical methods available at the time were rather primitive and this hampered progress in toxicology. The methods available to the toxicologist were various spot tests and color reactions that provided only a qualitative identification of poisons. In 1856, Hamberg became an honorary member of the Pharmaceutical Society of Great Britain and in 1878 he was elected to membership of the Royal Swedish Academy of Sciences. After his retirement, he received other honors and awards from the government in gratitude for his contributions and services to forensic toxicology and the many expert committees upon which he served. Hamberg enjoyed a long and productive life (87 years) always maintaining his

enthusiasm for teaching and the practice of forensic toxicology even after becoming blind in 1876 owing to cataracts [18].

Forensic toxicology 1876-1955

The appointment of Nils Peter Hamberg as the first forensic toxicologist in Sweden, with his dual-qualifications in chemistry/pharmacy and medicine, set a standard for future appointments. People with aspirations to become government forensic chemist needed MD and PhD degrees and the next incumbent in 1883 was Axel Johan Wimmerstedt, a gifted scholar qualified in medicine and chemistry as well as the classics (Greek). Hjalmar Dillner held the position as government forensic chemist between 1895-1898, when he met an untimely death by drowning - it seems that he fell into the river late one evening when walking home through Stockholm after an evening with friends [18]. The position as forensic toxicologist was held vacant for a number of years after Dillner's unexpected demise until Karl Axel Lindberger was appointed professor of forensic chemistry in 1901.

Lindberger received his MD degree form Uppsala University in 1893 for a thesis dealing with the epidemiology of poisoning in Sweden 1873-1892 [19]. Table 1 gives examples of the kinds of poisons detected in autopsy materials during this period and the frequency of their occurrence. At this time, there was a clear distinction made between inorganic poisons, with arsenic and phosphorous topping the list, and organic poisons dominated by alcohol, morphine and other opiates. Table 2 gives more details about the circumstances surrounding the administration of various poisons with a predominance in connection with abortion, suicide, and attempted murder. After 1833 when yellow phosphorous was widely used to manufacture matches, this substance became a major poison in Sweden and other countries [4, 19]. As shown in Table 3, yellow phosphorous was widely employed in attempts to induce an abortion, often unsuccessfully with loss of life of the mother and the fetus.

Table 1. Examples of poisons encountered in death investigations in Sweden 1873-1892, the frequency of their use according to official statistics. N = number of instances.

N	Inorganic Poisons	N	Organic Poisons
743	Phosphorous	273	Alcohol
405	Arsenic	20	Opiates
55	Carbon monoxide	19	Morphine
51	Potassium cyanide	16	Strychnine
16	Sulphuric acid	3	Veratrine
14	Hydrochloric acid	19	Carbolic acid
6	Nitric acid	14	Chloral hydrate
16	Potassium dichromate	3	Chloroform
4	Mercury	6	Nitrobenzene
3	Barium Carbonate	2	Prussic acid

Table 2. Percent distribution of fatal poisonings according to circumstances under which the poisons were administered 1873-1892. N = number of instances.

Circumstances	N	Percent
Abortion	680	36
Suicide	420	22
Murder	121	6.4
Accident	143	7.6
Medication (overdose?)	13	0.6
Quackery	8	0.4
Mistake with prescription	2	0.1
Alcoholic Intoxication	261	13.8
Unknown	242	12.8
Totals	1890	100

For many years the government forensic toxicologist was expected to analyze the autopsy specimens in his private apartment, because a laboratory building with facilities for chemical analysis and experimental work did not exist. After a number of written complaints about this unsatisfactory situation a government committee was appointed and they recommended establishing a State Laboratory of Forensic Chemistry. Accordingly, in 1908, a private house was purchased in central Stockholm, and it was equipped with gas, water, and other

facilities. Forensic chemistry disposed of 5 rooms (100 m²) although sin the same building laboratories specializing in bacteriology and pharmacy were also housed. This situation soon became unworkable, owing to shortage of space, increasing work-load and requests for chemical analysis in many situations, not just poisonings. A new government commission recommended a larger premises (300 m²) for the sole purpose of forensic chemical and toxicological investigations and such a building was officially opened in 1923 [18].

Table 3. The most commonly encountered poisons in Sweden over the period 1873-1892 and the circumstances under which they were used.

