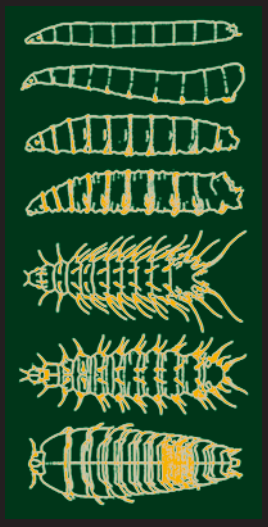

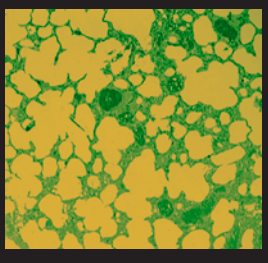

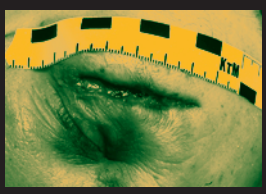

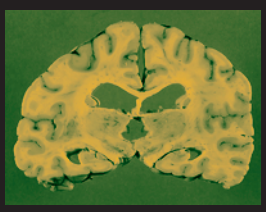

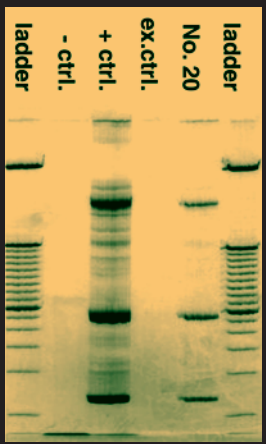

Forensic Pathology Reviews

Volume 2

Edited by

Michael Tsokos, MD

HUMANA PRESS

Forensic Pathology Reviews

Forensic Pathology Reviews

Michael Tsokos, *MD,* Series Editor

Forensic Pathology Reviews, Volume 3, edited by ***Michael Tsokos,*** *2005*
Forensic Pathology Reviews, Volume 2, edited by ***Michael Tsokos,*** *2005*
Forensic Pathology Reviews, Volume 1, edited by ***Michael Tsokos,*** *2004*

Forensic Pathology Reviews

Volume 2

Edited by

Michael Tsokos, MD
Institute of Legal Medicine, University of Hamburg, Hamburg, Germany

Humana Press
Totowa, New Jersey

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

humanapress.com

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel: 973-256-1699; Fax: 973-256-8341; E-mail: humana@humanapr.com; Website at humanapress.com

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute)
Permanence of Paper for Printed Library Materials.

Production Editor: Robin B. Weisberg

Cover design by Patricia F. Cleary

Cover illustrations from Fig. 1, Chapter 10, "Arthropods and Corpses," by Mark Benecke; Fig. 7, Chapter 2, "Infant and Early Childhood Asphyxial Deaths: *Diagnostic Issues,*" by Roger W. Byard and Michael Tsokos; Fig. 9, Chapter 8, "Sudden, Unexpected Death Related to Viral Myocarditis: *A Survey of Histological, Immunohistochemical, and Molecularpathological Methods for the Postmortem Diagnosis*," by Reinhard Dettmeyer and Burkhard Madea; Fig. 1, Chapter 2, "Skull Injuries Caused by Blows With Glass Bottles," by Burkhard Madea, Peter H. Schmidt, Eberhard Lignitz, and Stephan A. Padosch; and Fig. 3, Chapter 3, "Primary Cerebral Neoplasms as a Cause of Sudden, Unexpected Death," by Jakob Matschke.

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN 1-59259-872-2

Library of Congress Cataloging-in-Publication Data

Forensic pathology reviews, Volume 2 / edited by Michael Tsokos.
p. cm.
Includes bibliographical references and index.
ISBN 1-58829-415-3 (alk. paper)
1. Forensic pathology. I. Tsokos, Michael.
RA1063.4.F675 2004
614.1—dc22

2003027503

Dedication

To my son Titus for the joy and fun he brings to my life day by day.

—Michael Tsokos, MD

Series Introduction

Over the last decade, the field of forensic science has expanded enormously. The critical subfield of forensic pathology is essentially based on a transverse, multiorgan approach that includes autopsy, histology (comprising neuropathological examination), immunohistochemistry, bacteriology, DNA techniques, and toxicology to resolve obscure fatalities. The expansion of the field has not only contributed to the understanding and interpretation of many pathological findings, the recognition of injury causality, and the availability of new techniques in both autopsy room and laboratories, but also has produced specific new markers for many pathological conditions within the wide variety of traumatic and nontraumatic deaths with which the forensic pathologist deals.

The *Forensic Pathology Reviews* series reflects this expansion and provides up-to-date knowledge on special topics in the field, focusing closely on the dynamic and rapidly growing evolution of medical science and law. Individual chapters take a problem-oriented approach to a central issue of forensic pathology. A comprehensive review of the international literature that is otherwise difficult to assimilate is given in each chapter. Insights into new diagnostic techniques and their application, at a high level of evidential proof, will surely provide helpful guidance and stimulus to all those involved with death investigation.

It is hoped that this series will succeed in serving as a practical guide to daily forensic pathological and medicolegal routine, as well as provide encouragement and inspiration for future research projects. I wish to express my gratitude to Humana Press for the realization of *Forensic Pathology Reviews.*

***Michael Tsokos,* MD**

Preface

When asked by the Prussian king, "So what is new in heaven?" Friedrich Wilhelm August Argelander (1799–1875), astronomer at the University of Bonn, Germany, answered "Does his majesty already know what is old?" This second volume of *Forensic Pathology Reviews* is intended to complement rather than replace the classical textbooks of forensic pathology by providing those interested in death investigation with the state-of-the-art accounts of special topics from various fields of forensic pathology and death scene investigation.

Chapter 1 examines the medicolegal aspects of death resulting from starvation (i.e., as a result of deliberate withholding of food from infants). The author provides deep insight into how an expert opinion may be formed on the degree and duration of starvation by applying different classification systems of protein-energy malnutrition to such cases. In Chapter 2, the authors present a fundamental and detailed look at the pathological features of head injuries that are inflicted by glass bottles. The presentation of the characteristic morphological findings in such cases is complemented by relevant experimental biomechanical data and valuable guidelines for practical casework. Chapter 3 devotes attention to the current understanding of the clinical and pathological features of primary cerebral neoplasms, according to the World Health Organization's classification scheme. In particular, the role of these unique tumors as a cause of sudden, unexpected death is emphasized. Chapter 4 concerns obesity, one of the pre-eminent health issues in the Western world. In the United States, approximately 300,000 adult deaths can be attributed annually to obesity-related complications. The authors provide the reader with an exhaustive overview concerning aspects of the obesity epidemic, definitions and measurements of obesity, and risk factors, as well as other issues relevant to the forensic pathologist, such as premature death relating to obesity, pathologies, and causes of death.

Chapter 5 takes a comprehensive look at what the pathologist may encounter when dealing with infant and early childhood asphyxial deaths. The authors point to the differential diagnosis between inflicted (homicidal) and accidental asphyxias, airway obstruction from natural causes, foreign body impaction, and sudden infant death syndrome (SIDS). In Chapters 6 and 7, highly interesting topics related to suicide are discussed. Chapter 6 deals with planned and unplanned

complex suicides. In addition to a complete literature review of research published to date, the criminological points of view in association with the forensic pathological investigation of complex suicide cases are presented. A thorough examination of the pathological features of occupation-related suicides is provided in Chapter 7. The authors elucidate in detail the problems that may arise in the medicolegal interpretation of occupation-related suicides and provide practical guidelines for comprehensive and conclusive forensic casework.

Chapter 8 covers the subject of viral myocarditis in forensic autopsy cases. Cases of sudden, unexpected death represent a substantial proportion of forensic autopsy cases, and postmortem studies suggest that myocarditis accounts for up to 20% of all such cases. The diagnosis of viral myocarditis may present difficulties when solely based on conventional histological findings. The authors provide the reader with a survey of the latest immunohistochemical and molecular-pathological techniques that are appropriate to prove lethal myocarditis in cases with a high index of suspicion of an underlying viral myocarditis, but are not supported by traditional histological findings.

Chapter 9 comprehensively examines some curious phenomena that may occasionally be observed at a scene of death (e.g., hiding, covering, and undressing). Such phenomena generally appear dubious at first sight and may raise suspicion of a crime, even by experienced observers. These behavioral patterns that take place in agony, when the conscious, rational control of thoughts is fading, and the associated behaviors, are elucidated in detail. The knowledge of these peculiar behavioral patterns is most useful to all those involved in death scene investigation in order to correctly interpret the scene and to exclude involvement of a third party.

Chapter 10 addresses the subject of forensic entomology. A thorough understanding of the numerous ways in which arthropod evidence can be applied not only to the determination of the postmortem interval, but also to the proof of neglect of elderly or children, is essential for every forensic pathologist and medical examiner, respectively. Chapter 11 deals with the interpretation of toxicological findings in the setting of an entire death investigation, including a comprehensive presentation of potential pitfalls in toxicology testing that are always of concern.

In Chapter 12, thorough information about long-term effects of anabolic-androgenic-steroid abuse and the associated pathological findings is provided. Since recent studies suggest that 3–12% of male adolescents and about 1–2% of female adolescents use anabolic-androgenic-steroids at some time during their lives, this issue is of considerable importance to everyone involved in medicolegal investigations. Chapter 13 devotes attention to the autopsy findings of

subendocardial hemorrhages. The author gives a detailed review of the latest literature with special reference to the underlying pathophysiological mechanisms and the significance of subendocardial hemorrhages in forensic autopsy practice as a vital reaction.

This book is the result of many experts in forensic pathology coming together to share their expertise. I wish to express my deepest gratitude to all of the contributors for making their practical and scientific knowledge accessible to a broad international readership.

Michael Tsokos, MD

Contents

Contributors

Mark Benecke, PhD • International Forensic Research & Consulting, Cologne, Germany

Michael Bohnert, MD • Institute of Forensic Medicine, University Hospital of Freiburg, Freiburg, Germany

Roger W. Byard, MBBS, MD • Forensic Science Centre, Adelaide, Australia

Reinhard Dettmeyer, MD • Institute of Forensic Medicine, Rheinische Friedrich-Wilhelms-University Bonn, Bonn, Germany

James R. Gill, MD • Deputy Chief Medical Examiner, Bronx County, Office of Chief Medical Examiner, New York, NY

Roland Hausmann, MD • Institute of Legal Medicine, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

Donna M. Hunsaker, MD • Office of the Chief Medical Examiner, Louisville, KY

John C. Hunsaker III, MD, JD • Department of Pathology and Laboratory Medicine, University of Kentucky College of Medicine, Lexington, KY

Eberhard Lignitz, MD • Institute of Legal Medicine, University of Greifswald, Greifswald, Germany

Burkhard Madea, MD • Institute of Forensic Medicine, Rheinische Friedrich-Wilhelms-University Bonn, Bonn, Germany

Jakob Matschke, MD • Institute of Neuropathology and Institute of Legal Medicine, University of Hamburg, Hamburg, Germany

Stephan A. Padosch, MD • Institute of Legal Medicine, Johann Wolfgang Goethe University Frankfurt a.M., Frankfurt, Germany

Achim Th. Schäfer, MD • Office of Medicolegal Assessment, Aachen, Germany

Peter H. Schmidt, MD • Institute of Legal Medicine, Johann Wolfgang Goethe University Frankfurt a.M., Frankfurt, Germany

Stephan Seidl, MD • Institute of Legal Medicine, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

Michael Tsokos, MD • Institute of Legal Medicine, University of Hamburg, Hamburg, Germany

Death From Environmental Conditions

1

Death as a Result of Starvation
Diagnostic Criteria

Burkhard Madea, MD

Contents

Summary

Fatal starvation is a rare cause of death in industrialized countries but this entity may become of major medicolegal importance if death results from deliberate withholding of food, especially from infants. In such cases, the task of the forensic pathologist and the medical examiner, respectively, is not only to clarify the cause of death but also to give an expert opinion on the degree and duration of starvation. Several classification systems have been developed to estimate protein-energy malnutrition (PEM) in third world countries (e.g., Waterlow classification, Gomez classification). More simple classifications (e.g., the Gomez classification of PEM) use the weight expected for the respective age group as standard. When applying this standard, small infants

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

will always be light infants. Following the Waterlow classification, a stunted physical condition (referring to retardation in cases of chronic malnutrition) is calculated by using the ratio of the measured body height to the one expected for the actual age. Body weight can be used as a sign of acute malnutrition ("wasting"). However, body weight should be related to the expected weight for the actual height. Using such classification systems, a grading of stunting and wasting can be achieved that is of great value for the assessment of a given child's nutritional status in legal cases. The application of the Waterlow classification to this author's case material and cases published earlier in the literature is demonstrated. The Waterlow classification is not only of importance for grading the final stage in cases of fatal starvation, but also for the chronological development of the nutritional status, if anthropometrical data have been recorded repeatedly from the affected individual in vivo.

Key Words: Starvation; autopsy findings; protein-energy malnutrition (PEM); Waterlow classification; stunting; wasting; emaciation; undernutrition; malnutrition; malnourishment.

1. Introduction

Starvation is a rare cause of death in industrialized countries that may occur as a result of child abuse, fasting to death, or in mentally ill persons *(1–19)*. The diagnosis of death as a result of starvation is normally a simple *prima facie* diagnosis, the visual features of starvation being known from contemporary famines. If there is enough circumstantial evidence, the definite diagnosis of starvation will not be doubted. Some examples of conditions that may result in death from starvation are as follow *(2,20–26)*:

- Inability to eat (e.g., as a result of natural diseases such as carcinoma of the esophagus).
- Voluntary refusal of food (fasting to death, hunger strike).
- Mental disease (anorexia nervosa, schizophrenia).
- Accidental entombment (colliary disasters).
- Deliberate withholding of food.

Internal as well as external factors may lead to an identical picture of cachexia (Fig. 1). Therefore, in criminal acts related to starvation in which the cause of loss of body weight is suspected to be the result of deliberate withholding of food (e.g., in the course of neglect of infants), the forensic pathologist must collect as much evidence as possible because it is the underlying cause of the starvation (i.e., "deliberate withholding of food or neglect"), and not the diagnosis of starvation itself, that will be doubted in later legal pro-

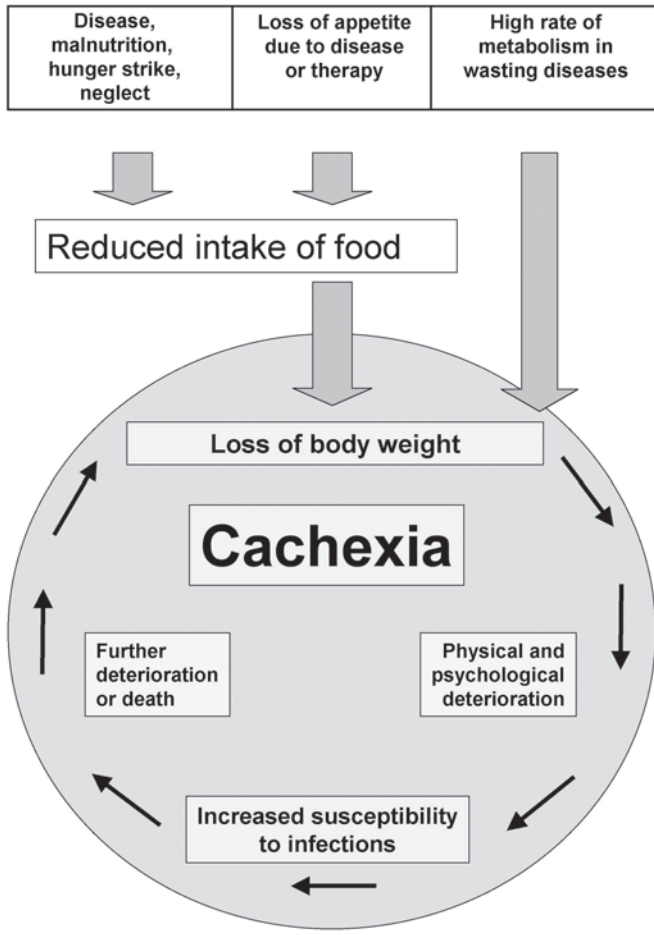

Fig. 1. Pathogenesis of cachexia. Circulus vitiosus in progredient stages of disease, malnutrition, and neglect.

ceedings. The distinction between cause and effect is of great importance when criminal charges are made.

In most cases, infants younger than 3 years of age and, more rarely, elderly and/or helpless people are affected as victims of deliberate withholding of food. Especially in infants, it is important not only to estimate the actual loss of body weight, but also to give an expert opinion if a reduced body height may have been caused by chronic malnourishment. Classifications of protein-energy malnutrition (PEM) that have been developed to estimate malnourishment in third world countries are of great value for such purposes *(7,27–36)*.

Table 1
Daily Requirement of Calories in Humans

Mode of energy turnover	Energy exchange	
Basic metabolic rate	F 6300 kJ/day	1500 kcal/day
(body weight 70 kg)	M 7100 kJ/day	1700 kcal/day
Basic metabolic rate plus	F 8400 kJ/day	1900 kcal/day
leasure time requirement	M 9600 kJ/day	2300 kcal/day
Basic metabolic rate for	F 15500 kJ/day	3700 kcal/day
heavy workers	M 20100 kJ/day	4800 kcal/day

F, female; M, male. (According to ref. *38*.)

2. Clinical and Autopsy Findings in Starvation

The daily calorie requirement of humans above the basic metabolic rate mainly depends on the physical activity (*37–39*; Table 1). Insufficient calorie intake compared to the requirement results in a negative energy balance with resultant loss of body weight. Malnutrition has to be differentiated from undernutrition. Undernutrition is the intake of an insufficient quantity of food, whereas malnutrition is defined as feeding of inadequate quality. Symptoms and pathology of starvation have been comprehensively reported since World War II, based on experiences and observations derived from the Nazi concentration camps *(22,40–52)*. The more or less constant symptoms of starvation develop in a characteristic chronological order *(50)*:

1. Loss of well-being and hunger, hunger pains, and craving for food.
2. Apathy and fatigue.
3. Weight loss, more rapid in the first 6 months of starvation than afterward.
4. Pigmentation, cachexia, and hypothermia.
5. Extreme lethargy, mental retardation, and loss of self-respect.
6. Hunger edema.
7. Reduced resistance to infections in general, and development of diarrhea and tuberculosis, or other intercurrent infections.

Even in advanced stages of starvation, death may be sudden and unexpected (*see* for instance witness reports from concentration camps *[45,52]* as well as more recent publications *[53–57]*).

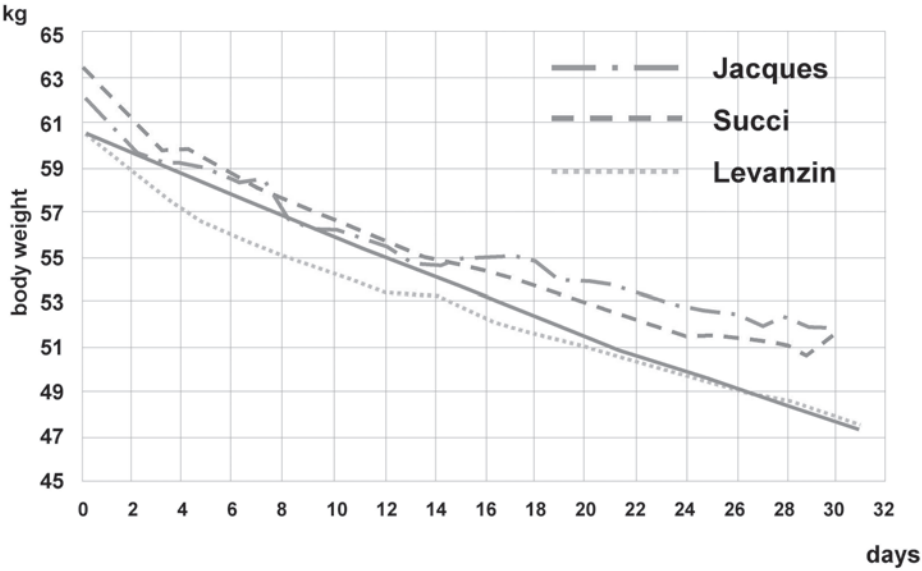

Fig. 2. Loss of body weight in three male volunteers after complete withdrawal of food for 30 days (only water intake). After a steep loss of body weight within the first days, the decrease of body weight is then retarded. The pulled through line represents the calculated loss of body weight. (Modified according to ref. *22*.)

The main autopsy finding is an extreme emaciation with loss of body weight and organ weights (Fig. 2, Table 2). Nearly all organs except for the brain are reduced in weight. Loss of weight is very rapid in the first place, but becomes slower after approx 3 months *(22,38,54,58,59)*. Loss of body weight mainly results from the loss of subcutaneous adipose tissue and adipose tissue surrounding internal organs, atrophy of internal organs, and atrophy of muscles. The loss of about 35–50% of body weight may cause death. Quite characteristic is also the loss of Bichat's fat pad (Corpus adiposum buccae). Furthermore, the atrophy of endocrine and reproductive glands (testes) is quite characteristic. In infants, mainly a complete atrophy of the thymus is symptomatic of starvation (*15,18,21,23*) as well as the diminution of the size of the lymph nodes.

The gallbladder is commonly distended as a result of the absence of food as the natural stimulant of bile excretion. Stomach and small bowel are normally empty, but the presence of extremely dry stool in the colon is another characteristic finding. Even foreign bodies may be found in the colon, indicating that the starving person had tried to eat everything accessible prior to death (*12,23*).