Substance*	Murder	Suicide	Abortion	Accident	Other	Totals
Phosphorous	20	74	616	2	31	743
Arsenic	90	199	49	41	26	405
Carbon monoxide	-	-	-	55	-	55
Potassium Cyanide	-	50	-	1	-	51
Mineral acids	4	19	4	8	1	36
Totals	114	342	669	107	58	1209

* Only the top 5 poisons are listed.

Owing to poor health, Karl Axel Lindberger took early retirement from his post as forensic chemist and in 1918 his nephew served as acting chief toxicologist for a few years. The next chief forensic chemist was Erik Wolff, MD, PhD, who was appointed in 1925 and held the post with great distinction until retirement in 1956. During Wolff's tenure as forensic toxicologist, the volume and diversity of the work undertaken expanded, especially the need for blood alcohol analysis in cases of drunken driving, because in 1941, a punishable blood-alcohol limit was established (0.80 ‰ (mg/g) [20,21]. Enforcement of this drink-driving law required use of an accurate and precise method of analysis considering that the results would serve as prosecution evidence in a criminal case [20,21].

Erik Wolff published many scientific papers during his tenure as chief forensic toxicologist including a survey of fatal poisonings in

Sweden between the years 1911-1930 [22]. Table 4 gives examples of the substances encountered during successive 5 year periods and can be compared with the types of poisons shown in table 1 covering the period 1873-1892. One can see that use of arsenic and phosphorous as poisons, which earlier had dominated, have virtually disappeared. Instead, sublimate (mercuric chloride) ranks high on the list as well as an upsurge in barbiturate poisoning after 1921 when this synthetic drug started to become prescribed as a sedative and hypnotic on a large scale.

Table 4. Examples of the substances encountered in poisoning deaths in Sweden over the period 1911-1930 and the frequency of their occurrence.

Substance	**1911-15**	**1916-20**	**1921-25**	**1926-30**
Phosphorous	1	0	0	0
Arsenic	1	5	5	5
Sublimate	15	11	10	10
Acids and bases	25	43	29	30
Other inorganic poisons	1	0	2	4
Phenol	7	0	2	2
Carbon monoxide	7	10	8	38
Alcohol	0	6	1	2
Methanol	0	1	1	2
Barbiturates	3	8	32	59
Morphine	3	8	3	11
Other substances	8	22	29	25
Totals	71	123	122	188

Wolff's laboratory was also responsible for blood-group serology in cases of disputed paternity [23,24] and also for the identification of blood and semen stains collected at crime scenes [11,18]. Accordingly, the typing of blood became a major responsibility for the department of forensic toxicology during the 1930-1940ies when the Rh factors were discovered [25]. The rapid escalation in road traffic in post-war Sweden with better roads and faster cars also meant that many accidents were caused by drunk drivers. This created a need for more laboratory space to deal with blood-alcohol analysis and at the

same time, the quality assurance of the results became of great concern and for this purpose statistical control charts were introduced [26]. Erik Wolff introduced an elegant method for the determination of carboxyhemoglobin in blood samples. This method, which was based on the principle that carboxyhemoglobin was more resistant to heat than oxyhemoglobin, became widely used in many forensic toxicology laboratories [27].

Erik MP Widmark


Fig 3. Erik MP Widmark.

Erik MP Widmark (1889-1945) was never formally employed as a forensic toxicologist in Sweden although for several years, during the 1920ies, his laboratory was responsible for making blood-alcohol determinations in drunk driving offences because Widmark had developed and tested the official analytical method [28]. Erik Widmark (figure 3) was appointed Professor of Medicinal Chemistry at the University of Lund in Southern Sweden at the age of 31 years and his life and scientific achievements have been reviewed elsewhere [20,21]. The research work for Widmark's MD thesis was presented in 1917 and this was concerned with quantitative analysis of acetone in blood and the disposition and fate of acetone in the body including excretion in breath and urine as well as clinical applications of the assay for monitoring ketoacidosis in diabetic patients [29]. Several original papers were published from his thesis in international journals and reading these articles today makes it abundantly clear that Widmark was without question the founding father of the scientific discipline that we now call pharmacokinetics [30,31].

As early as 1914, Widmark realized the need for a more objective test that a person was intoxicated by alcohol. To these ends, he suggested analyzing ethanol in urine samples as a clinical test to demonstrate alcohol in the body and also as a way to monitor absti-

nence [32]. He later turned his attention to the analysis of alcohol in blood samples by developing a micro-diffusion method, which was published in 1922 in a German journal (Biochemische Zeitschrift) (figure 4).

Biochemische Zeitschrift

Eine Mikromethode zur Bestimmung von Äthylalkohol im Blut.

Von

Erik M. P. Widmark.

(Medizinisch-chemischen Institut, Lund.)

(Eingegangen am 29. April 1922.)

Mit 3 Abbildungen im Text.

Eine Anzahl Probleme der Alkoholforschung stehen vor ihrer Lösung, sobald wir über eine hinreichend bequeme und genaue Methode zur Bestimmung der Alkoholkonzentration im Blute unter verschiedenen Versuchsbedingungen verfügen.

Die diesem Zwecke dienenden älteren Methoden, die alles gut bekannt sind, um hier besprochen zu werden, haben alle den gemeinsamen Nachteil, daß sie zu große Blutmengen erfordern (mindestens 1—2 ccm), um beim Menschen oder kleineren Tieren in größerer Ausdehnung verwendet werden zu können.

Das Verfahren, durch Bestimmungen des Alkoholgehaltes im Urin indirekt die Veränderungen desselben im Blute zu ermitteln, hat sicherlich einen gewissen Vorteil[1]). Aber nicht unter allen Versuchsbedingungen tritt ein Diffusionsgleichgewicht zwischen Alkohol des Blutes und den Urins ein und besonders rasche Schwankungen der Blutalkoholkonzentration widerspiegeln sich nicht immer getreu in der des Urins.

A

B

C

Fig 4. Erik MP Widmark's micro-diffusion method for blood alcohol analysis.

This micro-method proved highly reliable and was used for legal purposes in Scandinavian countries and in Germany when drunken drivers were prosecuted [28]. This procedure required only 80-100 mg of a capillary blood specimen and ethanol or other volatiles were separated from the biological matrix by distillation and then oxidation with a mixture of potassium dichromate and sulphuric acid in excess [28]. The amount of oxidizing agent remaining after the reaction with ethanol was determined by adding potassium iodide and back-titration with sodium thiosulfate using a starch indicator to detect the endpoint.

Thanks to the high reliability and practical usefulness of Widmark's blood-alcohol method Sweden was one of the first countries to introduce statutory alcohol limits as evidence of driving under the influence of alcohol [26]. Widmark also developed methods and protocols for conducting a clinical examination of drunk drivers and he established the relationship between blood-alcohol concentration (BAC) and

various signs and symptoms of intoxication in thousands of apprehended drunk drivers. Based on this investigation, Widmark was able to report percentage of individuals deemed impaired at any particular BAC. This information was very helpful when drunk drivers were prosecuted. Widmark recognised the existence of and defined the concepts of concentration tolerance and consumption tolerance to alcohol. He went on to study the mechanism of development of tolerance in animal models using dogs [21,26].

Perhaps the name of Erik Widmark is best known internationally for his pioneer contributions to clinical pharmacokinetics of drugs including acetone, methanol, and ethanol, which he called the indifferent or neutral narcotics [21]. Widmark's magnum opus was published in 1932 entitled *Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung* the front cover of which is shown in figure 5 [33]. A testimony to the impact and importance of this original German monograph is gleaned from the fact that it was translated into English 50 years later published in 1981 and entitled *Principles and application of medico-legal alcohol determination* [34].

The problems and pitfalls associated with the analysis and interpretation of blood-ethanol concentration in autopsy materials were also studied by Widmark and his findings were reported in a book coauthored with Einar Sjövall (1879-1964), who was Professor of Forensic Medicine at the University of Lund [35]. The concentrations of alcohol in body fluids are likely to change after death, owing to putrefaction processes. Widmark therefore recommended sampling blood from different parts of the body, such as femoral vein and cardiac blood along with bladder urine.


Die theoretischen Grundlagen
und die praktische Verwendbarkeit der
gerichtlich-medizinischen Alkoholbestimmung

Von

Prof. Dr. E. M. P. Widmark

Urban & Schwarzenberg

Fig 5. Title page from Widmark's German monograph.