Table 2
Loss of Body Weight (Total Body Weight) and Loss of Weight of Internal Organs as a Result of Inanition in Man

	Prym 1919	Krieger 1921	Giese 1944	Stein and Feinigstein 1946	Uehlinger 1948
	%	%	%	%	%
Body weight	up to 27	38–43[a]	up to 40	n.d.	5–40 in most cases 30–40
Liver	11	42	28	46	30
Heart	23	33	24	20	30
Pancreas	n.d.	n.d.	n.d.	n.d.	10
Kidneys	6	36	0	25	10
Spleen	33	46	20	48	0
Brain	n.d.	4	n.d.	7	10
Adrenal gland	25	n.d.	0	n.d.	n.d.
Pituitary gland	n.d.	n.d.	0	n.d.	n.d.

Note: For the loss of weight of internal organs maximum values are given in percent.
[a]Loss of body weight in malignant tumors 38%, in general infections and tuberculosis 43%, in chronic diarrhea 48.4%; n.d., no data available. (Modified according to ref. *22.)*

Typical picture of emaciation and exclusion of any other concurrent cause of death are prerequisite for a definitive postmortem diagnosis of death as a result of starvation *(3,7,9–11,27,28,60–62)*.

If the diagnosis of death as a result of starvation is established, the actual cause of death has to be determined: preexisting diseases (e.g., malabsorption, malassimilation, cancer) or withholding of food.

Histopathology serves mainly to exclude concurrent causes of death and to get clues regarding underlying natural causes of emaciation or to exclude them *(22,63,64)*.

The anthropometrical data of starved persons and organ weights are routinely compared to those of a reference population *(28,65,67)*. These data are the essential basis for the diagnosis of starvation. However, a plain orientation on the reference values or percentile charts alone does not permit a grading of the degree or stage of malnutrition.

Several classification systems have been developed to estimate PEM in third world countries over the last decades. Especially for forensic pathologists, these classifications are superior compared to percentile charts because

Fig. 3. Scene of death. These monocygotic twins were found dead in an apartment that was in a state of total neglect.

anthropometrical data allow also an estimate of the degree of malnutrition *(30–36)*. Those gradings of PEM have been successfully applied to affected individuals in third world countries, but they may be used also for the classification of infantile malnutrition in cases of starvation as a result of deliberate withholding of food. First experiences with the use of these classification systems were published by this author's study group in 1994 *(12)*. The application of such classification systems to this author's case material and cases published earlier in the literature *(1,6,12,19,23)* will be demonstrated in the following.

3. Exemplary Cases

3.1. Own Case Material

This author's own case material comprises six cases of fatal starvation in childhood *(12)*. At the time of death, the infants were between 3 months and 2.5 years old. Among them were monocygotic twins who were found dead at home on occasion of the visit of a nurse (Fig. 3). All six infants were found in apartments that were in a state of total neglect. Some of the bodies were already in an early state of putrefaction. All infants appeared severely emaciated at gross examination with nearly total absence of fat depots in cheek, abdominal

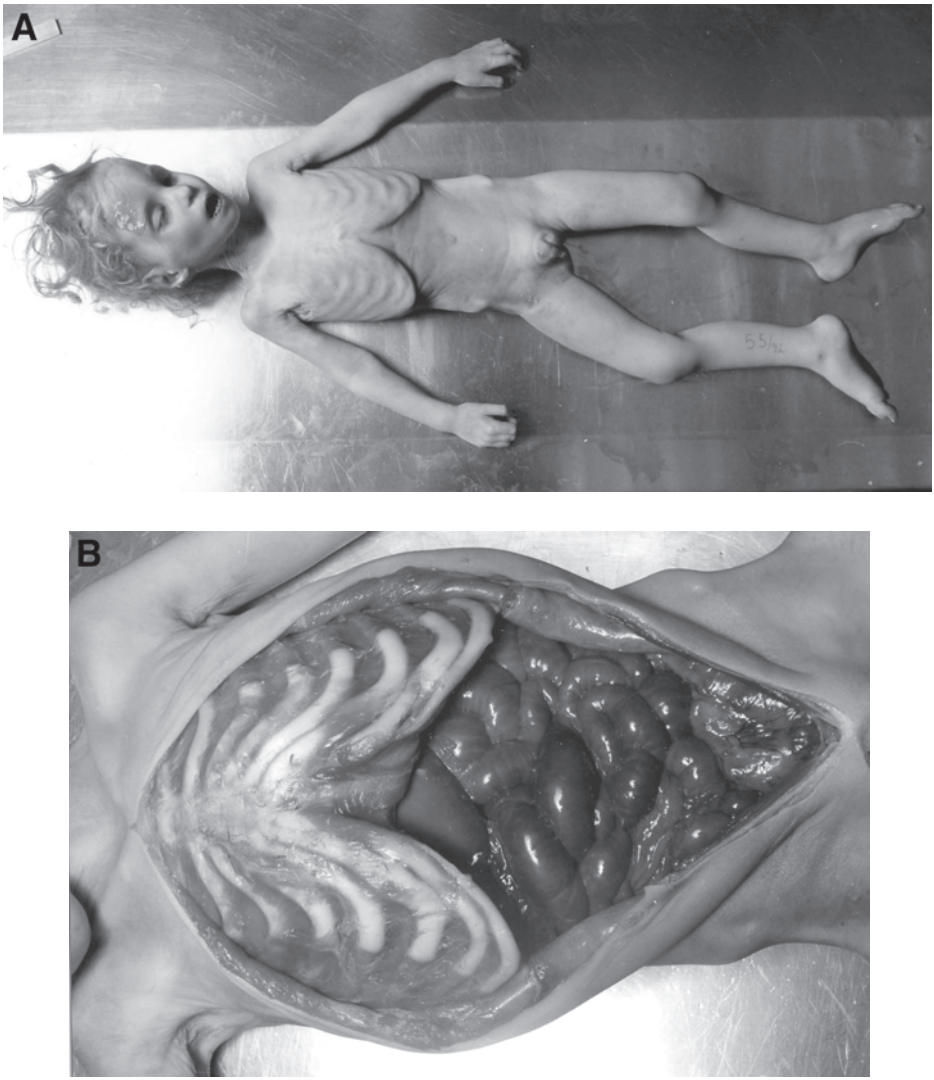

Fig. 4. Typical autopsy findings in starvation. **(A)** Emaciation, loss of Bichat's fat pad, and sunken eyes, **(B)** Complete loss of subcutaneous tissue with pronounced rib cage, **(C)** Loss of adipose tissue of the mesenterium.

wall, and mesentery (Fig. 4A–C). All infants had the classical signs of starvation as discussed previously. In all cases, a "dry" emaciation with the typical signs of dehydration was present. The loss of body weight and organ weight (in percent) in relation to the normal weight for the respective age group is

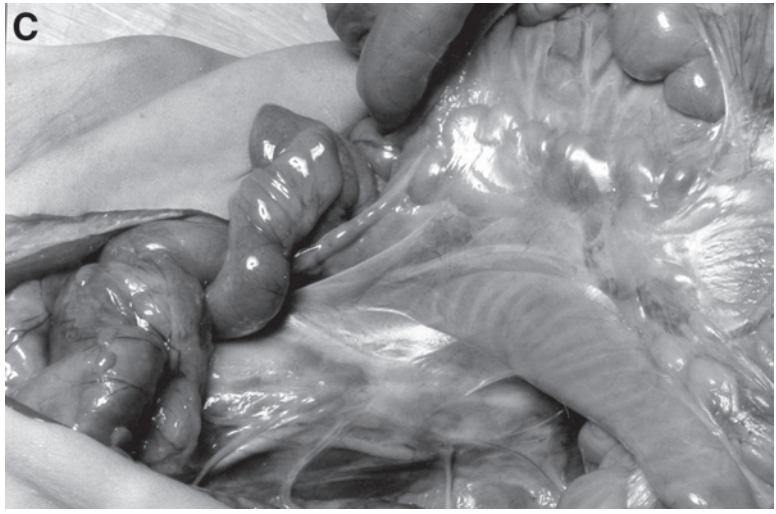

Fig. 4. *(continued)*

shown in Table 3 for five out of the six infants. The loss of body weight was more than 50% and a marked loss of organ weight was seen affecting the liver, spleen, and kidneys. As a result of edema of the brain, the weight of the brain was even increased in some cases.

3.2. Cases Reported in the Literature

Adelson reported on five cases of homicide by starvation in childhood giving details on body height and weight *(1)* so that the application of the Waterlow classification could be scrutinized on his cases here as well. Further data were taken from more recent publications *(6,19)*.

4. Classification of PEM

It is essential to take full body measurements (and organ weights) so that the total body size and proportions can be related to reference values *(28,29)*. The body weight should not only be related to the expected weight for the respective age group. Because undernutrition is not always acute but may also be chronic, classification systems that were developed for chronic PEM in the third world should be used, too (Table 4 *[30]*). They may be especially helpful in distinguishing acute from chronic malnutrition. More simple classifications like the Wellcome classification or the Gomez classification of PEM *(31)* use the expected weight for the respective age group as standard (Tables 4,5).

Table 3
Loss of Body Weight and Loss of Weight of Internal Organs (%) in Relation to Normal Weight Values for the Respective Age Group

Case no.	Age	Body weight	Heart	Liver	Spleen	Kidney	Lungs	Brain
Case 1	3 months	53.3	7.4	25	68.7	40.4	36	+13
Case 2	2.3 years	54	37	37	24	46	30	+10
Case 3	2.5 years	60	25	54	57	45	–	15
Case 4	2.5 years	55	30	40	51	69	39	11
Case 5	2.5 years	52	46	46	43	33	52	10

See text for further details on the individual cases.

However, with these classifications, small infants will always be light infants and chronic and acute undernutrition cannot be distinguished. Furthermore, infants who are tall for their age and have a reduced body weight would be classified as normal and, accordingly, a chronic state of malnutrition cannot be recognized in those infants *(12,66)*. However, these classifications are already superior compared to an orientation on the percentile charts in so far as a grading of the degree of malnutrition can be achieved.

The Waterlow classification of PEM *(34–36)* takes into account not only the weight, but also the height and the expected weight for the actual height as well (Tables 4,6). Using this classification system it becomes evident that those infants are not only light for their age (loss of body weight of 50% of the standard value of the same age group), but also, as a sequel of chronic malnutrition, are impaired in their growth.

Table 7 presents the development of height and weight of the monocygotic twins mentioned earlier. Results of anthropometrical measurements in vivo from four different times were available (birth, age of 1 month, age of 1 year, and at the time of death). Apparent is the loss of body weight at the time of death when compared to the normal weight, but also to the ideal weight for the actual height. As a result of chronic undernutrition, the twins were reduced in their height as well.

When medical records of starved infants are available, for instance from prior medical examinations, the dramatic deterioration of the nutritional state becomes evident, as shown in Table 7. The postnatal development in both twins was completely identical concerning the postnatal gain of weight and development of severe marasm. Both were found dead, in the same room, at the age of 2.5 years with nearly identical rectal temperatures and vitreous potassium values, indicating that both died at the same time. Toxicological

Table 4
Classification of Protein-Energy Malnutrition (PEM)

WELLCOME CLASSIFICATION OF PEM		
Body weight related to age	Without edema	With edema
60–80% <60%	Malnourishment marasmic	Kwashiorkor marasmic
GOMEZ CLASSIFICATION		
Body weight related to age (% of reference value)		
90–110% 75–89% 60–74% <60%	Normal Grade I: malnourishment (mild) Grade II: malnourishment (moderate) Grade III: malnourishment (severe)	
WATERLOW CLASSIFICATION OF PEM		
	Height (body height for age in %)	Body weight–height relation (weight related to height in %)
Normal Mild Moderate Severe	>95% 87.5–95% 80–87.5% <80%	>90% 80–90% 70–80% <70%

Table 5
Simplified Classification of Protein-Calorie Malnutrition

	Body weight as % of standard[a]	Edema	Deficit in weight for actual height
Underweight child	80–60	0	Minimal
Nutritional dwarfing	<60	0	Minimal
Marasmus	<60	0	++
Kwashiorkor	80–60	+	++
Marasmic Kwashiorkor	<60	+	++

[a]Standard taken as 50th percentile of Harvard values. (Modified according to ref. *30*.)

Table 6
Grading of Protein-Energy Malnutrition

Stunting (chronic malnutrition)				
Grade	0	1	2	3
Actual height in % of normal height of respective age group	>95%	95–87.5%	87.5–80%	<80%
Wasting (acute malnutrition)				
Grade	0	1	2	3
Actual weight in % of normal weight for height	>90%	90–80%	80–70%	>70%

Information based on the Waterlow classification. By using this table a grading of both chronic malnutrition (stunting) and acute malnutrition (wasting) can be achieved.

analysis was negative and the cause of death was stated as a combination of starvation and dehydration. The mother, who was a chronic alcoholic, suffered from severe hyperammonemia as a result of alcoholic liver damage, and had obviously left the infants without food and fluid for the last days of their lives, but witnesses confirmed that the infants had always been underweight. The nearly simultaneous death of twins as a result of starvation has, to the best of this author's knowledge, not been described before (for more details *see* ref. *12*).

Table 7

Development of Height and Weight of the Monocygotic Twins From Birth to Death

Date	Actual height (cm)	Normal height (cm) of respective age	Height in % of normal height of respective age	Actual weight (g)	Normal weight (50% percentile of respective age)	Ideal weight for height	Weight in % ideal weight for height
Case 1							
Birth	42	46	91.3	1500	2400	1700	88.2
1 month	44	50.5	87.1	2520	3200	2200	114.5
1 year	66.5	76.1	87.4	5900	10,150	7400	79.7
2.5 years	79	92.3	85.6	6510	13,600	10,700	60.8
Case 2							
Birth	42	46	91.3	1620	2400	1700	95.3
1 month	45	50.5	89.1	2520	3200	2300	106.36
1 year	64.5	76.1	84.8	6000	10,150	7000	85.7
2.5 years	79.5	92.3	86.1	6200	13,600	10,750	57.9

The data of 12 starved infants with an estimation of the state of nutrition according to the Waterlow classification are presented in Table 8. These calculations are based on measurements and weights determined at autopsy. Five cases were taken from the publication by Adelson *(1)*. In these cases, the actual body weight related to the expected body weight for the actual height reveals, according to the Waterlow classification, a severe life-threatening malnutrition. Nearly all infants were much below the critical values for severe malnutrition that are given in the literature. In all cases shown in Table 8, the actual weight in percent of the ideal weight for height is near or below 70%. Of course, limiting values for fatal starvation are missing in the literature so far; on the one hand there are only some published case reports on starvation using the Waterlow classification and on the other hand the actual weight at the time of death depends on various other factors such as dehydration, infections, and so on. But because this author's case material, as well as the cases published by Adelson *(1),* show a weight quotient below 70%, this may be a hint toward the validity of the grading of the Waterlow classification concerning the severity of starvation. Four of the infants over 1 year of age presented stunted (height below 90% of normal height for the respective age group), whereas infants younger than 1 year had mainly a quotient above 90%. One may speculate that in the older infants, undernutrition lasted longer (weight remained constant as a result of stunting), whereas in younger infants undernutrition caused death more rapidly without the possibility of compensation of body weight as a result of stunting. This hypothesis is strengthened by three cases reported by Wehner et al. *(19)*.

Three boys lived in a foster family. One of the boys (case 1) died from starvation at the age of 5 years. After his death, the other two boys (case 2,3; 6.5 and 8.5 years of age, respectively) underwent physical examinations. Both boys presented with a retardation of height and severe acute malnutrition (height retardation: 80% [case 1], 87% [case 2], and 81% [case 3]; acute malnutrition [weight related to height in percent]: 60% [case 1], 62.5% [case 2] and 65% [case 3]). An acute reduction of weight of 35–50% is usually considered to result in death and these infants showed a weight reduction of about 35–40% compared to the expected weight for the reduced height. It is remarkable that the 5-year-old boy who died (case 1) suffered from the highest loss of body weight compared to the actual height and the expected weight for the respective age. On the other hand, Fieguth et al. *(6)* reported on two cases of fatal starvation of very young infants (age: 5 weeks and 14 weeks, respectively) who received an inappropriate and inadequate nutrition. These authors reported also on an older child (3.5 years of age) who, left alone at home in the locked apartment, died of acute starvation and showed—corresponding to the afore-

Table 8
Data of 12 Infants Who Died of Starvation With Estimation of the State of Nutrition, According to the Waterlow-Classification

	Age	Sex (M/F)	Actual height in cm	Normal height for respective age in cm	Actual height in % of normal height for respective age	Actual weight in g	Normal weight in (50% percentile for age) in g	Actual weight in % of normal weight	Ideal weight for height in g	Weight in % of ideal weight for height
Case 1	7 weeks	m	53	58	91.4	2010	4540	44	3900	51.5
Case 2	3 months	f	55	59	93.2	2570	5600	54.8	4500	57.1
Case 3	5 months	m	61	66	92	4020	7300	55	5800	69.3
Case 4	6.5 months	f	56	68	96.5	3400	7500	45	4800	70.8
Case 5	7 months	m	58	70	82.8	3520	7700	45	5000	70.4
Case 6	7 months	f	59	68	86.8	2720	7700	35	5600	48.6
Case 7	8.5 months	f	53	70	75.7	2500	8300	30	3900	64.1
Case 8	14 months	f	68	76	89.5	4740	10,300	46	8000	59.25
Case 9	2.4 years	f	86	88	97.7	6800	12,700	53.5	12,300	55.3
Cases	2.5 years	m	79	92.3	85.6	6510	13,600	47.9	10,700	60.8
10 +11 (twins)	2.5 years	m	79.5	92.3	86.1	6200	13,600	45.6	10,750	57.9
Case 12	2.5 years	m	78	92.3	84.5	5450	13,600	40.1	10,900	50

Calculation based on measurements and weights determined at autopsy or on measurements given in ref. *1,* respectively. M, male; F, female.

mentioned hypothesis—only a light reduction in body height (95%, 88%, 98%), although the body weight in percent of height related value was reduced to about 70%.

5. Duration of Starvation, Physical Condition Prior to Death, and Immediate Cause of Death

5.1. Duration of Starvation

Frequently the medical expert witness is asked for an assessment of the duration of total food and liquid deprivation. An example for the calculation of the caloric deficit in order to determine the degree and duration of deprivation was published by Meade and Brissie in 1985 *(13)*. However, these calculations seem to be of value only in cases of acute starvation in which there was apparently a complete withholding of food, but not in cases of chronic malnutrition. Nevertheless, these calculations may give hints toward the minimal time interval of absolute deprivation of food.

Published data concerning the duration of starvation until death refer mainly to adults, acute withdrawal of food and liquid until death, or infants with inborn abnormalities of the upper gastrointestinal tract (Table 9). According to observations in 10 young, previously healthy hunger strikers (mean age 25.6 ± 0.7 years) the survival period until death varied between 53 to 73 days (mean 61 ± 2.5 days *[59]*). However, these data are of no use in cases of chronic starvation especially in infants in which birth was premature and failure to thrive is reported in the medical records.

5.2. Physical Condition Prior to Death

Medical records of the affected infants must be reviewed to determine evidence of the duration of malnutrition (body weight, height; Table 7). The medical expert witness may be asked whether some time (days to weeks) prior to death, the undernutrition of the respective child was recognizable (e.g., by caretakers, such as the parents or health care workers) and if so, the caretakers would have been obliged to request medical advice and care. In such cases, it is recommended to extrapolate on the time interval prior to death by taking as a basis that complete withholding of food results in a loss of body weight of about 0.7 to 1% of total body weight per day. Using the Waterlow classification, the extrapolated body weight related to the ideal weight for height gives an impression of the severity of malnutrition. When withholding of food was not absolute, it can be assumed that the real body weight for the extrapolated time was lower in a respective case of chronic starvation.

Table 9
Duration of Starvation Until Death

Hirschsprung	3–4 days (atresia of esophagus)
Hempel	3–5 days (atresia of bowel)
v. Hofmann	1–2 days (atresia of duodenum); 8 days (without fluid)
v. Neureiter	7–10 days
Prokop	8–21 days (without fluid); approx 60 days (with fluid)
Morgulis	17–76 days (mean 40 days)
Krück	45–60 days
Grafe	75 days (fasting to death)
Siegenthaler	50–80 days (fat depot >10 kg); 12 days (without fluid)
Leiter/Marlis	61.6 ± 2.5 days (fasting to death; $N = 10$)

Taken from refs. *12,23,26,58* and other publications cited there.

5.3. Immediate Cause of Death

Fatal starvation may be accompanied by dehydration as immediate cause of death. The diagnosis of dehydration is based on the classical autopsy findings as loss of body weight, sunken eyes, poor skin turgor, tinting of skin, and dry organ surfaces on cut sections. Biochemical methods—although recommended in some publications *(67,68)*—are not reliable at the present time to establish the diagnosis of dehydration postmortem. Especially vitreous humor is at present not a reliable medium for the interpretation of antemortem disturbances of electrolyte metabolism *(69,70)*. This is attributable to the fact that diagnosing abnormal electrolyte conditions from postmortem vitreous humor makes investigations of random samples with deviations (elevations and depressions, respectively) of the investigated analytes necessary to distinguish certainly normal from certainly abnormal values. All these requirements that are necessary for a sound scientific basis for the application of vitreous humor analyte values to predict serum analyte abnormalities at the moment of death have not yet been fulfilled. Investigations that correlate high or low vitreous values with serum values are missing in the literature. Additionally, completely missing in the literature is the investigation of reference material in which the diagnosis of dehydration was evident by autopsy findings and in which postmortem vitreous values were compared to antemortem serum values *(69–71)*.

Infectious complications as the immediate cause of death seem to be not as frequent as reported in the earlier literature on the subject of starvation or at least this author has not seen in his case material such fatal infections. Therefore, the question arises “What is the immediate cause of death in starved

individuals?" Recent reports on sudden death and anorexia nervosa suggest ventricular tachyarrhythmia or hypoglycemic coma as the immediate cause of sudden death in starvation and anorexia nervosa *(53–57)*. However, both conditions cannot be diagnosed postmortem.