Periods of change and reorganization 1955-1979

Even before Erik Wolff's retirement in 1956 several proposals were made to abandon the notion of having one central laboratory for forensic toxicology and instead contract the work to various university departments (e.g. medical chemistry and pharmacology). Other tasks such as analysis of blood and semen stains could be done at the police forensic science laboratory and blood grouping could be performed at the hospital laboratories that specialize in this kind of work. However, the Swedish government opted to retain a central forensic toxicology laboratory for the whole country motivated by the need to have personnel with a high level of expertise and experience in one and the same place. At this juncture a major organizational change took place because the work being done at the department was diverging away from chemistry and toxicology into other areas particularly into blood-group serology [11,18]. This made it virtually impossible to recruit a laboratory director with suitable qualifications, interest, and expertise in chemistry, toxicology, medicine, and serology to head the department. Accordingly, it was decided to create two independent departments, one specializing in alcohol and toxicology and the other in blood-grouping and serology. The heads of both departments were awarded the title of professor and the first person to hold the chemistry-toxicology position was Roger Bonnichsen MD, PhD (1913-1986).

Roger K. Bonnichsen

Roger Bonnichsen (figure 6) was born and educated in Denmark and he was awarded a doctor of medicine degree from the University of Copenhagen later qualifying as a physician. He migrated to Sweden in 1940 after his home country was invaded by the Germans [36]. On arrival in Stockholm, Bonnichsen was advised to join the research group at Karolisnka Institutet headed by the biochemist Hugo Theorell (1903-1982). With Theorell (figure 6) as his teacher and mentor, Bonnichsen embarked on studies for his PhD degree and

defended a thesis entitled "Studies on Blood and Liver Catalases" in 1948 [37].

Fig 6. Hugo Theorell and Roger K Bonnichsen.

In collaboration with a younger colleague Dr. Anders Wassén, Bonnichsen also managed to extract from horse liver the enzyme responsible for metabolism of ethanol as reported in a paper entitled "Crystalline Alcohol Dehydrogenase (ADH) from Horse Liver" [38]. With the ADH enzyme now in a pure crystalline form, the way was open to study the mechanism of physiological alcohol combustion and a new analytical method was development to determine ethanol in biological fluids, the so-called ADH method [39-42]. This series of articles on the preparation and properties of ADH, although mainly published together with Theorell, helped to establish Bonnichsen's name internationally and paved the way for his later appointment as Professor of Forensic Chemistry. Professor Hugo Theorell was awarded a Nobel Prize in Physiology or Medicine in 1955, which made him an influential person in Sweden concerning questions of medical and biological chemistry, including forensic chemistry and he served as government expert on many scientific committees.

After Erik Wolff retired, Bonnichsen was appointed as acting head of the Department of Forensic Chemistry mainly as a result of his research on the new and improved method of blood-alcohol analysis (ADH method), which appeared in print in 1951 [39]. With the recommendation and support of his mentor, Roger Bonnichsen was officially appointed professor and head of the National Laboratory of Forensic Chemistry in Sweden in 1957.

During Roger Bonnichsen's time as head of the Department of Forensic Chemistry the laboratory buildings were located close to the campus of Karolinska Institutet, although there were no official links between the medical faculty and scientists at the government laboratory. However, this close proximity to basic medical research gave many opportunities for joint research projects and for recruitment of new scientific staff. The two most senior scientific positions in Bonnichsen's department, besides the director himself, were the section heads with the title of laborator, a position roughly equivalent to an associate professor within the university. These positions were held by Stig Åqvist MD, PhD (1923-1976), who was responsible for the alcohol section and Andreas Maehly PhD (1918-1997), who supervised the work in postmortem toxicology. Maehly was subsequently appointed professor and director of the police forensic science laboratory, and moved to Linköping in 1972 when the laboratory was re-located.

Research Developments 1955-1979

During Bonnichsen's time as director of the forensic chemistry laboratory, profound and rapid developments took place in analytical chemistry and toxicology. The use of spot-tests and color reactions including colorimetry, which provided only qualitative or semi-quantitative results, were replaced by chromatographic separation methods (paper and thin layer) and spectrophotometric procedures (infrared and ultraviolet). This new era of instrumentation permitted both qualitative and quantitative analysis of drugs and poisons in body fluids and tissues. During the 1960ies scores of articles were published covering all aspects of forensic chemistry and toxicology by Bonnichsen Åqvist, Maehly and others at the laboratory [43-45].