Cases of sudden deaths of severely underweight and malnourished persons are already available in the earlier literature. In his book on malnutrition that was published in 1947, Wolf-Eisner reported that prisoners in concentration camps suffering from severe malnutrition died very suddenly, e.g., while talking to others *(52)*. Reports on PEM indicate that marasmic infants—compared to infants suffering from Kwashiorkor—are alert and conscious over a long period of time. The fact that death may be sudden and unexpected in severe marasmus and PEM has some medicolegal importance. Even in extremely marasmic infants, the life-threatening condition may be misjudged or overseen. However, the extreme emaciation is evident for everyone.

References

1. Adelson L. Homicide by starvation. The nutritional variant of the battered child. JAMA 1963;186:458–460.
2. Adelson L. Pathology of Homicide. Springfield, IL: Charles C. Thomas, 1974.
3. Campbell JAH. The morbid anatomy of infantile malnutrition in Cape Town. Arch Dis Child 1956;31:310–314.
4. Davis JH, Rao VJ, Valdes-Dapena M. A forensic approach to a starved child. J Forensic Sci 1984;29:663–669.
5. Ellerstein NS, Ostrov BE. Growth pattern in children hospitalized because of caloric-deprivation failure to thrive. Am J Dis Child 1985;139:164–166.
6. Fieguth A, Günther D, Kleemann WJ, Tröger HD. Lethal child neglect. Forensic Sci Int 2002;130:8–12.
7. von Harnack GA, Heimann G. Kinderheilkunde, 8th ed. Springer, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hongkong, 1990.
8. Helfer RE, Kempe CH. The battered child. The University of Chicago Press, Chicago, London, 1968.
9. Hughes EA, Stevens LH, Wilkinson AW. Some aspects of starvation in the newborn baby. Arch Dis Child 1964;39:598–604.
10. Listernick R, Christoffel K, Pace J, Chiaramonte J. Severe primary malnutrition in US children. Am J Dis Child 1985;139:1157–1160.
11. Madea B, Henßge C, Berghaus G. Fahrlässige Tötung eines Säuglings durch Fehlernährung. Arch Kriminol 1992;189:33–38.
12. Madea B, Michalk DV, Lignitz E. Verhungern infolge Kindesvernachlässigung. Arch Kriminol 1994;194:29–38.
13. Meade JL, Brissie RM. Infanticide by starvation: calculation of caloric deficit to determine degree of deprivation. J Forensic Sci 1985;30:1263–1268.

14. Mimasaka S, Funayama M, Adachi N, Nata M, Morita M. A fatal case of infantile scurvy. Int J Legal Med 2000;114:122–124.
15. Nishio H, Matusi K, Tsuji H, Tamura A, Suzuki K. Immunohistochemical study of tyrosine phosphorylation signalling in the involuted thymus. Forensic Sci Int 2000;110:189–198.
16. Sarvesvaran E. Homicide by starvation. Am J Forens Med Pathol 1992;13:264–267.
17. Schmidt P, Graß H, Madea B. Child homicide in Cologne (1985–94). Forensic Sci Int 1996;79:131–144.
18. Tanegashima A, Yamamoto H, Yada I, Fukunaga T. Estimation of stress in child neglect from thymic involution. Forensic Sci Int 1999;102:173–180.
19. Wehner F, Schieffer MC, Wehner HD. Percentile charts to determine the duration of child abuse by chronic malnutrition. Forensic Sci Int 1999;102:173–180.
20. Di Maio VJ, Di Maio DJ. Forensic Pathology. 2nd ed. CRC Press, Boca Raton, London, New York, 2001.
21. Gee D. Starvation and neglect. In Mant AK, ed. Taylor's Principles and Practice of Medical Jurisprudence. Churchill Livingstone, Edinburgh, London, Melbourne, New York, 1984, pp. 276–279.
22. Giese W, Hörstebrock R. Allgemeine Pathologie des exogenen quantitativen Nahrungsmangels. In: Büchner F, Letterer E, Roulet F, eds. Handbuch der allgemeinen Pathologie, Vol. 11, Umwelt II, part I. Springer Verlag, Berlin, Göttingen, Heidelberg, 1962, pp. 446–591.
23. Madea B, Banaschak S. Verhungern. In: Brinkmann B, Madea B, eds. Handbuch Gerichtliche Medizin, Vol. 1. Springer Verlag, Berlin, Heidelberg, New York, 2004, pp. 905–919.
24. Mueller B. Schädigungen und Tod infolge Nahrungsmangel. In: Mueller B, ed. Gerichtliche Medizin, Vol. 1, 2nd ed. Springer Verlag, Berlin, Heidelberg, New York, 1975, pp. 497–500.
25. von Neureiter F, Pietrusky F, Schütt E. Tod und Gesundheitsbeschädigung durch Entzug der Nahrung. In: von Neureiter F, Pietrusky F, Schütt E, eds. Handwörterbuch der Gerichtlichen Medizin und Naturwissenschaftlichen Kriminalistik. Springer Verlag, Berlin, 1940, pp. 811,812.
26. Prokop O. Das Verhungern. In: Prokop O, ed. Forensische Medizin, VEB Verlag. Berlin, 1966, pp. 141–143.
27. Becker M. Chronische Gedeihstörungen im Säuglingsalter. In: Bachmann KD, Ewerbeck H, Kleihauer E, Rossi E, Stalder E, eds. Pädiatrie in Praxis und Klinik., Vol. 1, 2nd ed. Gustav Fischer Verlag, Stuttgart, New York, 1989, pp. 545–552.
28. Behrmann RE, Vaughan VC, Nelson WE. Nelson's Textbook of Pediatrics, 13th ed. W.B. Saunders Company, Philadelphia, London, Toronto, Montreal, Sidney, Tokyo, 1987.
29. Bremer HJ. Protein-Energie-Malnutrition der Entwicklungsländer. In: Betke K, Künzer W, Schaub J, eds. Lehrbuch der Kinderheilkunde, 6th ed. Thieme Verlag, Stuttgart, New York, 1991, pp. 247–251.
30. World Health Organisation: Joint FAO/WHO Expert Committee on Nutrition, 8th report. Food fortification and protein-calorie-malnutrition. Tech Rep Ser Wld Hlth Org, No. 477 (WHO, Geneva, 1971).

31. Gomez F, Galvan RR, Cravioto J, Frenk S. Malnutrition in infancy and childhood with special reference to Kwashiokor. Adv Pediatr 1955;7:131–169.
32. Suskind RM. Primary protein-energy malnutrition: clinical, biochemical and metabolic changes. In: Suskind RM, ed., Textbook of Pediatric Nutrition. Raven Press, New York, 1981, pp. 189–307.
33. Suskind RM, Varma RN. Assessment of nutritional status of children. Pediatrics in Review 1984;5:195–202.
34. Waterlow JC. Classification and definition of protein-caloric malnutrition. Br Med J 1972;2:566–569.
35. Waterlow JC. Note on the assessment and classification of protein-energy malnutrition in children. Lancet 1973;2:87–89.
36. Waterlow JC, Buzina R, Keller W, Lane M, Nichaman MZ, Tanner JM. The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. Bull World Health Organ 1977;55:489–498.
37. Beaton GH. Nutritional needs during the first year of life. Pediatr Clin North Am 1985;32:275–288.
38. Bürger M, Grosse-Brockhoff F. Energiestoffwechsel. In: Grosse-Brockhoff F, ed. Pathologische Physiologie. Springer Verlag, Berlin, Heidelberg, New York, 1969, pp. 688–697.
39. Ulmer HV. Ernährung. In: Schmidt RF, Thews G, ed. Physiologie des Menschen, 22nd ed. Springer Verlag, Berlin, Heidelberg, New York, Tokyo, 1985, pp. 628–641.
40. Adelsberger L. Medical observations in Auschwitz concentration camp. Lancet 1946;2:317–319.
41. Cahill GF. Starvation in man. New Engl J Med 1970;282:668–675.
42. Chmelnizkij OK. Zur Rolle der Pathologen im belagerten Leningrad. Z allg Pathol pathol Anat 1987;133:307–310.
43. Giese W. Die Pathologie des Hungers. Allg Pathologie 1953;71(Pt II):98–100.
44. Girgensohn H. Pathologische Anatomie der Gefangenschaftskrankheit mit Bemerkungen zu ihrer Klinik und zur Frage der Spät- und Dauerschäden. Die Medizinische 1959;16:761–769.
45. Holle G. Über plötzliche Todesfälle bei schwerer Inanition. Z Ges Inn Med 1948;15/16:491–500.
46. Hottinger A, Gsell O, Uehlinger E, Salzmann C, Labhart A. Hungerkrankheit, Hungerödem, Hungertuberkulose. Benno Schwabe u. Co Verlag, Basel, 1948.
47. Leyton GB. Effects of slow starvation. Lancet 1946;2:73–79.
48. Mollison PL. Observation of cases of starvation at Belsen. Br Med J 1946;1:4–8.
49. Selberg W. Pathologische Anatomie der Unterernährung. Synopsis. 1948;1:23–50.
50. Simpson K. Exposure to cold-starvation and neglect. In: Simpson K, ed. Modern Trends in Forensic Medicine. Butterworth, London, 1953, pp. 116–132.
51. Uehlinger E. Die pathologische Anatomie der Hungerkrankheit und des Hungerödems. Helv Med Acta 1947;415:584–601.
52. Wolff-Eisner A. Über Mangelerkrankungen auf Grund von Beobachtungen im Konzentrationslager Theresienstadt. Lothar Sauer-Morhard Verlag, Würzburg, 1947.
53. Isner JM, Roberts WC, Heymsfield SB, Yager J. Anorexia nervosa and sudden death. Ann Intern Med 1985;102:49–52.

54. Missliwetz J, Mortinger H. Tod durch Hypoglykämie nach Hungerzustand—Pathophysiologie versus Morphologie. Beitr Gerichtl Med 1992;50:319–323.
55. Ratcliffe PJ, Bevan JS. Severe hypoglycaemia and sudden death in anorexia nervosa. Psychol Med 1985;15:679–681.
56. Rich LM, Caine MR, Findling JW, Shaker JL. Hypoglycaemic coma in anorexia nervosa. Arch Intern Med 1990;150:894,895.
57. Smith J. Hypoglycaemic coma associated with anorexia nervosa. Aust NZ J Psychiatry 1988;22:448–453.
58. Kanzow U. Beobachtung während einer 53-tägigen Hungerperiode an einem Hungerkünstler. Dt Arch Klin Med 1951;198:698–705.
59. Leiter LA, Marliss EB. Survival during fasting may depend on fat as well as protein stores. JAMA 1982;248:2306,2307.
60. Berwick DM. Nonorganic failure-to-thrive. Pediatrics in Review 1980;1:265–270.
61. Holzel A. Sugar malabsorption due to deficiencies of disaccaridase activities and monosaccharide transport. Arch Dis Child 1967;42:341–352.
62. Pipes PL. Nutrition in infancy and childhood, 2nd ed. The C.V. Mosby Company, St. Louis, Toronto, London, 1981.
63. Janssen W. Forensische Histologie. Verlag Max Schmidt Römhild, Lübeck, 1977.
64. Schocken DD, Holloway JD, Powers PS. Weight loss and the heart. Arch Intern Med 1989;149:877–881.
65. Roessle R, Roulet F. Mass und Zahl in der Pathologie. Verlag von Julius Springer, Berlin, 1932.
66. Madea B, Banaschak S. Remarks on: "Percentile charts to determine the duration of child abuse by chronic malnutrition." Forensic Sci Int 1999;105:191,192.
67. Coe JI. Postmortem chemistries on human vitreous humor. Am J Clin Pathol 1969;51:741–750.
68. Coe JI. Some further thoughts and observations on postmortem chemistries. Forensic Sci Gazette 1973;4:2–5.
69. Madea B. Zur Postmortalen Diagnostik von Störungen des Wasser-Elektrolyt-Haushaltes. Rechtsmedizin 1996;6:141–146.
70. Madea B. Zur Postmortalen Diagnostik der Hypertonen Dehydratation. Paper presented at the 16th Spring Meeting of the German Society of Forensic Medicine (Northern Group), Kiel, May 2003.
71. Madea B, Herrmann N. "Normal values" in vitreous humor and on dysregulations which can be diagnosed postmortem. In: Jacob B, Bonte W, ed. Advances in Forensic Sciences, Vol. 4., Forensic Criminalistics II. Verlag Dr. Köster, Düsseldorf, 1995, pp. 49–61.

Trauma

2

Skull Injuries Caused by Blows With Glass Bottles

Burkhard Madea, MD, Peter H. Schmidt, MD, Eberhard Lignitz, MD, and Stephan A. Padosch, MD

Contents

Summary

The medicolegal literature provides many reports on the morphological appearance of stab injuries caused by pieces of broken glass (e.g., glass splinters). The review presented here focuses on the particular aspect of blow injuries to the head and skull inflicted by glass bottles. Findings from an experimental biomechanical study conducted by the authors as well as 10 case reports are presented and discussed in detail. In order to characterize typical findings and provide valuable guidelines for practical casework, cases of blows to the head with glass bottles that were not followed by any serious injuries are compared to such cases in which the blows resulted in fatal outcome. Com-

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

binations of lacerations and incised wounds were encountered in most cases. Interestingly, lacerations were of major severity as opposed to the incised wounds. The latter were, as a rule, only superficial. Differences in bottle shape, weight, and filling conditions did not account for any differences of the resulting injuries and the breaking behavior of the bottles, respectively. Strikingly, even in the cases in which death was attributable to the blow with the glass bottle, the actual cause of death was not related to mechanical damage of bony structures or to brain injury (e.g., comminuted skull fractures or severe cerebral contusions). Here, rather exsanguination from the inflicted lacerations was found to be responsible for fatal outcome. Skull fractures resulting from blows to the head with glass bottles can be considered rare events. Regarding biomechanically relevant factors that are determined by the bottle itself, the minor elasticity of glass, as compared to bone, the filling condition, and the location of impact have to be considered as important. Additional factors related to the victim's head, such as the quantity of hair, the thickness of the scalp, the configuration and thickness of the skull, and the elasticity of bone, also must be taken into account. Considering the high frequency of assaults against the head using glass bottles, it would be most helpful for forensic practical casework to gain more detailed and sophisticated knowledge on the subject (e.g., about biomechanical principles of skull injuries caused by blows with glass bottles). However, the case reports presented here, complemented by experimental biomechanical data, will contribute to the understanding and assessment of analogous cases in practical forensic casework.

Key Words: Blow; glass bottles; skull injuries; lethal hemorrhage.

1. Introduction

The German medicolegal literature provides many reports on the morphological appearance of stab injuries caused by pieces of broken glass, for example, glass splinters *(1–8)*. Special emphasis is placed on morphological criteria, which may be used to differentiate between self-inflicted or accidentally sustained lesions caused by pieces of broken glass on the one hand and stab wounds caused by knifes or other sharp force instruments on the other *(9,10)*. More recent medicolegal literature has also reported falls into architectural glass surfaces, glass plates *(11)* as well as lethal stab wounds caused by smashed bottlenecks *(12)*.

Blow injuries to the head caused by glass bottles may be observed in daily clinical routine from time to time, but there are almost no data available on cases with fatal outcome in which bottles were used as a deadly tool *(13,14)*.

Even in the setting of large neurosurgical departments, severe injuries of the skull and brain caused by blows with glass bottles are rarely observed.

The following review presents a number of cases of blow injuries that were caused by glass bottles. In order to characterize typical findings and provide valuable guidelines for practical casework, cases of blows to the head with glass bottles that were not followed by any serious injuries are compared to cases in which the blows resulted in fatal outcome. Based on these case reports, which are complimented by experimental biomechanical data, crucial medicolegal issues and further considerations regarding the identification of skull injuries that were caused by blows with glass bottles are discussed.

2. Case Reports

2.1. Case 1

During a dispute between three teenagers, the two offenders covered the victim with a blanket and subsequently beat the victim's head with three bottles of different filling levels (an empty liquor bottle, one half-filled, and one completely filled wine bottle, respectively). The assailants had taken the neck of the bottles in their hands and directed the blows to the victim's parietal and occipital region, so that the bellies of the bottles hit the victim's head. Following impact on the head, each bottle broke into pieces. The victim did not sustain any injuries at all *(15)*.

2.2. Case 2

Two teenagers joined a heavily drunk 30-year-old alcoholic with the intention of robbing him. Initially, they drank alcohol with him on a park bench. When the man fell asleep on the bench as a result of his drunkenness, the teenagers beat an empty wine bottle on his vertex. Because the wine bottle broke, the teenagers repeatedly beat the man with another half-filled bottle. This bottle also broke into pieces. Finally, the victim woke up, raising his head asking "How now?" The offenders desisted from the man and took refuge immediately. Medical examination of the victim revealed a swelling and contusion of the scalp. However, severe injuries of the skull and brain were excluded *(15)*.

2.3. Case 3

In a brawl between several inebriated individuals, a 21-year-old sailor was hit on the head with a half-filled wine bottle. The blow with the neck-held

bottle was done from the front onto the forehead and vertex area. On impinging the head, the bottle burst immediately. The victim sustained only incised injuries of the forehead and of the midface that were related to the broken bottle neck *(15)*.

2.4. Case 4

A 56-year-old man became the victim of a holdup murder. Following excessive consumption of alcoholic beverages, the man was knocked down by several offenders using a beer bottle, a vodka bottle, and a pitcher. The victim sustained lacerations and incised wounds of the scalp. Glass splinters were observed sticking out of several of the wounds. The cranial bone and the brain had remained uninjured. It was concluded that the victim had initially been knocked down by the blows to the skull. Subsequently, the perpetrators killed the man by manual strangulation while he was lying on the ground *(15)*.

2.5. Case 5

During a physical assault that appeared to be sexually motivated, a 59-year-old female sustained three blunt lacerations of the head with concomitant avulsion of the scalp. The wounds were localized over the hind part of the skull and splinters deriving from a glass bottle were found inside one of the injuries. Numerous superficial scratches and incised wounds of the skin attributable to pieces of broken glass were also found on other parts of the body (e.g., the buttocks). The wounds were suspected to have been caused by the body being dragged through the glass splinters. Avital incisions on the exterior genital region provided morphological evidence for a sexually motivated background. At autopsy, the thickness of the cranial bone was found to range from 3 to 7 mm. Injuries to the skull or brain were not observed. Neck compression was determined as the cause of death. Nevertheless, marked loss of blood from the lacerations of the scalp was stated to have contributed to fatal outcome *(15)*.

2.6. Case 6

During a domestic argument that occurred after excessive consumption of alcohol, a 35-year-old male was hit by his wife with an empty beer bottle. The bottle burst into pieces, causing a severely bleeding laceration of the man's scalp. Subsequently, the man refused to be taken to the hospital by his wife and continued arguing. At that point, his wife left their apartment. Approximately 30 minutes later, a relative found the man dead in a puddle of blood in the bathroom. At autopsy, a superficial laceration (incomplete transection of

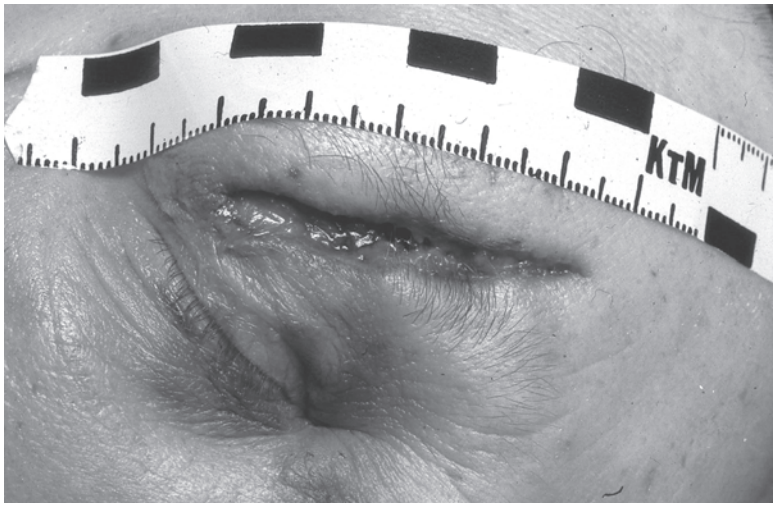

Fig. 1. Incised wound above the eyebrow after a blow to the head with a glass bottle (case 7).

the scalp) was noted, but the skull was intact. No intracranial bleedings or cerebral contusions were seen. Livor mortis was sparse and the internal organs were pale, indicating massive blood loss. Exsanguination was stated as the cause of death with the scalp laceration being the only identifiable source of hemorrhage. Postmortem blood alcohol concentration was 316 mg/dL.

2.7. Case 7

An 80-year-old woman clashed with her daughter-in-law who was placing lemonade bottles into a refrigerator. The daughter-in-law started beating the woman on the head with several bottles, breaking all the bottles. The victim suffered numerous lacerations of the scalp and a number of small superficial incised wounds of the skin caused by glass splinters (Figs. 1, 2A,B). However, a fracture of the 1-cm-thick cranial bone could not be encountered, nor were there any intracranial hematomas or contusions of the brain. Exsanguination from the incised wounds of the scalp was determined as the cause of death. As a result of the blows, hematomas of the back of both hands, scratches and dehiscent incised wounds of the skin on both arms (Fig. 3) and legs that were caused by the broken bottlenecks were noted *(15)*.