Among other things, one of the first gas chromatographic methods for quantitative analysis of volatiles in blood including ethanol, methanol, acetone, and acetaldehyde was reported in 1962 [46]. The use of mass spectrometry as a specific detector after initial clean-up and separation of the components of a mixture by gas chromato-

graphy was pioneered by workers at Karolinska Institutet such as Ragnar Ryhage and Bo Holmstedt. The combination of gas chromatography with mass spectrometry (GC-MS) revolutionized the structural identification of drugs and their metabolites in body fluids and furnished unsurpassed sensitivity and specificity. The analytical method of GC-MS was used extensively to answer many important questions about the pharmacology and toxicology of newly discovered psychoactive drugs and their metabolites [47-51]. In collaboration with Ryhage's group at the Karolinska Institute, the Department of Forensic Chemistry took advantage of GC-MS as an analytical technique and applied it to routine casework including blood-ethanol analysis [52].

The problems associated with analyzing alcohol in autopsy materials continued to attract attention especially when trauma to the body was extensive [53-55]. Even today difficulties exist in interpreting postmortem blood-alcohol determinations, despite the use of gas chromatography on two different stationary phases and the high selectivity offered by this method of analysis. Responsibility for the analysis of doping agents in sports such as horse racing also fell within the domain of the forensic toxicology laboratory during these early years [56].

This dynamic phase of development and research in forensic toxicology was cut short in the early 1970ies for two principal reasons. First, the future of the department was overshadowed and made uneasy by the Swedish parliament's decision to relocate various government organizations, including the Department of Forensic Chemistry away from Stockholm to smaller provincial towns. Second, Andreas Maehly, who was the driving force in postmortem toxicology, moved to take up a position as Professor and Head of the State Laboratory of Forensic Science and also the untimely death of Stig Åqvist aged 52 years. After these events, it proved difficult to fill the vacant senior positions with suitably qualified personnel having a genuine interest in the subject of forensic toxicology.

Department of Toxicology at Karolinska Institutet

During the 1960-1970ies a considerable amount of research was being done at Karolinska Institutet in the field of analytical toxicology of drugs and poisons, at the Department of Toxicology, headed by Professor Bo Holmstedt. Among other things, Holmstedt and his coworkers pioneered some of the first applications of the powerful technique of gas chromatography-mass spectrometry (GC-MS) in clinical pharmacology and toxicology. Analysis of therapeutic drugs by mass fragmentography (a term coined by Holmstedt) was described for determination of the prototype tranquilizer drug chlorpromazine and its metabolites in human blood already in 1966 [57].

This was followed by quantitative GC-MS analysis of the tricyclic antidepressants nortriptyline in blood after therapeutic doses [58]. Several major reviews were written on the application of GC-MS for the analysis of drugs and their metabolites in biological media [59,60]. The concentration-time profiles of illicit drugs in blood such as tetrahydrocannabinol after smoking cannabis [61] and cocaine in the blood of coca chewers were reported [62]. Scores of papers and reviews appeared highlighting the application of GC-MS to study the clinical pharmacokinetics of therapeutic and illicit drugs, including hallucinogens. Many of these new methods have had a direct and immediate usefulness in forensic toxicology when dealing with the poisoned patient [63]. Holmstedt's expertise in analytical toxicology was required during the investigation of several high profile murder cases in the USA involving alleged poisoning by the skeletal muscle relaxants succinylcholine and *d*-tubocurarine [64,65]. The isolation, purification, and identification of succinylcholine in putrefied tissues taken from embalmed bodies proved a challenging analytical problem and the Department of Toxicology at the Karolinska Institute was actively involved with this work [66].