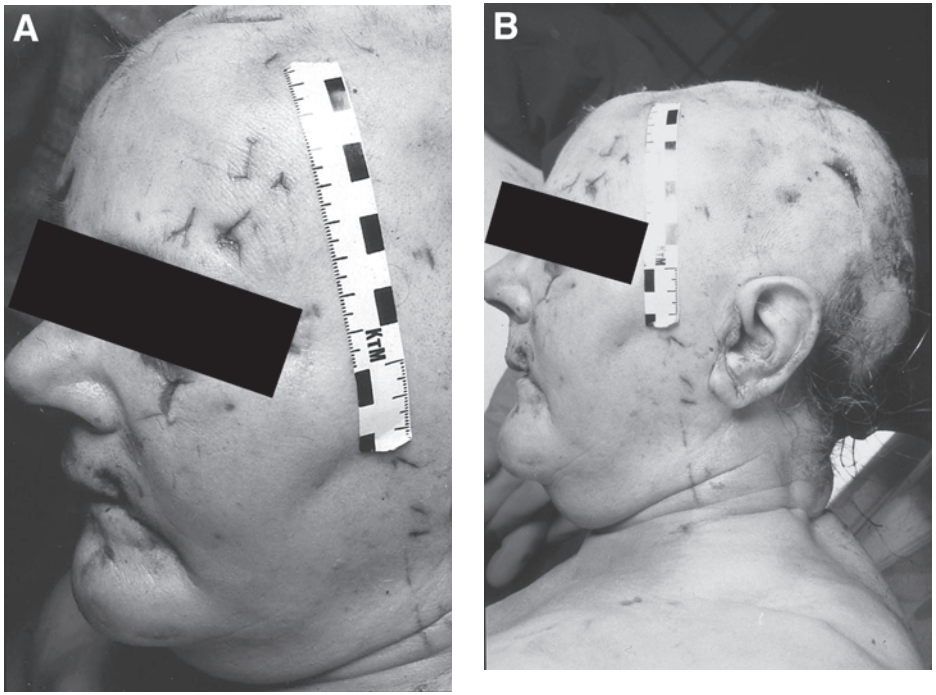

Fig. 2. (A,B) Numerous lacerations of the scalp and a number of small superficial incised wounds of the skin caused by glass splinters from blows to the head with glass bottles (case 7).

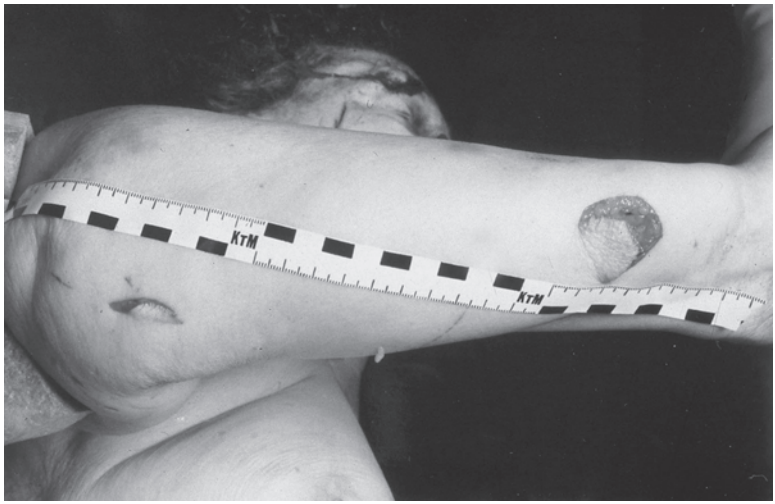

Fig. 3. Dehiscent incised wounds of the skin on both arms, caused by the broken bottle neck(s) (case 7).

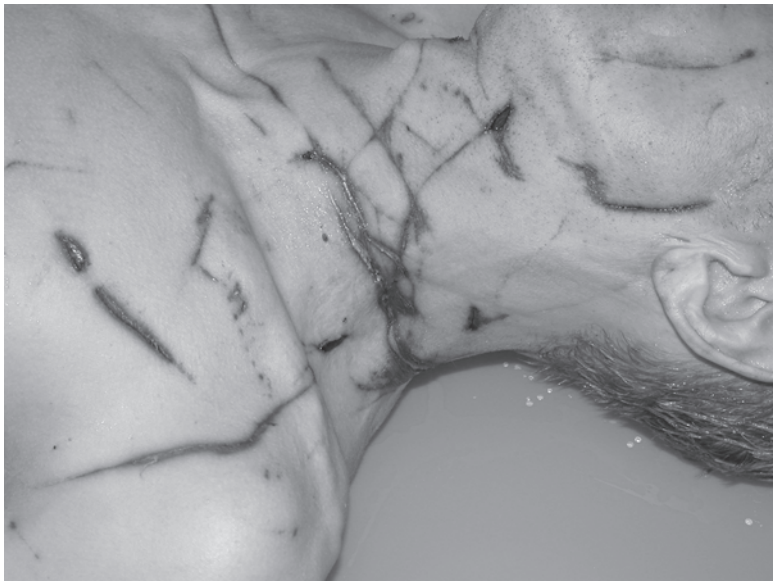

Fig. 4. Several incised wounds as well as stab wounds of the neck and thorax that were attributed to an assault by a knife and to glass splinters from the broken bottle (case 8).

2.8. Case 8

During homosexual intercourse, a 52-year-old man (the eventual victim) demanded further bizarre sexual activities from his partner, who refused. Thereupon, the man tried to hit his partners head with a beer bottle. The partner escaped this assault and subsequently repeatedly hit the victim's head with a beer bottle. The bottle burst into pieces but the victim did not lose consciousness. During the fight that followed, the victim sustained several stab wounds. At autopsy, exsanguination caused by several stab wounds and incised wounds of the thorax and the neck (Fig. 4) was determined as cause of death. The incised wounds were attributable to assaults with a knife derived from glass splinters, too. In addition to the incised wounds that were caused by the glass splinters, lacerations of the scalp that were attributed to the blow with the beer bottle were observed (Fig. 5). These injuries comprised large-sized hematomas with several short and angled lacerations, as well as streaky impressions of the tabula externa accompanied by subarachnoidal hemorrhage.

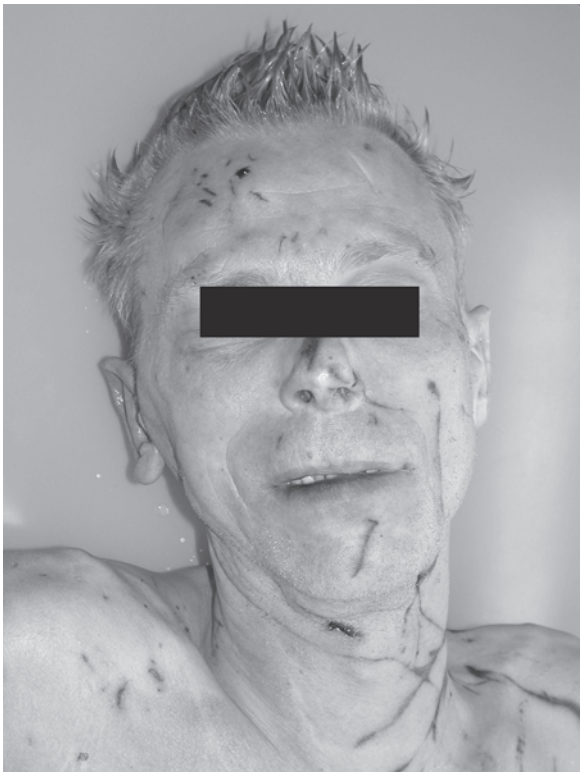

Fig. 5. Lacerations of the scalp of the forehead resulting from blows to the head with a beer bottle. Incised wounds caused by glass splinters and hematomas with several short and angled lacerations were accompanied by streaky impressions of the tabula externa (not shown) (case 8).

2.9. Case 9

In the course of an argument between two homosexuals, the assailant repeatedly beat the 47-year-old victim's head with a beer bottle. The victim sustained several sharp-force injuries and died. At autopsy, cause of death was determined as exsanguination resulting from multiple stab wounds and incised wounds located on thorax and neck. The deceased's blood alcohol concentration was 289 mg/dL and his urine alcohol concentration was 382 mg/dL. The sharp-force injuries, as well as 13 lacerations of the skin of the face and the scalp (Figs. 6A,B, 7), two depressed fractures of the left parietal bone, a slight subdural hematoma, and cerebral contusions were attributed to repeated blows with the beer bottle.

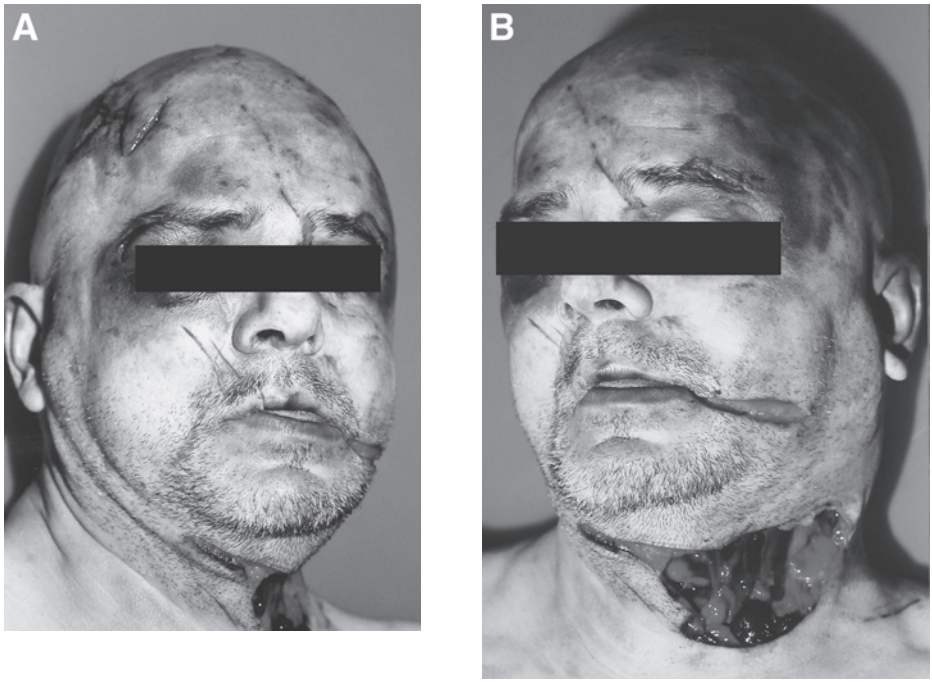

Fig. 6. (A) Injuries after repeated blows with a bottle. **(B)** Note large incised wound on the left side of the neck with transection of large vessels that caused fatal blood loss (case 9).

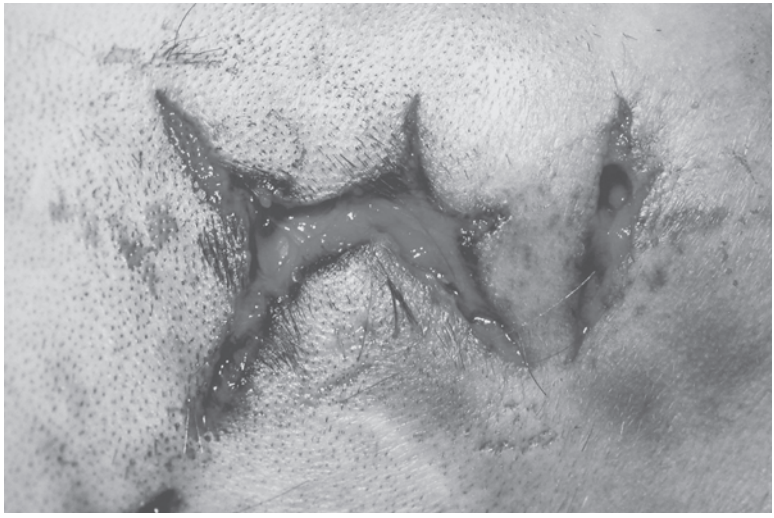

Fig. 7. Characteristic X-shaped laceration of the scalp after a blow to the head with a glass bottle (case 9).

2.10. Case 10

A 16-year-old girl was found dead in her room by her foster mother. The deceased was lying in a prone position on the floor between a sofa and a writing table. Substantial blood stains, most probably caused by being dragged, were noted on the floor in the vicinity of the body. Blood splatters and flocci of the victim were found on a baseboard. Police investigations and autopsy revealed that one assailant had inflicted the following injuries: four deep stab wounds to the victim's face, two stab wounds to her chest with penetration of the right lower lobe of the lung, one abdominal stab wound without wounding the internal organs, and multiple defense wounds of both arms. It was speculated that a second assailant had inflicted several heavy blows with a full bottle of water, which caused severe contusions on the right side of the forehead, the chin, the left midfacial area, and a spider's web fracture of the frontal bone. Assessing the contribution of the single injuries to the occurrence of death, the severity was quantified using the injury severity score (ISS *[16]*). According to this, the stab wounds unequivocally were the leading cause of death. In this case, the bottle remained intact and was found on a table next to the victim.

A summary of the individual case characteristics is presented in Table 1.

3. Experimental Biomechanical Investigations

Case 1 was the subject matter of an expert opinion report on request of the prosecution authorities. To provide a scientific basis, several biomechanical investigations and experiments were performed. Postmortem blow tests with three different types of bottles (sparkling wine, wine, and liquor bottles with volumes of 0.7–0.8 L) in different filling conditions were performed. Altogether, 20 bottles were held on the bottle neck and the body of the bottle was beaten on the vertex area of corpses with a medium intensity. Without any exception, all bottles broke at the time of impact. Detailed postmortem examination did not reveal any injuries of the cranial bones and no damage to the brain.

These experiments lead to the conclusion that blows to the head by wine, liquor, or sparkling wine bottles in the described way are not suitable to cause any serious injuries of the skull and/or the brain. The breaking of the bottles following impact on the skull, may apparently be explained by "inner tensions" and inhomogeneity of the bottle material (glass). The energy to break a glass bottle is in general assumed to be lower than the energy required to break a normal stable cranial bone without any pathological changes *(15)*.

Table 1
Individual Characteristics of 10 Cases of Blow Injuries Caused by Glass Bottles

	Age	Gender	Type of bottle/ filling condition[a]	Bottle broken	Autopsy findings	Cause of death
Case 1	18	Male	Liquor, wine/half emptied and full	Yes	No injuries	Individual survived
Case 2	30	Male	Wine/half emptied and full	Yes	Swelling and contusion of the scalp	Individual survived
Case 3	21	Male	Wine/half emptied	Yes	Incised wounds on front of the head and midface area	Individual survived
Case 4	43	Male	Vodka, beer, glass jar	Yes	Lacerations	Neck compression
Case 5	56	Female	Liquor	Yes	Lacerations	Neck compression, exsanguination
Case 6	35	Male	Beer	Yes	One superficial laceration of the scalp	Exsanguination
Case 7	80	Female	Lemonade	Yes	Lacerations	Exsanguination
Case 8	52	Male	Beer	Yes	Large sized hematomas with several short and angled lacerations, streaky impressions of the tabula externa, subarachnoidal hemorrhage	Exsanguination
Case 9	47	Male	Beer	Yes	13 lacerations of the scalp, two depressed fractures of the left parietal bone, subdural hematoma, cerebral contusions	Exsanguination
Case 10	16	Female	Water/full	No	Severe contusions of the forehead, chin and left midfacial area, spider's web fracture of the frontal bone, subarachnoidal hemorrhage	Exsanguination

[a] Only given if data were available.

4. Discussion

In synopsis, the cases presented here have considerable similarities. In all cases, the head was the main target of the assault. In one case (case 4), the offenders probably had planned both where to place the blow (occipital area) and with how much intensity the blow needed to be applied to assure that the victim was incapable to act. Moreover, combinations of lacerations and incised wounds were encountered in most of the cases. Interestingly, lacerations were of more severity than incised wounds. The latter were, as a rule, only superficial. Thus, the incised wounds observed in the cases discussed here can be thoroughly considered as coincidental sequelae of glass splinters. However, no injuries were observed in only one case (case 1), in which the victim had been covered with a blanket by the perpetrators prior to the assault. The total absence of injuries might be attributable to the fact that the covering of the head with the blanket absorbed the energy of the blow impact and thus protected the victim's head from sustaining any injuries.

Regarding the observed breaking of the bottles in all cases except for one, it must be noted that the differences in shape, weight, and filling conditions of the bottles did obviously not account for any differences of the resulting injuries and the breaking behavior of the bottles, respectively. Interestingly, as far as it can be concluded from our experiments, the filling level of glass bottles does not seem to have any impact on either the severity of the resulting injuries or the bottle's breaking behavior.

Despite different thickness of cranial bones, it is interesting that the elasticity of the affected cranial bones is obviously sufficient enough to absorb the energy of the blow impact. Strikingly, even in the cases where fatal outcome was in some way attributable to the blow with the glass bottle, the actual cause of death was not in any circumstances related to mechanical damage of bone or brain (e.g., comminuted skull fractures or severe cerebral contusions). Interestingly, lacerations were ascertained to be of more major severity than incised wounds that were, as a rule, only superficial. Here, rather exsanguination from the inflicted lacerations was found to be responsible for fatal outcome.

It should be mentioned that, in contrast to the findings just presented, Zimmer et al. reported on 11 fatalities presenting with severe injuries that were attributed to blows with glass bottles *(17)*. In seven cases, these authors observed injuries of the skull that turned out to be solely caused by blows with glass bottles, and resulted in fatal outcome. The authors speculated that fractures of the skull might be expected if the bottles do not break and transfer the complete energy of the blow to the skull. However, the authors did not pro-

vide further detailed data to confirm this hypothesis based on the findings in their case material.

Furthermore, Weyrich reported on a fatal terraced depressed fracture of the skull caused by a blow with a glass beer mug *(18)*.

As a result of the small number of cases presented, general conclusions regarding skull injuries caused by blows with glass bottles should be drawn with considerable caution. Nevertheless, the observed pathological and biomechanical features allow the following considerations. Despite different shapes and filling conditions of the bottles, the morphological appearance of the injuries resulting from blows with different bottles resembles each other very much. Concerning the probability of an occurrence of skull fractures in cases of blows with glass bottles it should be emphasized that skull fractures were observed only in 2 of the 10 cases presented here. Under experimental conditions, no skull fractures could be produced in 20 postmortem experiments with corpses. Taken together, in an overall number of 30 cases (authentic cases plus experimental setting), skull fractures were only present in 2 cases. Therefore, skull fractures resulting from blows to the head with glass bottles can be considered rare events. Factors influencing the probability that a fracture occurs are depending on the bottle used, characteristics of the victim's head, and, finally, variable constellations determined by the individual mode of assault.

Regarding biomechanically relevant factors that are determined by the bottle itself, the minor elasticity of glass, as compared to bone, the filling condition, and the location of impact have to be considered as important. One is tempted to speculate whether the observed absence of pond fractures is attributable to the fact that the bottle's belly and not the edge of the bottles bottom hit the head in the cases presented here.

Additional factors related to the victim's head, such as the quantity of hair, thickness of the scalp, configuration and thickness of the skull, and elasticity of bone have to be taken into account, too. Finally, one case reported by Prokop and Radam *(13)* seems to indicate that age seems to be another very important factor that must be considered as well. These authors describe an extensive system of bending fractures of the left parietal bone extending to the left temporal bone in a 73-year-old alcoholic who was killed by a blow with a wine bottle.

The final outcome and sequelae of a blow to the head with a glass bottle also depend on constellational factors determined by the mode of commitment like covering of the head (case 1) or the mobility of the cervical spine and head, respectively, at the moment of impact (case 10). Rare cases in which

depressed fractures of the skull following a blow with a glass bottle can be observed are in particular those in which the victim was lying on the ground with the head fixed when being hit by the bottle.

Considering the high frequency of assaults against the head using glass bottles, it would be most helpful for forensic practical casework to gain more detailed and sophisticated knowledge on the subject (e.g., about biomechanical principles of skull injuries caused by blows with glass bottles). Such data are already partially available regarding drinking glasses *(19)*. However, the case reports presented here, complemented by the given experimental biomechanical data, will contribute to the understanding and assessment of analogous cases in practical forensic casework.

References

1. Patscheider H. Eine ungewöhnliche Stichverletzung der Brustorgane. Arch Kriminol 1972;150:44–48.
2. Dietz G, Waltz H. Stichverletzungen des Herzens durch Glassplitter. Arch Kriminol 1973;152:7–12.
3. Behrens S, Tryba M, Otte D, Gotzen L, Suren EG. Der Einfluss von Rückhaltesystemen auf Glasverletzungen von Pkw-Insassen. Unfallheilkunde 1978;81:502–507.
4. Sauer G, Paar O, Munk P, Passl R. Zur Problematik der Verletzungen mit Glas. Unfallheilkunde 1978;81:406–408.
5. Ambach E, Rabl W, Tributsch W. Glassplitter im Schädel, Kriminalistik 1990;8/9: 463–470.
6. Ambach E, Tributsch W, Rabl W. Tödliche Verletzungen durch Glasfragmente. Falldarstellungen und Sektionsbefunde. Arch Kriminol 1991;187:39–46.
7. Bajanowski T, Varro A, Sepulchre MA. Tod durch scharfe Gewalt. Kriminologische und kriminalistische Aspekte. Arch Kriminol 1991;187:65–74.
8. Schulz F, Hildebrand E. Ungewöhnliche Todesfälle durch Glassplitterverletzung. Arch Kriminol 1992;189:145–152.
9. Bajanowski T, Paldauf E, Brinkmann B. Morphologie von Glasschnittverletzungen. Rechtsmedizin 1991;1:47–50.
10. Rothschild MA, Karger B, Schneider V. Puncture wounds caused by glass mistaken for stab wounds with a knife. Forensic Sci Int 2000;121:161–165.
11. Karger B, Rothschild MA, Pfeiffer H. Accidental sharp force fatalities—beware of architectural glass, not knives. Forensic Sci Int 2001;123:135–139.
12. Madea B. Hämorrhagische Gastroenterocolopathie als Folge einer Halsstichverletzung. Rechtsmedizin 1992;2:74–77.
13. Prokop O, Radam G. Atlas der gerichtlichen Medizin. Karger, Basel, 1987, p. 361.
14. Kratter J. Gerichtsärztliche Praxis. Lehrbuch der gerichtlichen Medizin. Enke, Stuttgart, 1919.

15. Madea B, Lignitz E, Weinke H. Schädelverletzungen durch Schlag mit Glasflaschen. Arch Kriminol 1993;192:73–79.
16. Schmidt PH, Orlopp K, Dettmeyer R, Madea B. Zur praktischen Anwendung des Injury Severity Scores (ISS) in der forensischen Begutachtung. Arch Kriminol 2002;210:172–177.
17. Zimmer G, König HG, Pedal I. Zur Gefährlichkeit von Schlägen mit Glasflaschen. Zentralbl Rechtsmedizin 1992;38:21.
18. Weyrich G. Zur Diagnose des verletzenden Werkzeugs aus Schädelwunden. Dtsch Z ges Gerichtl Med 1933;21:380–386.
19. Bohnert M, Kneubuehl BP, Ropohl D, Pollak S. Zum Verletzungspotential von Trinkgläsern. Rechtsmedizin 2003;4:224.

Forensic Neuropathology

3

Primary Cerebral Neoplasms as a Cause of Sudden, Unexpected Death

Jakob Matschke, MD

Contents

Summary

This chapter deals with primary intracranial neoplasms as a cause of sudden, unexpected death, giving an overview of our current understanding of both clinical and pathological features of these tumors. A review of the literature and this author's autopsy files shows that the incidence of sudden death as a result of primary intracranial neoplasms has declined over the last decades.

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

Additionally, a proposal for a guideline for cases of sudden, unexpected death that are presumed to have an intracranial cause is presented.

Key Words: Sudden death; brain neoplasms; forensic neuropathology; oncology.

1. Introduction

Sudden death has been defined as "unexpected death following so rapidly from the onset of symptoms that the cause of death could not be certified with confidence by a medical practitioner familiar with the patient" *(1)*. However, uncertainty exists regarding the length of time given by the term "rapidly." Most researchers agree on a time interval between as short as 1 hour or as long as 24 hours *(1,2)*.

Among the causes leading to sudden, unexpected death in adults (for the most part cardiovascular of origin) we also find some of the more common neurological disorders located in the cranial vault such as hypertensive intracerebral bleeding or subarachnoid hemorrhage as a result of ruptured berry aneurysms of larger intracranial arteries. Such cases will for the most part not present any difficulties to the forensic pathologist. However, the correct diagnosis and classification may be difficult in cases of sudden death as a result of intracranial neoplasms. This is even more true regarding the widespread used brain autopsy technique in forensic practice, which allows only the gross examination of a few coronar slices of the fresh brain, often without thorough investigation of the hindbrain with its dense accumulation of vital structures.

This chapter is geared to the forensic pathologist and medical examiner, respectively, who, from time to time, deal with cases of sudden death as a result of a certain intracranial cause (i.e., a primary intracranial neoplasm). The chapter provides an overview of current concepts of these unique tumors together with a guideline for handling such cases.

2. Definition of Terms

In clinical and pathological practice, the term "brain tumor" is often used and comprises quite a heterogeneous collection of unique neoplasms. Because some of these tumors do not originate from the actual brain tissue (e.g., meningioma, schwannoma), the term "intracranial neoplasm" or "intracranial tumor" should be used.

As with other organ systems, intracranial neoplasms are classified using a specifically designed World Health Organization (WHO) classification scheme *(3)*, which is used and understood by pathologists and clinicians world-

wide. This classification scheme, with its seven categories, is discussed in further detail.

Among the three categories discarded from earlier versions of the WHO classification scheme is the former section "cysts and tumor-like lesions" *(4,5)*. Although the individual tumors in this category (e.g., epidermoid, dermoid, and colloid cysts) are not neoplasms in the strict sense of this term, they often enough present clinically as any other "real" neoplasm with space-occupying characteristics. Moreover, the forensic pathologist often comes across one of the members of this former category because actually a colloid cyst of the third ventricle is the single most often observed tumor of all intracranial neoplasms that cause sudden death when taking the number of published cases as a basis. To date, there are roughly 40 published cases available in the literature *(6)*, in contrast to only approx 75 cases of any other neoplasm listed in the latest version of the WHO classification. Therefore, it is arguable to discard the cysts and, among others, the pituitary adenomas from this discussion because there have been published cases of sudden death as a result of pituitary adenoma, too *(7,8)*. However, this author believes it is necessary, especially for the sake of a better comparison of various investigative papers from various times, to use the present, latest classification scheme in forensic practice and scientific research. As a consequence, the following discussion will neither include cases of colloid cysts (*6*) nor of epidermoid cysts *(9)* or pituitary adenomas *(7,8)* as cause of sudden death but will focus on cases with tumors that are listed in the latest WHO classification. Considerable caution must be taken because some tumors were known earlier under other terms. For example, the study by Huntington and coworkers from 1965 listed a "reticulum cell sarcoma," which, with reasonable accuracy, is a "lymphoma" *(7)*. But whether the "mixed glioma and sarcoma" from their study would indeed be the "gliosarcoma" of 2003 is a matter of debate. Figure 1 shows the distribution of intracranial neoplasms as cause of sudden death according to the available literature.

3. Classification and Grading

The latest (third) version of the WHO classification *(3)* comprises seven major categories of primary intracranial neoplasms:

1. tumors of neuroepithelial tissue
2. tumors of peripheral nerves
3. tumors of the meninges
4. lymphomas and hemopoietic neoplasms

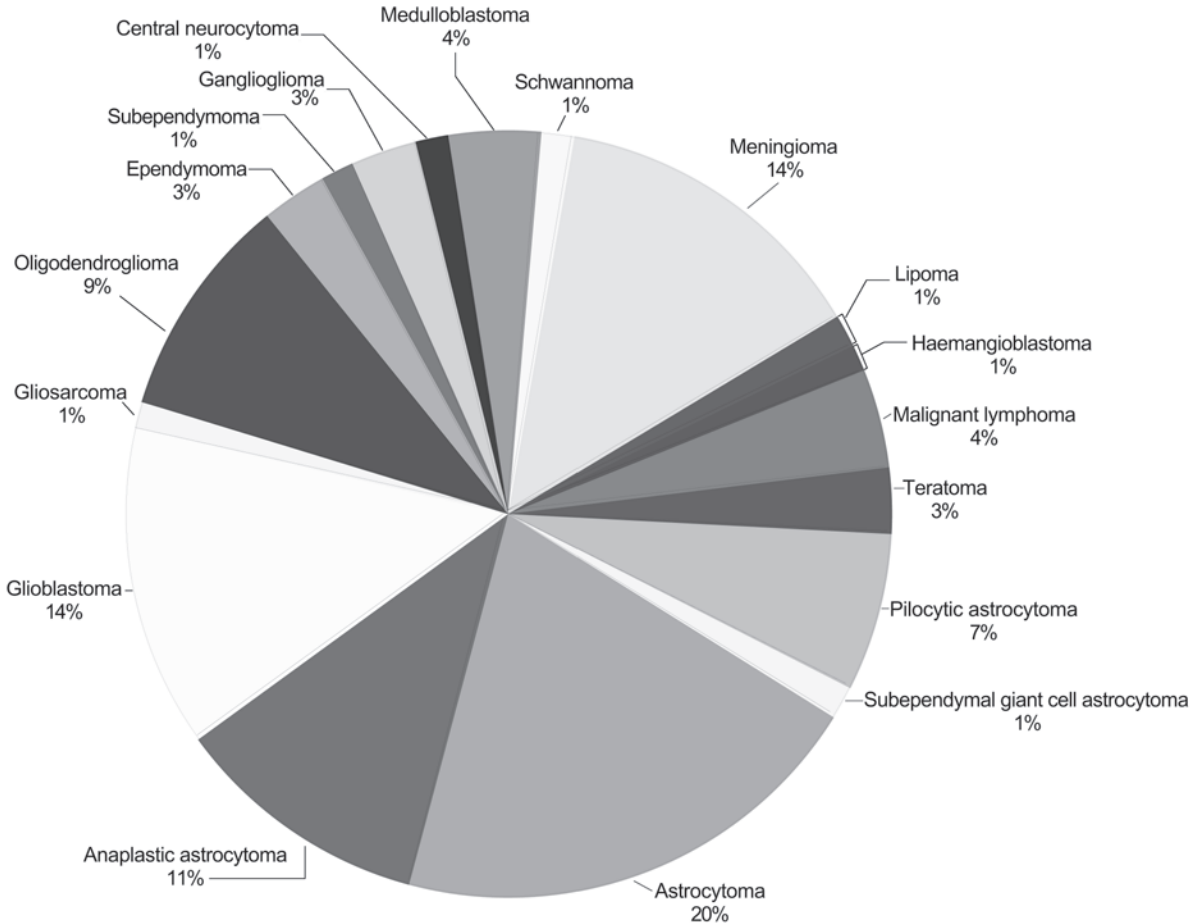

Fig. 1. Distribution of different types of intracranial neoplasms as cause of sudden death according to a literature review ($N = 74$).

5. germ cell tumors
6. tumors of the sellar region
7. metastatic tumors

An abbreviated overview of the classification and the individual tumors most likely to be encountered by the forensic pathologist is presented in Table 1.

The issue of grading intracranial neoplasms differs from that of most peripheral tumors. As, for example, epithelial neoplasms are labeled "malign" (being a carcinoma then) at the time when a basal lamina is invaded and/or metastases are found, this criterion cannot simply be applied to intracranial neoplasms because these tumors almost never metastasize and a basal lamina in the strict sense of the term does not exist in the brain proper.

An issue associated with any tumor grading system is the biological behavior regarding the survival time of a respective patient. After analyzing an increasing wealth of epidemiological data from follow-up studies of large cohorts of patients with intracranial neoplasms, a four-tier grading system that applies histological criteria, first introduced by Kernohan and coworkers in 1949 *(10)*, became widely accepted. So the 5-year relative survival rate for patients with astrocytoma WHO-grade I (pilocytic astrocytoma) is more than 80%, whereas in those with a grade IV lesion (glioblastoma), it is only less than 5% *(11)*. The grading for some selected intracranial neoplasms is also shown in Table 1.

4. Clinical Presentation and Diagnosis

As a rule, intracranial neoplasms present with either nonspecific, generalized symptoms, or with focal neurological symptoms as a result of the unique location of the neoplasm. Generalized symptoms result from a rise in intracranial pressure and comprise headache, nausea and vomiting, altered mental status, and papilledema. Because intracranial neoplasms can virtually grow in any part of the intracranial compartment, including the brain and the spinal cord, the focal neurological symptoms are protean. Nevertheless, attention should be focused on certain clinical features as they may help to identify the localization of a certain tumor, for example, focal seizures usually result from cortical tumors, ataxia is associated with tumors arising in the cerebellum, and hydrocephalus and Parinaud's syndrome are connected to tumors of the pineal region or of the third ventricle *(12)*.

Nowadays, the single most important diagnostic tool to diagnose an intracranial neoplasm with reasonable certainty is magnetic resonance imaging. Plain x-ray skull films are no longer considered valuable, and even com-

Table 1
WHO Classification of Tumors of the Nervous System

I. Tumors of Neuroepithelial Origin
Astrocytic tumors
- Diffuse astrocytoma (grade II) *(8,17,27–29)*
- Anaplastic astrocytoma (grade III) *(8,27)*
- Glioblastoma (grade IV) *(8,30,31)*
- Pilocytic astrocytoma (grade I) *(15,32–34)*
- Subependymal giant cell astrocytoma (grade I) *(35)*

Oligodendroglial tumors *(8,28,32,36)*
Mixed gliomas
Ependymal tumors
- Ependymoma (grade II) *(37)*
- Anaplastic ependymoma (grade III) *(29)*
- Subependymoma (grade I) *(38,39)*

Choroid plexus tumors
Glial tumors of uncertain origin
Neuronal and mixed neuronal-glial tumors
- Gangliоglioma (grade I, II or III) *(34,40)*
- Central neurocytoma (grade II) *(41)*

Pineal Parenchymal Tumors
Embryonal Tumors
- Medulloblastoma (grade IV) *(8,17)*

II. Tumors of Peripheral Nerves
III. Tumors of the Meninges
Tumors of meningothelial cells
- Meningioma (grade I) *(32)*

Mesenchymal, nonmeningothelial tumors
- Lipoma *(42)*

Tumors of uncertain histogenesis
- Hemangioblastoma (grade I) *(7)*

IV. Lymphomas and Hemopoietic Neoplasms
- Malignant lymphomas *(8)*

V. Germ Cell Tumors
- Teratoma *(17)*

VI. Tumors of the Sellar Region
VII. Metastatic Tumors

Note: For further reading, related references of cases of sudden death are given in parentheses. (Modified according to ref. *3.*)

puted tomography scanning can easily miss tumors in the posterior fossa or nonenhancing benign gliomas. Further therapeutic options (operation, radiation, chemotherapy) are initiated as soon as a definite morphological diagnosis is established following open or stereotactically guided biopsy *(13)*.

5. Pathophysiological Mechanisms of Sudden Death as a Result of Intracranial Neoplasms

Although intracranial neoplasms comprise individual tumors with a vast biological and morphological diversity, their inherent capacity to threaten the patient's life basically nearly always a result of their mass effect *(14)*. This common final pathway is responsible for any rapid increase in intracranial pressure (ICP), be it (a) as a result of acute decompensation of chronic obstructive hydrocephalus resulting from a small brainstem tumor invading or compressing the aqueduct *(15)*, or (b) fatal bleeding into a hitherto clinically silent glioblastoma *(16)* or ependymoma *(17)*.

Any inexorably growing mass inside the rigid compartment of the cranial vault is capable of raising the ICP beyond a level incompatible with life. More important than the actual value of the ICP is the rapidity of its rise. Thus, slowly expanding lesions are far better tolerated by the affected patient because they allow compensatory mechanisms to develop *(18,19),* which is not the case in neoplasms that quickly expand as a result of inherent growth capacities or intratumoral hemorrhage. Nevertheless, compensatory mechanisms inevitably become exhausted at some point because any sudden, even tiny, increase of ICP (e.g., as a result of sneezing, coughing, or pressing) can suddenly lead to terminal failure of the respiration centers located in the lower brainstem owing to herniation phenomena *(15)*.

More rare mechanisms by which intracranial neoplasms endanger an individual's life are potentially slow-growing, benign neoplasms located in the vicinity of vital centers. This is often hypothesized in small lesions in or near the hypothalamus *(20)* by interference with centers of thermoregulation or neural discharge in autonomic pathways leading to cardiac suppression or lethal arrhythmias *(14)*.

6. Epidemiological Features of Sudden Death as a Result of Intracranial Neoplasms

Primary intracranial neoplasms are relatively rare, with an overall reported incidence of about 12 per 100,000 person-years in the United States *(21,22)*.

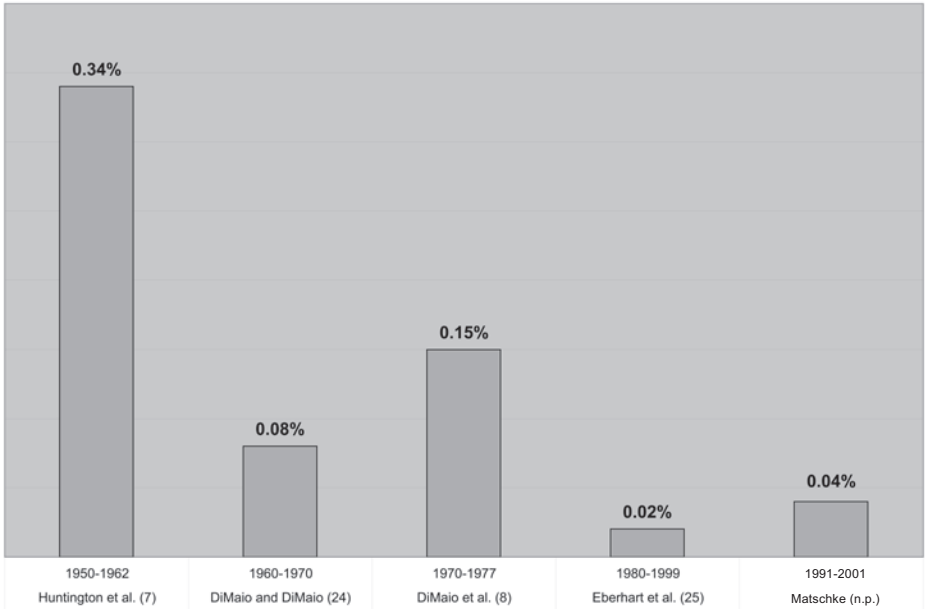

Fig. 2. Frequency of primary intracranial neoplasms as cause of sudden, unexpected death according to a review of the literature dealing with larger autopsy series as well as the author's autopsy files. (n.p.: data not published.)

Nevertheless, owing to their intricate association with vital structures and their most often malignant clinical behavior, primary intracranial neoplasms represent one of the leading causes of deaths. Although intracranial neoplasms account for less than about 2% of all cases of cancer, they are responsible for 7% of years lost as a result of cancer in patients up to the age of 70 *(23)*.

Because of their unique location in the intracranial vault, most primary intracranial neoplasms will result in symptoms rather early in the course of the disease. Consequently, only very few cases of sudden, unexpected death resulting from intracranial neoplasms and only a paucity of studies has analyzed larger autopsy series (not counting some 50 to 100 case reports published that have been addressed to this issue). All the aforementioned studies of larger series derive from autopsy material investigated in institutions of forensic medicine.

The first study this author is aware of was done by Huntington and coworkers in 1965 at the Kern's County Coroner's Office in Bakersfield, California *(7)*. Among 3543 autopsies performed between 1950 and 1962, the authors found 14 cases of sudden death as a result of undiagnosed primary

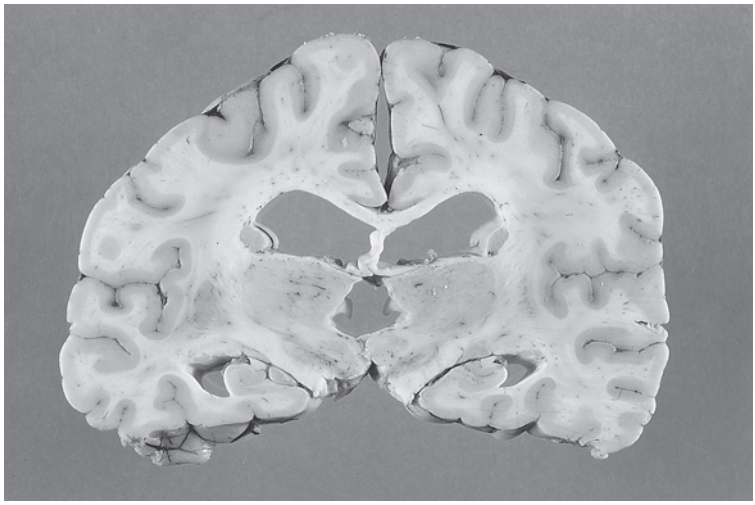

Fig. 3. Marked hydrocephalus as a result of prior to death undiagnosed pilocytic astrocytoma of the brainstem (*see* Fig. 4) in a 29-year-old man showing massive enlargement of the cerebral ventricles including temporal horns of the lateral ventricle and the third ventricle.

intracranial neoplasms (0.4%). These figures are recalculated as 12 cases (0.34%) after dismissing one case of "chromophobe [pituitary] adenoma" and "anaplastic pituitary tumor" each.

Out of 17,404 autopsies performed between 1960 and 1970 at the Brooklyn Office of the Medical Examiner, New York, DiMaio and DiMaio *(24)* came up with 17 cases (0.1%). Here, after elimination of three cases of colloid cysts, there were 14 cases (0.08%).

Among 10,995 autopsies performed at the Dallas County Medical Examiner's Office from 1970 to 1977 *(8)*, there were 19 cases of primary intracranial neoplasms (0.17%). After dismissing one case of colloid cyst and another one of chromophobe adenoma, these figures read as 17 cases (0.15%).

The most recent study by Eberhart et al. *(25)* from the Office of the Chief Medical Examiner of the State of Maryland evaluated 54,873 autopsies from 1980 to 1999 and found 11 cases (0.02%). Again, these figures were recalculated after eliminating two colloid cysts and one pituitary adenoma, thus yielding 9 cases (0.02%).

At the Institute of Legal Medicine in Hamburg, Germany, 11,959 autopsies were performed from 1991 to 2001. Among these, 5 cases of sudden death as a result of a primary intracranial neoplasm were found (0.04%).

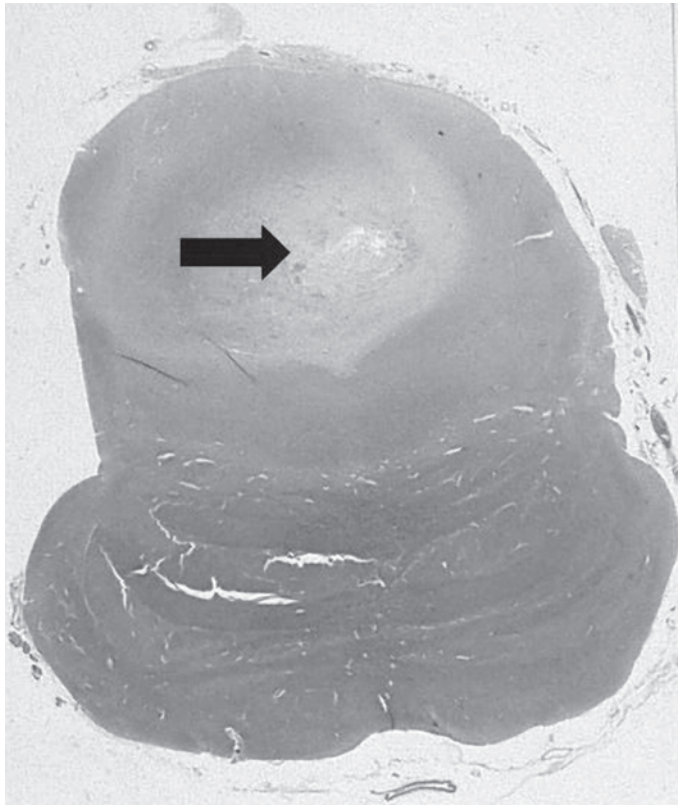

Fig. 4. Pilocytic astrocytoma of the ponto-mesencephalic junction with blurring of original parenchymal structures distorting and occluding the aqueduct (arrow) leading to occlusive hydrocephalus (*see* Fig. 3) (Hematoxilin & eosin).