Forensic toxicology moves to Linköping

In 1971, the Swedish parliament approved plans to relocate certain government agencies, including the forensic laboratories, from Stockholm to Linköping with the aim of creating more job opportunities outside the capital city. The National Laboratory of Forensic Chemistry was ordered to start relocating from Stockholm to Linköping in 1972 and many people were unhappy with this decision including Professor Bonnichsen, who fought vigorously to delay the move as much as possible. Indeed, he successfully blocked the move to Linköping and kept the laboratory in Stockholm until he reached the retirement age in 1978. Moreover, a few years before he retired, Bonnichsen suggested that breath-alcohol testing might replace blood-alcohol analysis in traffic law enforcement. Because the analysis of blood samples from drunk drivers was one of the main duties of the forensic toxicology laboratory, the loss of this work would require a major reorganization. With the support of other interested parties, Bonnichsen persuaded the central police authority (Rikspolistyrelsen), which in turn managed to convince the Department of Justice, that evidential breath-alcohol testing was feasible and should be seriously considered. Studies on the reliability and performance of various evidential breath-alcohol instruments were commissioned and when this work was in progress, the blood-alcohol section of the laboratory was to remain in Stockholm with Bonnichsen still in charge of the work. If breath-alcohol testing proved to be a realistic alternative to blood-alcohol analysis, it was thought that the alcohol section would not need to relocate to Linköping because the number of blood specimens from drunk drivers would be drastically reduced.

Bonnichsen officially retired as Professor and Director of the National Laboratory of Forensic Chemistry in 1979 when his position was opened for applicants. Six people applied for the vacant position and their scientific publications were sent for peer-review and critical appraisal to experts in Forensic Medicine/Toxicology (Sten Orrenius),

Clinical Chemistry (Bo Sörbo), and Forensic Chemistry (Alf Lund). The external reviewers were unanimous in their decision that Jan Schuberth, MD, PhD, who worked for his thesis under Hugo Theorell, was the best candidate to succeed Bonnichsen. This recommendation was endorsed by the Minister of Health and Schuberth became professor and head of forensic toxicology in 1979 with the unique opportunity of building-up a new department at the University Hospital in Linköping. Schuberth moved to Linköping in 1980 although the blood-alcohol section and many of its staff remained in Stockholm where Bonnichsen still exerted considerable influence. Indeed, he remained actively involved with the breath-alcohol testing program after his retirement in 1979 until he died of colon cancer in 1986.

Under Schuberth's leadership after moving to Linköping the analytical instruments for a modern forensic toxicology laboratory were improved considerably, with a major emphasis on gas chromatography-mass spectrometric methods for qualitative and quantitative analysis. The solvent extraction of drugs from tissue using reagents such as chloroform and ether was gradually replaced with solid phase extraction and use of less toxic solvents such as methanol and butyl acetate [67]. The technique of capillary column gas chromatography was introduced to replace packed columns and whole blood was used as the specimen for screening of acidic and basic drugs instead of the traditional use of liver tissue [68,69].Verification was done by gas-chromatography-mass spectrometry whenever possible thus providing the ultimate selectivity for identification of drugs and poisons in forensic casework [70,71]. Many original contributions were made in analytical toxicology during Schuberth's time as director of the laboratory including the first report of significant interference with opiate assays after eating poppy-seed cakes [72]. Schuberth's own research interest during later years dealt with the analysis of low-molecular volatiles in biological specimens by headspace extraction

and the applications of GC-MS and ion-trap detection for identification [73,74]. This approach was applied successfully to the analysis of body fluids from solvent abusers and also during investigations of suspected arson [75].

Alcohol toxicology moves to Linköping

During the period 1979-1985, the alcohol section of forensic toxicology was located in Stockholm although the rest of the department and most of the staff were already established in Linköping. This isolation of the alcohol group from the rest of forensic toxicology and the lack of a formal head of the section created problems and a major blunder occurred when blood samples from two individuals suspected of drunken driving were wrongly identified. This mishap and the resulting news-media coverage prompted the government to relocate the alcohol section to Linköping as quickly as possible without waiting for the introduction of evidential breath-alcohol testing.

In 1985, A.W. Jones, PhD, DSc, was appointed head of the alcohol toxicology section (laborator) when the unit moved to Linköping. Hitherto, Jones worked as a research assistant at the Department of Experimental Alcohol and Drug Addiction Research at Karolinska Institutet and also served as consultant at the forensic department in questions related to alcohol and drunken driving. Jones held a degree in chemistry from the University of Cardiff, Wales, UK, and obtained his PhD in 1974 for a thesis concerned with analytical and physiological aspects of blood and breath-alcohol analysis. This was followed by postdoctoral work at the Department of Alcohol Research at Karolinska Institutet in Stockholm, where Jones first collaborated with Professor Leonard Goldberg between 1973-1977 and later with Professor Erik Änggård between 1980-1984.

After the alcohol section was eventually relocated from Stockholm to Linköping in October 1985, rapid developments took place and the ADH method, which had been used for blood-alcohol analysis since the mid-1950ies, was replaced by computer-aided headspace gas

chromatography [76]. This method is still used today and has become the standard procedure for quantitative and qualitative analysis of volatile substances in biological fluids. During the past 12 years, besides routine analytical work dealing with drunk and drugged drivers, an active research programs has been created in forensic alcohol toxicology. Since 1986 hundreds of papers have been published dealing with forensic alcohol research, particularly the distribution of ethanol in blood, plasma, urine, and saliva [77-79], the theory and application of breath-alcohol analysis [80-82], the pharmacokinetics of ethanol alone [83-85] and in combination with other drugs [86,87], and more recently the use of biological markers of excessive drinking [88,89]. Most articles have appeared in major forensic science and toxicology journals and can be easily located with the help of on-line searching of various databases, such as PubMed.

In 1994, A.W. Jones was appointed adjunct professor in experimental alcohol research at the University of Health Sciences in Linköping. This part-time appointment gave more opportunity for collaboration with clinical staff at the University Hospital in Linköping and also the supervision of students for research degrees.

Evidential breath-alcohol testing in Sweden

In 1989 the Swedish government approved the use of evidential breath-alcohol testing as evidence to prosecute drunken drivers. The first instrument approved was Intoxilyzer 5000S, a quantitative infrared analyzer [90]. The introduction of evidential breath-alcohol testing meant that the number of blood samples submitted for determination of alcohol after 1990 decreased appreciably (figure 7). However, blood-alcohol analysis will always be needed because some drunk drivers refuse to co-operate in providing a breath sample or they might be too impaired to exhale into the evidential breath-analyzer for a sufficiently long time. Furthermore, some victims of road traffic crashes might require emergency medical treatment, which makes it more convenient to take blood for analysis instead of breath.

When an evidential breath-test instrument is not functioning properly or if an interfering substance is detected in the person's breath, this also leads to blood samples being taken for analysis of alcohol.

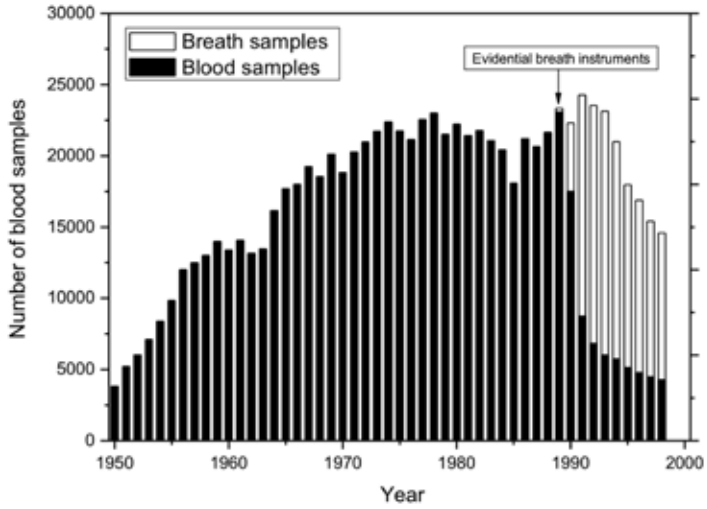

Fig 7. Graph showing the development in number of blood samples for alcohol analysis.

Creation of the National Board of Forensic Medicine

The National Board of Forensic Medicine (Rättsmedicinalverket, RMV) was established by the Swedish government in 1991 with responsibilities for forensic chemistry, forensic medicine, forensic psychiatry, and blood-group serology in disputed paternity investigations. Dr. Kurt Roos was appointed as the first director general of this organization, which presently has about 450 employees. Roos was trained as a physician in Göteborg and after graduation worked as a clinical chemist for a few years before joining the Department of Health and Social Welfare. Since taking up his appointment as chief administrator for the forensic medical services in Sweden, Roos has been an enthusiastic and dynamic leader with a keen interest in quality assurance issues and education and training of staff at all levels within the organization. Despite a weak and troubled economy in Sweden

during the 1990ies, Kurt Roos has managed to secure substantial government funding to help initiate and support various research projects of special interest to forensic medicine, forensic genetics and forensic toxicology.