Although all data from the aforementioned studies derive from different regions and decades, the almost identical methodology of each seems to allow comparison: all studies retrospectively analyzed autopsies that were performed at medicolegal or forensic pathological institutions. As Fig. 1 clarifies, the data corroborate that sudden death as a result of primary intracranial neoplasms has become more rare over the last decades. As hypothesized by Eberhart et al. *(25)*, this finding is most probably the result of improvements in both neuroimaging methods and access to health care.

7. Proposal for a Guideline

In a case of sudden, unexpected death that is presumed to have an intracranial cause, the following guidelines are proposed for the forensic pathologist or medical examiner, respectively.

- Remember that the causes of death most often encountered by the forensic practitioner are the most obvious ones: subarachnoid bleeding as a result of a ruptured berry aneurysm and hypertensive intracerebral hemorrage. Both conditions are diagnosed easily.
- Apart from the aforementioned pathological changes of the brain, it is strongly suggested that the brain is drained in buffered formaline for fixation for a duration of at least 2 weeks.
- Remember that apart from subarachnoid bleeding and intracerebral hemorrage every other intracranial cause of sudden death is overlooked all too easily in the brain sliced in the native ("fresh") state. This is especially true for the hindbrain that is much too often "autopsied" with only one horizontal slice through both cerebellum and brain stem.
- Keep close contact with a neuropathologist and let him or her do a thorough brain autopsy including histology and immunohistochemistry.

If a neuropathologist is not available, do the neuropathological autopsy yourself as follows:

- Hindbrain (cerebellum and brainstem) are separated from the cerebral hemispheres by a traverse cut across the upper midbrain (level of substantia nigra/oculomotor nerve) at right angle to the long axis of the brain stem.
- Then separate the cerebellum from the brain stem by dissecting all the three cerebellar peduncles on each side.
- Slice the brainstem at 5-mm-thick intervals again at right angles to its long axis.
- Dissect the cerebellum in slices of 5-mm thickness by cuts at right angles to the folia.
- The cerebral hemispheres are best cut in horizontal slices of about 10-mm thickness. The first cut should be through the mamillary bodies. The anterior part is then put cutface down—preferably between centimeter guides—and cut into slices with identical thickness. The same is done with the remaining posterior part of the cerebral hemispheres.
- Sections for histological studies are taken according both to clinical history and macroscopic findings in the respective case.

For details the reader is referred to any of the many neuropathological textbooks *(26)*.

References

1. Mason JK. Forensic Medicine for Lawyers, 3rd ed. Butterworths, London, Dublin, Edinburgh, 1995.
2. Knight B. Forensic Pathology, 2nd ed. Arnold, London, 1996.
3. Kleihues P, Cavenee WK. Pathology and Genetics of Tumours of the Nervous System. IARC Press, Lyon, 2000.
4. Gonzales M. The 2000 World Health Organization classification of tumours of the nervous system. J Clin Neurosci 2001;8:1–3.
5. Kleihues P, Louis DN, Scheithauer BW, et al. The WHO classification of tumors. J Neuropathol Appl Neurobiol 2002;61:215–225.
6. Büttner A, Winkler PA, Eisenmenger W, Weis S. Colloid cysts of the third ventricle with fatal outcome: a report of two cases and review of the literature. Int J Legal Med 1997;110:260–266.
7. Huntington RW, Cummings KL, Moe TI, O'Connell HV, Wybel R. Discovery of fatal primary intracranial neoplasms at medicolegal autopsies. Cancer 1965;18:117–127.
8. DiMaio SM, DiMaio VJ, Kirkpatrick JB. Sudden unexpected deaths due to primary intracranial neoplasms. Am J Forensic Med Pathol 1980;1:29–45.
9. Matschke J, Stavrou D, Püschel K. Sudden unexpected death due to epidermoid cyst of the brain. Am J Forensic Med Pathol 2002;23:368–370.
10. Kernohan JW, Mabon RF, Svien HJ, Adson AW. A simplified classification of gliomas. Proc Staff Meet Mayo Clin 1949;24:71–75.
11. Lantos PL, Louis DN, Rosenblum MK, Kleihues P. Tumors of the nervous system. In: Graham DI, Lantos PL, eds. Greenfield's Neuropathology. Arnold, London, New York, New Delhi, 2002, pp. 767–1051.
12. Black P, Wen PY. Clinical, imaging and laboratory diagnosis of brain tumors. In: Kaye AH, Laws ER, eds. Brain Tumors. An Encyclopedic Approach. Churchill Livingstone, Edinburgh, Hong Kong, London, 1995, pp. 191–214.
13. De Angelis LM. Brain tumors. New Eng J Med 2001;344:114–123.
14. Leestma JE. Forensic Neuropathology. Raven Press, New York, 1988.
15. Matschke J, Tsokos M, Püschel K. Pilocytic astrocytoma of the brainstem as the cause of death in a 29-year-old man [Article in German]. Rechtsmedizin 2000;10:221–225.
16. Silbergeld DL, Rostomily RC, Alvord ECJ. The cause of death in patients with glioblastoma is multifactorial: clinical factors and autopsy findings in 117 cases of supratentorial glioblastoma in adults. J Neurooncol 1991;10:179–185.
17. Byard RW, Bourne AJ, Hanieh A. Sudden and unexpected death due to hemorrhage from occult central nervous system lesions. A pediatric autopsy study. Pediatr Neurosurg 1991;17:88–94.
18. Black M, Graham DI. Sudden unexplained death in adults. In: Love S, ed. Neuropathology. A Guide for Practising Pathologists (Current Topics in Pathology Vol. 95), Springer, Berlin, Heidelberg, New York, 2000, pp. 125–148.
19. Black M, Graham DI. Sudden unexplained death in adults caused by intracranial pathology. J Clin Pathol 2002;55:44–50.

20. Sperhake JP, Matschke J, Orth U, Gal A, Püschel K. Sudden death due to cerebrotendinous xanthomatosis confirmed by mutation analysis. Int J Legal Med 2000;113:110–113.
21. CBTRUS 1997. Annual Report. Central Brain Tumor Registry of the United States, Chicago, 1998.
22. CBTRUS 1999. Annual Report. Central Brain Tumor Registry of the United States, Chicago, 2000.
23. Giles GG, Gonzales MF. Epidemiology of brain tumors and factors in prognosis. In: Kaye AH, Laws ER, eds. Brain Tumors. An Encyclopedic Approach. Churchill Livingstone, Edinburgh, Hong Kong, London, 1995, pp. 47–68.
24. DiMaio TM, DiMaio DJ. Sudden death due to colloid cysts of third cerebral ventricle. N Y State Med J 1974;74:1832–1834.
25. Eberhart CG, Morrison A, Gyure KA, Frazier J, Smialek JE, Troncoso JC. Decreasing incidence of sudden death due to undiagnosed primary intracranial tumors. Arch Pathol Lab Med 2001;125:1024–1030.
26. Esiri MM. Oppenheimer's Diagnostic Neuropathology: A Practical Manual, 2nd ed. Blackwell Science, Oxford, 1996.
27. Büttner A, Gall C, Mall G, Weis S. Unexpected death in persons with symptomatic epilepsy due to glial brain tumors: a report of two cases and review of the literature. Forensic Sci Int 1999;100:127–136.
28. Lindboe CF, Svenes KB, Slordal L. Sudden unexpected death in subjects with undiagnosed gliomas. Am J Forensic Med Pathol 1997;18:271–275.
29. Shemie S, Jay V, Rutka J, Armstrong D. Acute obstructive hydrocephalus and sudden death in children. Ann Emerg Med 1997;29:524–528.
30. Matsumoto H, Yamamoto K. A case of sudden death by undiagnosed glioblastoma multiforme. Jpn J Legal Med 1994;47:336–339.
31. Unger PD, Song S, Taff ML, Schwartz IS. Sudden death in a patient with von Recklinghausen's neurofibromatosis. Am J Forensic Med Pathol 1984;5:175–179.
32. Abu Al Ragheb SY, Koussous KJ, Amr SS. Intracranial neoplasms associated with sudden death: a report of seven cases and a review of the literature. Med Sci Law 1986;26:270–272.
33. Buzzi S, Verdura C, Arlati S, Colecchia M. Sudden death in a child due to rare endocranial neoformation. Med Sci Law 1998;38:176–178.
34. Gleckman AM, Smith TW. Sudden unexpected death from primary posterior fossa tumors. Am J Forensic Med Pathol 1998;19:303–308.
35. Prahlow JA, Teot LA, Lantz PE, Stanton CA. Sudden death in epilepsy due to an isolated subependymal giant cell astrocytoma of the septum pellucidum. Am J Forensic Med Pathol 1995;16:30–37.
36. Rajs J, Rasten-Almqvist P, Nennesmo I. Unexpected death in two young infants mimics SIDS. Am J Forensic Med Pathol 1997;18:384–390.
37. Poon TP, Solis OG. Sudden death due to massive intraventricular hemorrhage into an unsuspected ependymoma. Surg Neurol 1985;24:63–66.
38. Mork SJ, Morild, I, Giertsen JC. Subependymoma and unexpected death. Forensic Sci Int 1986;30:275–280.

39. Schwarz KO, Perper JA, Rozin L. Sudden, unexpected death due to fourth ventricular subependymoma. Am J Forensic Med Pathol 1987;8:153–157.
40. Nelson J, Frost JL, Schochet SS. Sudden, unexpected death in a 5-year-old boy with an unusual primary intracranial neoplasm. Am J Forensic Med Pathol 1987;8: 148–152.
41. Balko MG, Schultz DL. Sudden death due to a central neurocytoma. Am J Forensic Med Pathol 1999;20:180–183.
42. Zappi E, Zappi M, Breithaupt M, Zugibe FT. Cerebral intraventricular lipoma and sudden death. J Forensic Sci 1993;38:489–492.

Death From Natural Causes

4

Obesity Epidemic in the United States

A Cause of Morbidity and Premature Death

Donna M. Hunsaker, MD
and John C. Hunsaker III, MD, JD

Contents

Summary

Regarded as preeminent health issues in the Western world, overweight (OW) and obesity (OB) are overwhelmingly prevalent in the United States. Currently the United States, characterized by one writer as "Fat Land," leads the epidemic of fat-related morbidity. Approximately 190 million Americans (approx 64% of the population) are estimated to be OW or OB. The energy balance equation defining relative homeostatic roles of energy intake and expenditure is not the sole etiological factor in a genetically defined subset of individuals with OB and OW. Beyond this subset, the energy balance is crucial for maintaining a healthy weight, free of significant premature natural

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

disease. In the Western civilization, there is a ready supply of a high-energy, low-nutrient foods, which, when coupled with decreased physical activity, promote adiposity. OB-related complications and risks of premature death are growing concerns to the medical community as the costs of treatment for this essentially preventable condition explode continually in the wake of rising trends of OW and OB. In the adult age ranges of greater than 20 years, OW and OB have increased to 54.9% within the last decade. Life expectancy declines by 20 years if a person is OB by the age 20. A high prevalence (15%) of American children between 6 and 19 years is classified as OW or OB. OB elderly report a poorer health-related quality of life in comparison to nonobese age-matched individuals. In the United States alone, approx 300,000 adult deaths are attributed annually to OB complications. Extensive research addresses the effects of OW/OB on the health of Americans. Many health care professionals now classify OW/OB in the general public as a chronic disease state, resulting in a vast array of medical comorbidities with debilitating psychological and behavioral sequelae. In forensic death investigation, autopsy findings correlate well with this clinical diagnosis. Calculating the body mass index (BMI) and measurement of abdominal circumference (AC) offers the most accurate postmortem diagnosis of OW and OB. In addition to BMI and AC, less specific parameters (i.e., adipocyte hypertrophy and hyperplasia) are included in the definition of OB. Clearly, evaluation of adipocyte size and quantity is impractical either antemortem or postmortem. In our experience, many OW or OB individuals coming to autopsy even without antemortem clinical diagnoses have died predominately of complications of ischemic heart disease, inclusive of hypertensive cardiovascular disease and atherosclerotic coronary artery disease. Other significant extra-cardiac causes of death directly related to OW and OB are ascribed to complications of diabetes mellitus, lower extremity deep venous thrombosis and pulmonary thromboemboli, liver disease, and acute and chronic respiratory embarrassment. Both nonfatal and lethal complications of surgery—either unrelated to or specifically for treatment of OB—also occur at higher rates in the OB patient.

Key Words: Obesity; overweight; body mass index (BMI); ischemic heart disease; medical complications of obesity; chronic disease; premature death; forensic autopsy; obesity epidemic.

1. Background

1.1. Aspects of the Obesity Epidemic

Hippocrates observed that "Sudden death is more common in those who are naturally fat than lean" *(1)*. Overweight (OW) and obesity (OB) are the

most common nutritional disorders in America *(2)*. Greater morbidity and poor quality of health are more prevalent in OB than in tobacco abuse, alcoholism, and poverty *(3)*. OB, although viewed by the public as a cosmetic problem, is a major health problem. If current trends continue in the United States, OB will soon overtake smoking as the primary preventable cause of death *(4)*. The National Health and Nutrition Examination Survey (NHANES) and other researchers record a drastic increase in adult OB from 14.5% between 1976 and 1980 to 22.5% between 1998 and 1999 *(5)*. Approximately 63% of men and 55% of women older than 25 years are considered OW or OB in the United States. One-fifth of American adults have a body mass index (BMI) greater than 30 (for definition and measurement see Section 1.2). Both genders with a BMI greater than 30 have a 50 to 100% higher mortality rate than those with a BMI less than 25. A BMI between 25 and 30 portends an increased mortality rate between 10 and 25% (*6*). A BMI greater than 40 strongly relates to an increased risk of various diseases and premature death. Seventy-five percent of class III (extreme) OB adults have at least one comorbid condition. In the 18- to 29-year-old population, a significant trend in class III OB has also been established in comparison to 1975 studies *(7)*. A current comprehensive review with recommendations for the diagnosis and treatment of OW and OB was published by Robert H. Eckel in 2003 *(8)*.

1.2. Definitions and Measurements of Obesity

The traditional definition of morbid or severe OB is weight at least 45 kg above normal weight or 100% greater than ideal body weight defined by standard life insurance tables. The Metropolitan Life Insurance Company weight-for-height tables have traditionally defined normal weight range. These tabulations are seriously limited by invalidated frame-size estimation, reliance on Caucasian populations, and table derivation from mortality data. Insurance weight tables have predicted mortality outcomes but not morbidity. BMI is also referred to as the Quetelet index, which combines the measurement of height and weight and assumes that any variation of weight in persons of the same height is predominantly due fat mass *(6,9)*. BMI, the most common means of assessment, provides better accuracy in measurement of total body fat than weight alone. The BMI calculation is kilograms of body weight per meter-squared height (kg/m^2). Simply stated, a calculated BMI of 30 suggests an overall excess weight gain of 30 pounds.

BMI does not directly measure body fat level and also does not measure body fat distribution. The 1995 fourth edition of the dietary guidelines for Americans recommends that adults maintain a healthy weight corresponding to a BMI between 19 and 25 *(10)*. The BMI provides an excellent measure of

weight adjusted for height in individuals, but is not a perfect measurement of adiposity because it does not distinguish lean from fat mass. Therefore, BMI requires conservative interpretation: very muscular individuals have a higher calculated BMI without an increased risk of premature morbidity or mortality. Similarly, the elderly, with less muscle density, have a lower calculated BMI, even with greater adiposity *(6,9)*. Table 1 shows BMI and other types of body fat measurement with their limitations *(5,6,9–14)*.

Individuals with increased abdominal fat relative to weight are more greatly predisposed to clinically significant cardiovascular disease. BMI combined with measurement of waist circumference (WC) predicts relative disease risks (DR) coexistent with OW and OB *(13,15,16)*. Table 2 shows the weight categories with associated DR. WC assesses abdominal fat, and identifies those individuals in the "normal or overweight" BMI classes who have a resultant relative increased risk of disease. Its simplicity of measurement is clinically useful. WC is not helpful in individuals with a BMI greater than 35. Men and women with larger WC (>102 and 88 cm [40 and 35 inches], respectively) have increased DR for diabetes mellitus (DM), hypertensive and atherosclerotic cardiovascular diseases, and dyslipidemia. Clinicians assign these individuals one risk category higher than defined by the calculated BMI (Table 2). WC smaller than the standard cutoff points, even at a given abdominal adiposity, predicts an increased incidence of risk for several chronic diseases: in men WC of 94 to 102 cm (37–40 inches) carries a relative risk of 2.2 for one or more cardiovascular risk factors; in women, a relative risk of 1.5 for cardiovascular disease at WC of 80–88 cm (32–35 inches). Insulin-resistant DM, hypertension, hyperlipidemia, and hyperandrogenism in women are linked to an increase in intra-abdominal and upper body fat. Use of the WC modality requires that other causes of increased abdominal girth, for example, ascites or elderly kyphosis, be ruled out *(5,13,14)*. The waist-to-hip ratio (WHR), a measure of the intra-abdominal and abdominal subcutaneous fat, more directly impacts DR than buttock and lower extremity subcutaneous fat. The WHR greater than 0.9 in women and greater than 1.0 in men is abnormal *(13,14)*.

The term "overweight" refers to a BMI between 25 and 30. Clinically, the classification represents a medically significant category because it predicts potential risk factors such as hypertension and glucose intolerance. Increased body weight of 20% above desirable is associated with comorbidities that both decrease overall health and increase morbidity *(5)*. The classification of OW individuals has remained relatively stable during the past three decades. The prevalence of OB has increased more than 50% within the past 10 to 15 years from 14.5 to 22.5% *(10)*. The 1995 dietary guideline advisory

Table 1
Measurements of Body Adiposity

Methods of measurement	Measurement	Interpretation	Limitations
Body mass index (BMI)	Weight (kg)/height (m^2) or lbs × 703/in^2	BMI >25 ↑ disease risk (DR)	Inconsistencies with muscular build and elderly atrophy
Waist circumference (WC)	Horizontal abdominal measurement at iliac crest level	WC >40/35 in (102/88 cm) ♂/♀: ↑ DR	Unhelpful measurement in BMI ≥35. Artifactual ↑ with elderly kyphosis
Waist-to-hip ratio (WHR)	Horizontal waist measurement 1 in above umbilicus. Hip (HC) measurement at suprapubic inguinal region	>1.0/0.9 ♂/♀: ↑ DR	Artifactual ↑ with elderly kyphosis
Panniculus index (PI)	Thoracic fat thickness (xiphoid process) + abdominal panniculus (3 cm below umbilicus) divided by the square of body height (cm/m^2)	3.25/4.07 ♂/♀: strongly correlates with BMI of obesity definition	False positive probability ≤2.5%
Hydrodensitometry	Under water body weighing	Fat is less dense than muscle/bone tissues. Density is calculated from subject's weight in air	Inconvenient; subject's concern of water submersion, technical inaccuracy of measurement
Dual-energy x-ray absorptiometry (DEXA)	X-ray provides broad filtered photon beam yielding 2 energy peaks	Regional resolution of bone mineral, fat and lean soft tissue. Estimates total fat	Not capable of visceral fat estimations. Cannot measure extremely obese subjects, pregnant patients. Expensive

Table 1
(continued)

Methods of measurement	Measurement	Interpretation	Limitations
Bioimpedance analysis (BIA)	Resistance to an applied electrical current across the extremities is a function of tissue composition	Lean conducts electrical current better than fat mass; with height and weight estimates body fat	No more accurate than derivations of simple BMI. Not helpful in short-term changes in body fluid or fat mass
Anthropometry	Calipers measure 4 skinfold thick-nesses: biceps, triceps, subscapular and suprailiac regions	Calculation of fat/ fat-free body mass: Durnin-Womersley 4-skinfold method. May add WC/HC	High technical error. Mechanical limitations for extreme obese
Computed tomography (CT) or magnetic resonance imaging (MRI) anthropometry	High resolution cross sectional radiographic images through selected anatomic regions of body	Distinguishes lean body mass and adipose tissue distribution and estimates percent body fat	Expensive and inconvenient. CT: radiation exposure. MRI: lengthy tedious study
Inverted BMI	1/BMI creates a “J”- or “U” -shaped curve generally in Caucasians	Better body fat measure than standard BMI. Provides prediction of mortality in YLL	No YLL estimation in African-American population for any age group until BMI ≥32

YLL, years of life lost; HC, hip circumference. (Modified according to refs. *5*,*6*,*9–14*.)

Table 2
BMI Classification Adjusted for Waist Circumference (WC) and Relative Disease Risks (DR)

BMI (kg/m^2)	Class	DR WC: smaller/larger waist
<18.5	Underweight	NA
18.5–24.9	Normal weight	NA
25.0–29.9	Overweight	Increased/high
30.0–34.9	Obese (class I)	High/very high
35.0–39.9	Obese (class II)	Very high/very high
≥40	Extreme obesity (class III)	Extremely high/extremely high

NA, nonapplicable. (Modified according to refs. *13*,*15*,*16*.)

committee underscores a clear increase in mortality at a BMI greater than 25. With a BMI less than 25 there still is an increase in the incidence of DM, hypertension, and coronary heart disease (CHD). If the committee's cutoff of normal were designated to a BMI less than 25, then 50% of American adults would be classified OW *(13)*.

1.2.1. Genetic, Hormonal, Racial, and Environmental Factors

OB is a heterogeneous disorder resulting from complex metabolic derangements, neuroendocrine factors, genetic influences, and environmental circumstances. Adipocytes, besides storing fat, are also a part of the neuroendocrine system regulating numerous, specific molecules. OB-linked secretory products of fat cells include leptin, uncoupling proteins, and peptide neurotransmitters, all of which by various mechanisms regulate the balance between energy intake and expenditure. Table 3 summarizes the major facets of these interrelated features and compares them to environmental factors *(2,5,13,17–25)*.