Concluding Remarks

Sweden has a population of approximately 9.5 million people living in a land area roughly the size of California or twice that of the United Kingdom. Each year about 5,000 medico-legal autopsies are performed in Sweden and in over 99% of these a comprehensive forensic toxicology service is requested [91]. Roughly 4,600 blood samples are submitted by the police from drunk or drugged drivers and about 800 specimens are analyzed for the presence of narcotics and psychoactive prescription drugs. The main abused drugs in Sweden are amphetamine, cannabis, and various prescription medications, mainly benzodiazepines (e.g diazepam, flunitrazepam). The laboratory receives annually about 30,000 urine samples from prison inmates to control abuse of drugs. More recently, blood and/or urine samples from individuals detained by the police on suspicion of taking illicit drugs are also sent to the forensic toxicology laboratory. This workload includes both screening and verification analysis and amounts to about 9,000 samples annually. Within the past few years efforts have been made to develop GC-MS methods for identification of anabolic steroids in urine specimens, because it seems likely that the use of these doping agents will shortly become a criminal offence in Sweden [92].

During the roughly 200 year history of the National Laboratory of Forensic Chemistry, the names of the department heads, the periods of their service and their main research interests are summarized in table 5. Although the main function of the government forensic toxicology laboratory is to provide a comprehensive and effective analytical service for forensic pathologists and police authorities, a program of research and development work is essential to ensure high standards.

Table 5. Chief toxicologists, relevant time period and main research interests

Chief toxicologist	Time Period	Main Research Interest
Professor Nils Peter Hamberg, MD. PhD	1875-1883	Medicinal plants. Isolation and analysis of inorganic and organic poisons from tissue.
Professor Axel J. Wimmerstedt, MD, PhD	1883-1894	Composition of natural waters from Swedish health spas.
Professor Hjalmar Dillner, MD, PhD	1895-1898	Developed methods for analysis of phosphorus and arsenic and other metals in biological materials.
Professor Valter H. Lindberger, MD. PhD	1908-1924	Epidemiology of poisoning deaths in Sweden
Professor Erik Wolff, MD, PhD	1925-1956	Blood grouping in paternity disputes, detection of poisons, carbon monoxide and pharmacokinetics of ethanol.
Professor Roger K. Bonnichsen, MD, PhD	1956-1978	Alcohol analysis by enzymatic and chromatographic methods, first applications of GC/MS for drug analysis in toxicology.
Professor Jan S. Schuberth, MD., PhD	1979-1990*	Development and application of modern analytical methods in toxicology especially capillary GC and GC/MS for analysis of organic volatile substances.
Professor Göran Larson, MD, PhD	1996-1998	Molecular and cell biology of complex sugars, glycobiology , analysis of drugs of abuse in hair

* Between 1990 and 1996, mainly to deal with administrative tasks, John Jonsson PhD, and Johan Killander MD, PhD served as acting heads of the department.

Figure legends

1. Jöns Jacob Berzelius (1779-1848) internationally renowned Swedish chemist, who first suggested the need for a government forensic chemist.
2. Nils Peter Hamberg (1815-1902) the first Professor of Forensic Chemistry in Sweden.
3. Erik MP Widmark (1889-1945) Professor of Physiological Chemistry, University of Lund.
4. Title page from Widmark's article published in the journal Biochemische Zeitschrift in 1922, which described a micro-diffusion method for determination of alcohol in blood.
5. Title page of Erik MP Widmark's German monograph first published in 1932 and translated into English 50 year later entitled "Principles and applications of medico-legal alcohol determinations."
6. Professor Hugo Theorell (1903-1982) chairman of the Department of Biochemistry at Karolinska Institutet and Nobel Prize winner in Physiology or Medicine in 1955.
   Professor Roger K. Bonnichsen (1913-1986) Director of the National Laboratory of Forensic Chemistry in Sweden from 1956 to 1979.
7. Development in the number of blood samples sent for alcohol analysis from apprehended drivers in Sweden 1950-1998 before and after introduction of evidential breath-alcohol testing on 1st July 1989.

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