Men are more likely to be OW and women are more likely to be OB. American women with a BMI greater than 30 constitute the fastest growing group of fatness. This pattern is closely followed by children and adolescents. Twenty-five percent of all US children are OB. Eighty percent of OW/OB children are likely to become OW/OB adults *(26)*.

Thirty-seven percent of non-Hispanic African-American women and 34% of Mexican-American women are OB, underscoring a higher prevalence of OB in defined minority populations *(10,27)*. Inconsistent findings between BMI and mortality among African-Americans are statistically linked to

Table 3
Proposed Intrinsic and Extrinsic Mechanisms of Overweight (OW) and Obesity (OB)

Intrinsic factors (molecular basis of disease)		Extrinsic factors	
Genetic	Hormonal	Environmental	Behavioral
To date, 24 mendelian disorders with OB as a clinical feature. Seven single gene mutations produce human OB. Ten have autosomal recessive traits. Five have x-chromosome defects.		Nonexercise activity thermogenesis (NEAT): Activity other than volitional exercise (fidgeting, muscle contractions and daily activities of living). ↑ NEAT causes significant ↑ energy expenditure.	
Leptin: Adipocyte-derived hormone, with insulin, regulates appetite, energy expenditure and neuroendocrine function. Establishes a molecular basis for the body weight "set point." Leptin resistance in OW/OB resulting in point mutation in leptin, OB gene or its hypothalamic "Adipostat" receptor. In hypogonadotrophic hypogonadism, neither the leptin gene nor its receptor has been identified. Ghrelin: An acylated 28-amino-acid peptide which acts as an anorexigenic hormone, ↑ in blood shortly before, and ↓ after mealtime to hasten the urge of eating. Secreted by stomach/duodenum, may be implicated in a lessened appetite accompanied by impaired ghrelin secretion after gastric bypass surgery. Plasma ghrelin levels release growth hormone from the pituitary, which ↑ food intake. This ↑ appetite in normal individuals in response to diet-induced weight loss suggesting why there is a certain "set" amount of weight loss after dieting.		Lifestyle physical activity: Exercise thermogenics constitutes 5–10% of energy expenditure. ↑ energy expenditure with ↑ weight gain because metabolically active lean tissue mass ↑ in OW/OB. The US sedentary life style accounts for a substantial rise in OW/OB. 60% American adults are not regularly active. 33/41% OW ♂/♀ report no leisure time physical activity. As ↑BMI (regardless of gender), physical activity levels ↓. ↑ participation in sedentary activities (i.e., television, video games, and computerization of daily activities) predisposes to ↑weight gain.	

Table 3
(continued)

Intrinsic factors (molecular basis of disease)		Extrinsic factors	
Genetic	Hormonal	Environmental	Behavioral
Peptide YY_{3-36} (PYY) is a hormone fragment peptide, synthesized and secreted by L cells in the distal gastrointestinal tract. Secretion results in↓ ghrelin levels, which ↓appetite and food intake. Also modulates hypothalamic appetite circuits. Plasma PYY ↑15 minutes after food intake, peaks approx 16 minutes, and with elevation up to 6 hours. The sustained release is a direct effect of pressure on the intraluminal gut L cells secondary to intraluminal gut contents.			
Proopiomelanocortin (POMC), through activity of its melanocortin one receptor (MC1R) at the hypothalamic level, ↑ energy expenditure and ↓ food intake. Deletion of MC1R gene results in obesity hyperphagia, hyperinsulinemia and ↓ energy expenditure. (May account for 1–7% OB patients with BMI ≥40 and extreme childhood OB ≤10 years old). Mutations may also involve genes encoding for POMC and proenzyme convertase 1 (PC-1), which prevent synthesis of α-melanocyte-stimulating hormone (α MSH).			

Table 3
(continued)

Intrinsic factors (molecular basis of disease)		Extrinsic factors	
Genetic	Hormonal	Environmental	Behavioral
Other rare mutations causing severe human OB: OB, hypogonadism, and mental retardation Triad: Prader-Willi, Lawrence-Moon-Bidel, Bardet-Bidel, Cohen and Carpenter, and Ahlström syndromes. Prader-Willi syndrome is the most common genetic cause of OB		Overeating: The capacity to store energy, as adipose tissue in the form of triglycerides, in excess of that required for immediate utilization permits humans to survive poor nutritional intake, or starvation, for variable periods of time. Contrarily, when nutritional abundance with sedentary life style occurs, excess energy stores add on body fat. OW/OB individual compensates for ↑energy requirements by eating more than the average lean person in order to maintain ↑ weight. OW/OB may have a ≥2.3 kg weight gain during mid November to early or mid January months, (termed "holiday weight gain"), which may not be lost during rest of year. From 1970 to 1994 American food supply increased 15% with a 500 calorie ↑/person/day (↑ from 3300 to 3800 calories with an ↑ average individual caloric intake from 1876 to 2043 calories/day). Commercial "super-sizing" the intake of food	
Alterations in lipid homeostasis: Leptin, cytokines including tumor necrosis factor (TNF)-α, compliment factors including factor D, addisin, prothrombotic agents including plasminogen activator inhibitor I, and angiotensinogen Dysregulation of hypothalamic function: Leptin, Neuropeptide Y (NPY),		Dietary habits: More meals are eaten away from the home in US. ↑intake of "fast foods" ↑ that are high calorie dense meals with poor nutritional value rather than energy poor with micronutrient rich vegetables and fruit in school setting and at home. ↑ consumption of new convenience foods, snacks and pastries that have	

Table 3
(continued)

Intrinsic factors (molecular basis of disease)		Extrinsic Factors	
Genetic	Hormonal	Environmental	Behavioral
Agouti-related peptide (AgRP), αMSH, melanin concentrating hormone (MCH), insulin, cortisone, and cholecystokinin; serotonergic, catecholaminergic and opioid signaling pathways. NPY and AgRP are co-expressed in a different sub group of hypothalamic neurons and are considered appetite stimulating peptides. Polymorphisms in AgRP gene offer protection against anorexia nervosa and OB.		the contents of either or high fructose corn syrup or palm oil. High fructose corn syrup is six times sweeter than cane sugar with a very high glycemic index. Palm oil has 45% saturation (compared to hog lard which is 38% saturated). Chronic consumption of foods with a high glycemic index, which may result in OB, hyperinsulinemia and hypoglycemia, which may lead to preferential consumption of subsequent high glycemia index foods offering a continual cycling of hyperglycemia and hyperphagia.	
Hypothalamic OB: Secondary to trauma, tumor, inflammatory disease, increased intracranial pressure or intracranial surgery. Craniopharyngioma is the most neuroendocrine cause for OB.		Drug induced: Oral contraceptives, antipsychotics (phenothiazine, butyrophenone), tricyclic antidepressant amitriptyline, lithium, valproate, glucocorticoids, megestrol acetate and other progestins, serotonin antagonist cyproheptadine, insulin, sulfonylureas, thiazolidinodes, chlorpropamide, glyburide (glibenclamide).	
Endocrine disorders: Cushing's disease, polycystic ovarian disease, growth hormone deficiency, hypothyroidism, pregnancy.		Economic: ↑ Incidence OW/OB in lower socioeconomic groups and non-Caucasians, especially in childhood.	

Modified according to refs. *2*,*5*,*13*,*17–25*.

underreporting current diseases in this particular population *(28)*. Between 1960 and the mid-1990s, the prevalence of class III OB increased from 1 to 3%, occurring at highest rates among African-American women *(7)*.

Energy intake and expenditure are influenced by both endocrine and neural components. Western societies exemplify the mismatch between energy expenditure and energy intake *(3)*. Fat cells store excess energy efficiently as triglycerides, which are released as free fatty acids *(13)*. At any stage of OW, those with relatively more visceral fat tend to experience serious health conditions. Subcutaneous and intra-abdominal fat are the main stores of body fat. In the android OB pattern, body fat predominates in the abdomen, contrasted to the gynoid expression surrounding the hips and thighs *(10)*.

The capacity to store energy beyond immediate requirements supports human nutritional depravation, or starvation, for variable periods of time. Contrarily, when nutritional abundance and sedentary lifestyle blend, excess energy stores predispose to adverse health consequences *(5)*. There is a clear role in environmental associations with OB because it is distinctly uncommon in famine. Cultural factors influence the composition of diet and the level of physical activity. A prime example is rampant OB in children and women in the lower socioeconomic groups of industrialized societies *(5)*. Lifestyle preferences are partly environment-dependent. Several environmental influences are listed in Table 3. Interrelated features of energy expenditure include basal metabolic rate (BMR), energy cost of storing and metabolizing food to components, exercise thermogenics, and thermogenesis related to rising caloric intake. Seventy percent of daily energy expenditure supports BMR. Physical activity constitutes only 5–10% of energy expenditure *(5)*. Enlargement of fat cells produces changes in peptide and nutrient signals responsible for onset and persistence of OB. The first law of thermodynamics, $\delta E = Q - W$ [E = energy; Q = calories in; W = work] facilitates insight in understanding the imbalance between the energy value of food stuffs and energy expenditure. The equation is basically: change in energy = energy in/energy out. Intrauterine growth, growth hormone, and reproductive hormones all generally influence fat partitioning or fat distribution. There are three components that regulate daily energy expenditure. First, two-thirds of energy expenditure supports basal or resting metabolism, which is 70%. BMR is a function of fat-free mass, age, gender, protein turnover, and the relative amount of thyroid hormones. The tight relationship between energy expenditure and fat-free mass implies that this mass is a major contributor to the metabolic process. Energy expenditure also has strong familial relationship, suggesting that relatively low metabolic rates may be a factor in familial obesity. Thermogenesis is the second component, amounting to about 15%. Ten percent of this energy expenditure is dis-

sipated through the thermal effect of food. Finally, 15% of the body's energy expenditure is through activity and exercise *(25)*. A specific form of thermogenesis, nonexercise activity thermogenesis, associated with OB is unrelated to volitional exercise and accounts for two-thirds of overfeeding-induced increased daily energy expenditure *(5)*.

1.3. Risk Factors/Comorbidities With Years of Life Lost

OB and OW are unhealthy conditions with attendant comorbidities that increase the risk for premature death. Table 4 shows lethal risk factors in terms of years of life lost (YLL) and those related to morbidity *(16)*. YLL denotes the difference between the years of life expectancy in the normal weight individual and those in an OB person. Table 5 summarizes the calculation pertaining to individual effects of OB in terms of the expectant number of YLL *(4,11)*. Regarding nonlethal but dysfunctional conditions, OW/OB individuals self-report a poor status of health. These individuals also report higher rates of chronic conditions, less functional health, more days spent ill requiring bed rest, and the greater likelihood of succumbing to at least one serious illness. With increasing age, obese individuals are more likely to declare functional limitation, especially in performing daily living basic activities. This, in turn, may lead to social withdrawal and dependence on others for conduct of the activities of daily living *(11)*. Even moderate amounts of excess weight among the Caucasian population are associated with a decrease in life expectancy *(4)*.

In a dynamic model using data from the Third National Health and Nutritional Examination Survey, the Framingham Heart study and other secondary sources reviewed the relationship between BMI and the risk of developing other comorbid conditions, such as hypertension, hypercholesterolemia, type II DM, CHD, and stroke. Figures 1, 2, and 3 display age- and gender-specific lifetime risk estimates of hypertension, hypercholesterolemia, and type II DM, respectively, compared to BMI *(29)*.

Unlike standard height and weight tables, the calculated BMI predicts the risk of dying by assigning a mortality ratio *(9)*. A BMI of 21 has the lowest risk of premature death. The risk of morbidity and mortality increases as BMI increases. At BMI 35, premature death doubles, characterized by a mortality ratio of about 200. A BMI greater than 30 predicts a 50–100% increase in premature death from all bodily causes as compared to normal BMI *(9,30)*. The Düsseldorf Obesity Mortality Study in 1999 by Bender et al. shows an inverse relationship of BMI and mortality: BMI greater than 40 compared to less than 25, among ages 18–29 years, predicts a fourfold mortality risk, as compared to the 30–39 age range having a 3.5-fold increased mortality risk, and at ages 50–74 with only twofold increased mortality *(14,31)*.

Table 4
Risk Factors/Comorbidities for Years of Life Lost From Overweight and Obesity

High absolute risk of subsequent mortality	Less than lethal risk conditions
Hypertensive or coronary artery disease	Physical inactivity
ASCVD	Osteoarthritis
Family history of early ASCVD (♂/♀: ≥45/55 years)	Cholelithiasis
Impaired fasting glucose or type 2 diabetes mellitus	Stress incontinence or gynecological abnormalities (amenorrhea/menorrhagia)
↑ Low-density or ↓ high-density lipoprotein cholesterol	
Sleep apnea	
Tobacco usage	

ASCVD, atherosclerotic cardiovascular diseases. (Modified according to refs. *4,11*.)

Table 5
Definition and Calculation of Years of Life Lost

Years of life lost secondary to overweight and obesity
Individualizes morbidity prediction by calculating an expectant number of YLL secondary to direct OW/OB effects
Difference between the years of life expectancy in the normal weight individual vs an OB person
The calculation of YLL as a result of obesity is available at: http/www.soph.uab.edu//statgenetics/Research/Tables/YLL-Calculation-Steps.pdf
YLL is estimated by surveying three criteria: • BMI average from each year of adult life • Applying an HR for death rates at various BMI levels in each year of adult life (18–85 year range) • Applying the probability of death at each adult life year

YLL, years of life lost; OW/OB: overweight/obesity; BMI, body mass index; HR, hazard ratio. (Modified according to ref. *16*.)

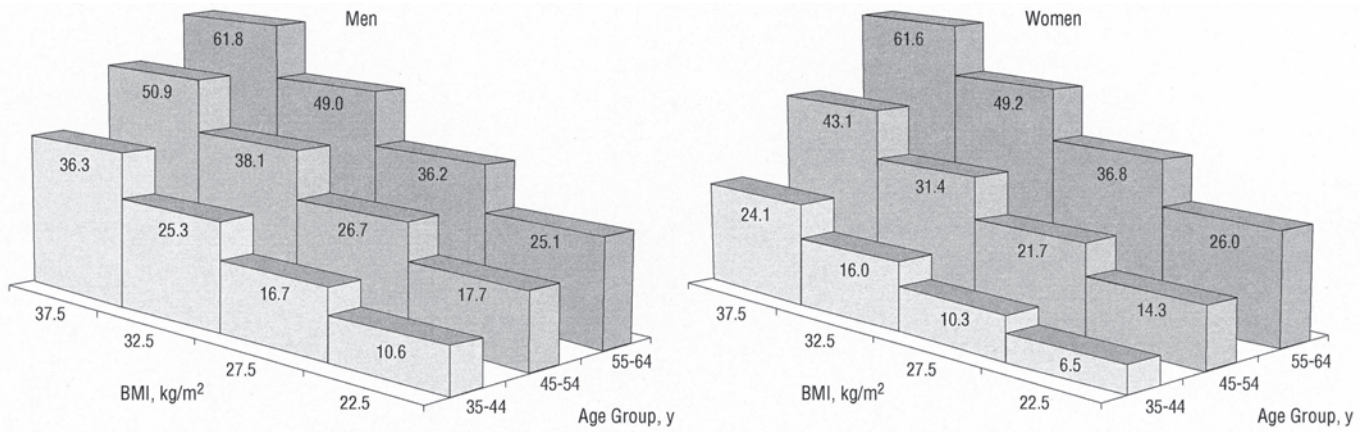

Fig. 1. Estimated risk (%) of hypertension by gender, age group, and body mass index *(29)*.

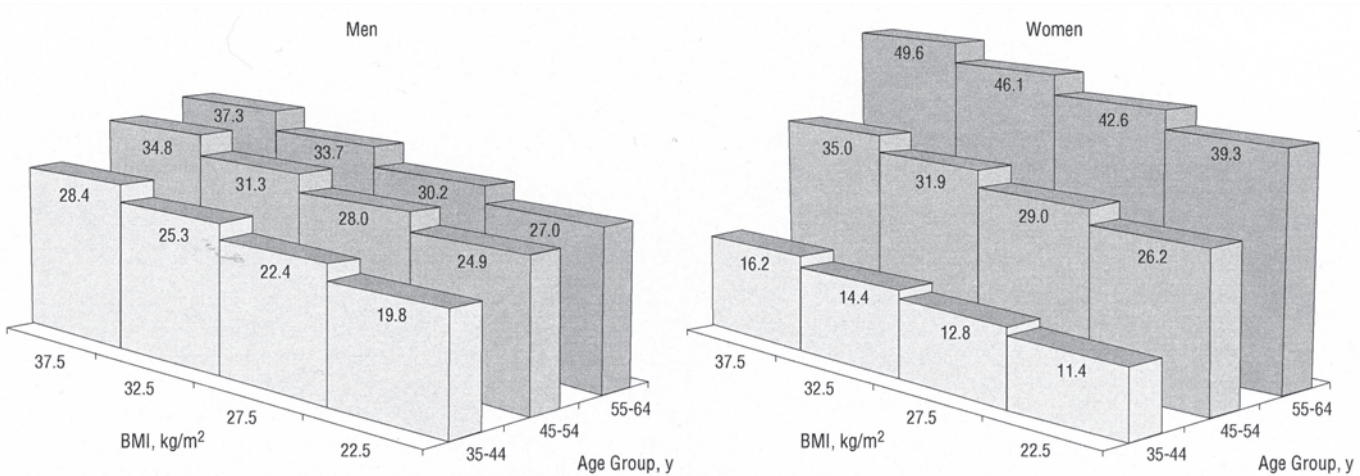

Fig. 2. Estimated risk (%) of hypercholesterolemia by gender, age group, and body mass index. *(29).*

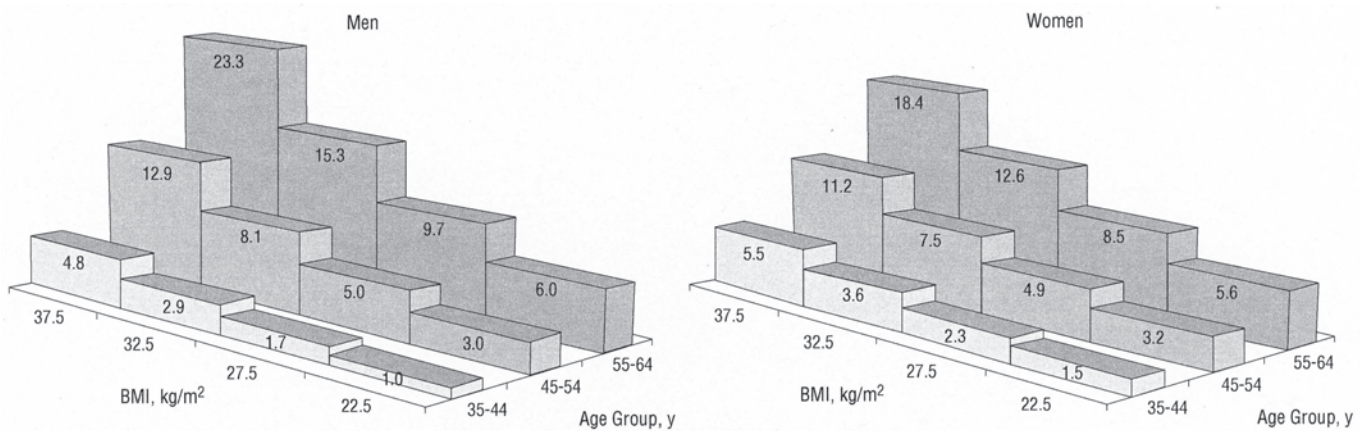

Fig. 3. Estimated risk (%) of type 2 diabetes mellitus by gender, age group, and body mass index (29).

1.4. Variety of Weight Loss Strategies or Pathologies

Weight loss is generally regarded as a process to improve health. "Reduced obesity" is defined as the achievement of a behavioral and metabolic "status" by an OB individual after weight reduction coupled with maintenance of a new steady-state isocaloric intake *(32)*. This new state may be one of the many physiological reasons for relative low success in sustained weight reduction in the OB. There is generally an increased appetite and preference for energy-dense foods, defined as foods containing higher fats and refined sugar. OB individuals tend to consume more calories than lean individuals. These more pronounced behavioral preferences may be secondary to decreased leptin and increased ghrelin levels in the reduced obese state. Isocaloric maintenance also increases insulin sensitivity and tissue-specific changes in lipoprotein-lipase activity, which results in both an overall decrease in fat oxidation and promotion of fat storage *(32)*.

Nonpharmacological weight-reduction efforts combine restrictive caloric intake with increased physical activity. Exercise, which facilitates only a small component of weight loss, aids in long-term maintenance of reduced weight. Yet, for the OW or OB individual, weight loss is generally followed by a slow climb to or beyond the pre-intervention body weight *(2)*.

Unhealthy weight loss occurs in eating disorders. Five million Americans suffer various eating disorders yearly. Table 6 classifies the various eating disorders highlighting diagnostic criteria and their features *(33–35)*. Approximately one-half of patients with either anorexia nervosa or bulimia nervosa have full recovery after treatment. About 20% of those who are diagnosed with either of the disorders show no substantial improvement in symptoms. Underweight is defined as a BMI less than 20, and very underweight less than 17.5. Complications of anorexia and bulimia nervosa include cardiac ventricular dysrhythmias, sudden death, bone loss, amenorrhea, and a cognitive/psychiatric defect secondary to undernutrition *(33,34)*.

2. Premature Death Relating to Obesity

Individuals with a BMI greater than 30 have a 50–100% increased risk for death from all causes compared to a BMI of 20–25. Most of these deaths are as a result of cardiovascular causes *(10,36,37)*.

Table 6
Eating Disorders

Disorder type	Characteristics	US incidence	Population affected	Morbidity and mortality/year
Anorexia nervosa (AN)	Extreme weight loss (weight <85% of normal, or a BMI ≤17.5); inaccurate perception of body size, weight, shape; intense fear of weight gain; amenorrhea after menarche	5–15% w/BN	3% young ♀ w/ BN/BE/ AED 0.48% ♀ (15–19 years old)	0.56% mortality/year Depression; anxiety; somatic complaints secondary to weight reduction; Abnormalities of electrolytes/ hematopoiesis; Cardiac dysrhythmias; hepatic steatosis
Bulimia nervosa (BN)	Binge eating ≥2 times per week for ≥several months. A binge-eating episode = consumption of large food quantities at a discreet time period with no control over the eating episode. Excessive concern about body (within 85% of normal weight). Inappropriate weight or shape compensatory behaviors to weight gain (self-induced vomiting, laxative, diuretic, enema misuse; recurrent purging, fasting ≥2 times per week for ≥3 months and excessive exercise). Absence of AN.	5–15% w/AN	3% young ♀ w/ AN/BE/ AED 2% ♀ college freshman	Association with depression and anxiety

Table 6
(continued)

Binge eating (BE)	Binge episodes ≥2 days per week for 6 months. Marked distress with at least three of the following criteria: eating very rapidly, eating until uncomfortably full, eating when not hungry, eating alone and feeling guilty after the binge episode. Absence of AN/BN characteristics	3% young ♀ w/ AN/BN/ AED 40% ♂	Association with theft, depression, suicide, self-mutilation, substance abuse
Atypical Eating Disorders (AED)	Inappropriate weight control; excessive concern of body weight and shape with disordered eating habits that do not meet all criteria for AN/BN/BE classes	3% young ♀ w/ AN/BN/ BE	

Modified according to refs. *33–35*.

2.1. Cardiovascular Causes

2.1.1. Sudden Cardiac Death

Sudden and unexpected death in morbid (stage III BMI) OB presents at a rate 40 times greater than that of age-controlled lean persons. Sudden death is here defined as death occurring within 6 hours of the onset of symptoms previously determined to be medically stable, or the unwitnessed death of a person who had been medically stable within 24 hours before death *(37)*.

The stable-weight OB has an increased risk of sudden death and cardiac dysrhythmias. Premature ventricular complexes are reported in the OB at a rate 30 times higher than in lean subjects. Electrocardiographic abnormalities with higher frequencies of delayed cardiac repolarization and refractory periods appear as a prolonged Q-T interval, which correlates with BMI and increases the risk for ventricular arrhythmias *(38)*. Upper limits of the normal Q-Tc interval range from 0.425 to 0.44 seconds. Even with mild increases in the Q-Tc interval (0.46 seconds), malignant dysrhythmias may still evolve in the morbidly OB patient *(39)*.

2.1.2. Hypertension

Hypertension, defined as persistent, resting systolic blood pressure greater than 140 mmHg and diastolic greater than 80 mmHg, is the most common pathological condition affecting individuals with OW/OB *(6)*. Myocyte hypertrophy and hypertrophy of the left ventricular (LV) heart, pathological features of hypertension, are usually reflective of elevated BMI *(38,39)*. By itself, LV hypertrophy is a compensatory response to increased arterial vascular pressure. Heart weight increases in proportion to the increased body weight up to 105 kg *(40)*. Individuals with an elevated BMI are twice as likely to have hypertension as those with a normal BMI *(30)*. Hypertension is two to three times more common in both men and women at BMI 26, as contrasted to BMI 21 *(13)*. The prevalence of hypertension increases at relatively low levels of OW *(10)*.

Adipose tissue makes up a substantial amount of body weight. For each kilogram of fat produced in the body, the body generates 3000 m of capillaries to supply this tissue, and results in increased cardiac output over 100 mL per minute to perfuse the hyperplastic fatty tissue *(26)*. Therefore, the expanded interstitial space contains an excessive amount of fluid. With increased metabolic demand induced by excess body weight, OB increases total blood volume, cardiac output, increased stroke volume, and cardiac workload *(41)*. Cardiac chamber dilatation is produced by incremental increases in LV filling pressure and volume, as the Frank-Starling curve of LV function is shifted to the left, and predisposes to congestive heart failure (CHF) *(38,41,42)*.

OB-related increases in stroke volume, cardiac output, and diastolic dysfunction commonly produce systemic hypertension, exacerbated eventually by CHF *(38,42,43)*. Hypertension and OB are related disorders. Even though hypertension and OB are associated with cardiac enlargement, each disease state has a different cardiac adaptation. As a response to increased arterial pressure (afterload), hypertension results in concentric LV hypertrophy, generally without chamber dilatation at its onset. OB causes increased preload. LV dilatation develops with minimal increases in wall thickness or LV hypertrophy. Often there is a twofold burden on the heart caused by coexistent hypertension and OB, which lead to both LV hypertrophy and dilatation. This dual risk imposed on the heart causes greater prevalence in complex ventricular dysrhythmias, predisposing to premature sudden death. Hypertensive OB persons commonly have higher systemic vascular resistance and a lower central blood volume in comparison to their OB nonhypertensive counterparts of similar weight *(41,42)*. The resulting increase in the wall thickness is, according to Laplace's Law, accompanied by reduction in wall stress *(44)*. Over variable time, the LV wall becomes electrodynamically unstable, which may prompt ventricular dysrhythmias. Systolic function is relatively preserved in the early states of hypertension. However, with time, diastolic and systolic ventricular functions both decrease in long-term stable OB and hypertensive OB patients. OB-associated hypertension also results in an increase in sympathetic nervous system tone *(45)*.

OB-related cardiomyopathy occurs in the extremely morbid OB patient, coexisting with systemic hypertension and pulmonary abnormalities *(46)*. Altered LV remodeling, increased hemodynamic load, increased oxidative stress, and neurohormonal activation also increase the myocardial wall stresses leading to CHF. O_2 consumption by myocardial fat raises O_2 demand *(40,41)*. Impaired cardiac oxidation of fatty acids, which results in accumulation of triglycerides in the cardiomyocytes, may trigger heart failure *(47)*. Cardiac steatosis and lipoapoptosis in animal models of OB reported by Zhou et al. provide evidence of the direct effect of OB on the myocardium: 11% of male and 15% of female subjects have heart failure attributable to OB alone *(48,49)*.

OB cardiomyopathy occurs predominantly in patients who have a persistent BMI greater than 40 for more than 10 years. Ninety-five percent of autopsied OB individuals have excessive epicardial fat, associated with lipomatous infiltration of the right ventricular (RV) myocardium. Many symptomatic normotensive morbidly OB exhibit LV, left atrial, and RV enlargement. Altered chamber size and elevated intracardiac pressure frequently result in pulmonary hypertension, CHF, and lethal tachyarrhythmias, the principal mechanisms of death *(38)*.

Table 7
Goals for "Healthy" Cholesterol Levels (mg/dL)

Total cholesterol	LDL cholesterol	HDL cholesterol
<200 desirable	<100 optimal	≤40 low
200–239 borderline high	100–129 near optimal/above optimal	>40, <60 normal
≥240 high	130–159 borderline high; 160–189 high	≥60 high
	≥190 very high	

LDL, low-density lipoprotein; HDL, high-density lipoprotein. (Modified according to refs. *30,50*.)

Lipomatous hypertrophy of the interatrial septum, although sparing the oval fossa itself, projects toward the right atrium. At autopsy, less than 4% of such hearts exhibit myocardial fat infiltration: lipomatous cords in the RV myocytes, the sinus nodal musculature, the atrioventricular node, and the right bundle branch conduction tissues. Adipositas cordis, a term applied to a type of restrictive cardiomyopathy of OB, specifically consists of infiltrating adipose bands displacing myocardial fibers, which display variable degrees of atrophy *(36,38)*.

2.1.3. Atherosclerosis and Lipid Disorders

Diet-limited correction of abnormal triglycerides and blood lipids in OB is commonly ineffective without imposition of a lipid-lowering drug regime. Table 7 provides health-related cholesterol goals recommended by the National Cholesterol Education Program *(30,50)*.

The Framingham Heart Study concludes OW/OB states are independent risk factors for the development of major CAD in addition to hypertension and CHF *(45)*. An increase in the intimal-medial wall thickness of coronary arteries results in higher cardiovascular morbidity and mortality even in young adults *(14)*. A BMI of 25–29 in middle-aged men, compared with a cohort having a BMI less than 23, is associated with a significantly increased risk of cardiovascular atherosclerosis, independent of other recognized risk factors *(10,51)*. In women at BMI of 26, there is about a twofold increase of CHD compared to a BMI less than 21. In men with a BMI of 26, the risk of developing CAD is about 1.5 times higher than in men with a BMI less than 21 *(13,52)*. OB in childhood and adolescence is associated with elevated low-density lipoprotein cholesterol and triglycerides, lower high-density lipid cholesterol, increased risk for hypertension, all carrying a higher risk of atherosclerosis and cardiovascular disease in adulthood *(53)*.

Table 8
Summary of American Heart Association Recommendations for Stroke

American Heart Association guidelines for primary prevention of cardiovascular disease and stroke: 2002 Update
Maintain blood pressure <140/90 mmHg (<130/85 mmHg in individuals with renal insufficiency or congestive heart failure; <130/80 mmHg in diabetics)
Consume a healthy diet
Reach healthy cholesterol levels (LDL/HDL goals based on individual risk factors)
Moderate intensity physical activity (5–7 days per week for ≥30 minutes)
Achieve and maintain a desirable weight (BMI between 18.5 and 24.9)
Maintain a normal fasting blood glucose <110 mg/dL; HbA1c <7%
No exposure to tobacco smoke

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index. (Modified according to ref. *55*.)

2.1.4. Vascular Disorders: Stroke and Venous Thromboembolism

An increase of BMI accompanies a significant increase in the relative risk of stroke, independent of effects with hypertension, DM, and cholesterol *(54)*. Each unit increase of BMI was linked to a significant 6% increase in the adjusted relative risk of total stroke, ischemic stroke, and hemorrhagic stroke. Underlying thrombogenic factors may contribute to an increased risk for stroke, primarily in OW/OB women *(54)*. A 75% increase in ischemic stroke risks occurs in women with a BMI greater than 27 and is 130% higher in women with a BMI greater than 32 compared to normal BMI *(10)*.

Table 8 outlines strategies developed by the American Heart Association to promote cardiovascular health, including desirable BMI *(55)*. The plan also addresses aspirin usage, limited alcohol intake, and goals directed toward patients with chronic atrial fibrillation. The design of the guidelines is to perform risk factor screening, which minimally requires a determination of BMI with WC, blood pressure, and pulse recording at least every 2 years, and testing for glucose and cholesterol profiles every 5 years beginning at the age of 20.

Deep venous thrombosis (DVT) secondary to venous insufficiency is a comorbidity of OW/OB. DVT and pulmonary thromboembolism (PE), or together called venous thromboembolism, are independently associated with graded increases in BMI *(26)*. In a study of women older than 60 years, the highest rate of PE attended the group with highest BMI *(56)*. Mortality rates for PE approach 20%. Individuals with BMI of more than 40 have a threefold

Table 9
The National Cholesterol Education Program Adult Treatment (NCEP) and World Health Organization (WHO) Criteria for Metabolic Syndrome Diagnosis

NCEP criteria: (three of the five components)	Modified WHO definition
Abdominal obesity: Definition 1: ↑ WC (♂/♀>102/88 cm) Definition 2: ↑ WC (♂/♀>94/80 cm)	Hyperinsulinemia (upper quartile of nondiabetic population) or fasting plasma glucose ≥110 mg/dL
Insulin resistance/glucose intolerance (fasting serum glucose ≥110 mg/dL)	AND at least two components:
Fasting serum triglycerides ≥150 mg/dL	Abdominal obesity (♂): Definition 1: ↑WHR >0.90 or BMI ≥30 Definition 2: ↑WC ≥94 cm
Serum HDL cholesterol (♂/♀: <40/50 mg/dL)	Dyslipidemia: Serum triglycerides ≥150 mg/dL OR Serum HDL cholesterol <35 mg/dL
Prehypertension (BP ≥130/85 mmHg) or use of antihypertensive medication	Hypertension (BP ≥140/90 mmHg) or use of antihypertensive medication

BMI, body mass index; BP, blood pressure; WC, waist circumference; WHR, waist-to-hip ratio; HDL, high-density lipoprotein. (Modified according to refs. *58,59*.)

likelihood of developing DVT as compared with adults with a BMI less than 25 *(26,57)*.

2.2. Metabolic Syndrome

The metabolic syndrome, or insulin-resistance syndrome, developed by the National Cholesterol Education Program Adult Treatment Panel III, and modified by the World Health Organization, establishes concurrently graded parameters linking abnormal glucose and insulin metabolism in the OB/OW with abdominal fat distribution, serum lipid abnormalities, hypertension, development of type II DM, and cardiovascular disease. Table 9 summarizes criteria for diagnosis *(58,59)*.

2.2.1. Diabetes Mellitus

The epidemic rise in OB and DM is reciprocal. An estimated 50.6 million adults in the United States have DM, 95% of which is type II. A 25% increase in the prevalence of type II DM is co-existent with a dramatic increase of OB in the United States *(10)*. Survey data confirm significant increases of OB and DM in the United States from 1991 to 2000, and more recent studies report greater acceleration of these trends *(61,62)*.

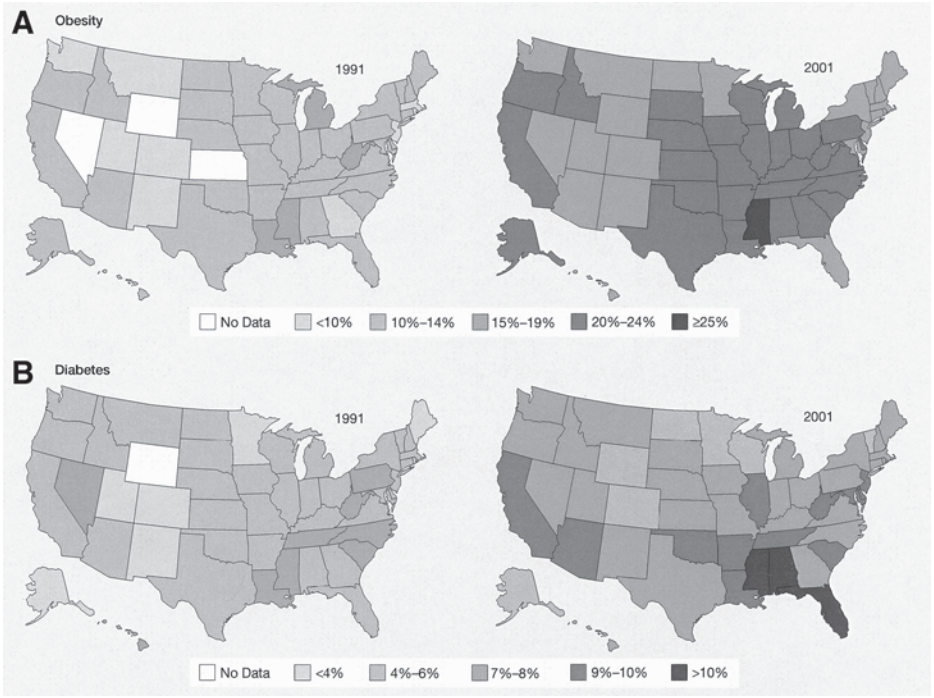

Fig. 4. Prevalence of obesity and diagnosed diabetes among US adults, 1991 and 2001.

The self-reported prevalence of DM increased from 4.9% in 1990 to 7.3% in 2000, a 49% increase *(61)*. A similar study in 2003, using the data from 2001, showed even greater increases in the prevalence of OB and DM. OB among the American adults increased from 19.8% in 2000 to 20.9% in 2001, an overall increase of 5.6% *(62)*. This study conservatively estimated 44.3 million OB American adults. African-Americans made up the highest rate of OB at 31.1%. DM prevalence increased from 7.3% in 2000 to 7.9% in 2001, an annual increase of 8.2% and an overall increase of 61% since 1990. The cohort of American adults who had both OB and DM in 2001 increased from 1.4% in 1991 to 3.4% in 2001; 2.9% of men and 3.8% of women were considered both OB and diabetic. The highest rate of diagnosed diabetics (11.2%) predominated in the African-American population. Epidemiological data developed at the Centers for Disease Control (CDC) connect BMI greater than 40 to a more than sevenfold risk of DM *(61–63)*. Figure 4 illustrates the parallel rise of OB and type II DM in US adults from 1991 to 2001. The figure incorporates the two separate but similar CDC studies by Mokdad et al. *(61–63)*.

More than 80% of people with diabetes are OW or OB *(30,64)*. OB-related insulin resistance in hyperinsulinemia is very strongly related to intra-abdominal adiposity, and often leads to lipoprotein abnormalities and cardiovascular disease *(5,64,65)*. Debilitating comorbidities resulting from chronic diabetes most commonly include circulatory and renal diseases, retinal diseases, arteriosclerosis and neuropathy, especially in the extremities *(5,64,65)*.

2.3. Respiratory Dysfunction

OB-related pulmonary disease causes increased work of breathing, increase minute ventilation as a result of the increased metabolic rate, decreased chest-wall compliance from increased weight on the thoracic cage and abdomen, decreased total lung capacity, and decrease in functional residual capacity *(5)*.

Sleep apnea/obesity hypoventilation syndrome (SA/OHS) causes recurrent arousals from sleep and sleep deprivation. The cessation of airflow during sleep for more than 10 seconds defines SA, which occurs up to 12–30% more commonly in OW/OB individuals *(10,66)*. Obstructive sleep apnea (OSA) is recurrent complete cessation of airflow during sleep secondary to general collapse of the pharyngeal upper airway *(67)*. OB-related SA results from overgrowth of peripharyngeal fat. Blockage of the upper airway during sleep causes increased loading of the wall and restricted dimension of the upper airway. Generally obstructive in nature, SA has central or mixed forms. Central SA is defined as failure of spontaneous respiratory effort; OSA manifests itself by continued respiratory effort, and mixed SA includes features of central and obstructive components. OSA is characterized by vigorous breathing efforts *(10,66,67)*. The SA/OHS is essentially an alternation of respiratory control distinguished by impaired responsiveness to carbon dioxide, resulting in hypoxemia and exacerbation of increasingly ineffective respiratory muscular function *(10,66,67)*. Because of the arterial hypoxemia with related pulmonary artery vascular constriction and resultant pulmonary and systemic hypertension, the individual is prone to cardiac arrhythmia and sudden death *(10,66,67)*.

Pickwickian syndrome is an extreme form of OSA. OB, hypercapnia, and hypersomnolence are the characteristic triad of findings *(67)*. It is simply OSA/OHS with awake respiratory failure. Typical complications include biventricular hypertrophy, hypertension, and sudden cardiac death (*20,30,67)*.

OB have more difficulty tolerating acute asthmatic episodes, which may lead to sudden death *(30)*. Preadolescent OW/OB children are seven times more likely to develop asthma than those of normal weight *(20)*.

2.4. Hepatic Disorders

Macrovesicular steatosis, reversible with weight loss, occurs in OB *(30,68)*. Free fatty acids in the portal circulation of OB patients adversely affect hepatic metabolism *(5)*. Nonalcoholic steatohepatitis (NASH) is much more common among OB individuals who also have type II DM. Free fatty acids and hyperinsulinemia coexisting with increases in visceral adiposity may play a role in the pathogenesis of NASH. Untreated severe steatosis and NASH may progress to cirrhosis, liver failure, and death *(10,30,68)*.

The following criteria greatly predispose patients with NASH to develop hepatic fibrosis: age over 45 years old, OB with a BMI greater than 31.1/32.3 in men and women, respectively, DM, and an alanine aminotransferase/aspartate aminotransferase ratio greater than 1 *(68)*. A sixfold increase incidence of symptomatic gallstones occurs in the OW.

Supersaturation of bile by cholesterol in OB or in extreme dieting is a nidus for cholesterol gallstones, a substrate for potentially lethal conditions such as cholecystitis and obstructive choledocholithiasis *(5,68)*.

2.5. Cancer

OW/OB account for cancer-associated mortality in approx 14% of US men and 20% of US women. Risks for cancer of the colon, breasts, uterus, kidney, gallbladder, and prostate are increased in OB *(30)*. Men and women with BMI greater than 40 have mortality rates from all combined cancers of 52 and 62%, respectively, compared to normal-weight cohorts. Men with elevated BMI have higher mortality from gastric and prostatic cancer *(69,70)*. Longstanding gastroesophageal reflux may contribute to esophageal adenocarcinoma *(69)*. Women face an increased risk of mortality from cancers of the breast, uterus, cervix, and ovary *(69,70)*. If a woman gains more than 20 pounds (9 kg) between 18 years and mid-life, the risk of breast cancer is doubled *(10,30,70)*. The risk of gallbladder cancer is increased with the presence of gallstones *(69,70)*.

2.6. Reproductive

Pregnancy complications of OB, with increased risk for death, include maternal hypertension, gestational diabetes, fetal macrosomia, and neural tube defects *(30)*. The increased incidence of uterine cancer in postmenopausal OB women is likely associated with the increased conversion of androstenedione to estrogen, a complication of gynoid obesity *(5,70)*.

Table 10
Representative Anorectics With Reported Complications

Treatment	Mechanism of action	Complications
Fenfluramine–phentermine "fen-phen" (Phentermine: β-phenethylamine Fenfluramine) and dexfenfluramine	Appetite suppressants	Valvulopathy (aortic and mitral regurgitation); bacterial endocarditis; primary pulmonary hypertension with thrombotic arteriopathy
Ephedra alkaloids/Ma-huang derived from plants of the *Ephedra* species	Active ingredient epinephrine: stimulant and thermogenic agent	Acute hepatitis; hypersensitivity myocarditis; hypertension, ↑ heart rate, palpitations, headache, nausea, agitation or restlessness, psychiatric disturbances, seizures, heart attack, stroke, sudden death
Phenylpropanolamine (PPA)	Sympathomimetic amine (α adrenergic agonist) used as appetite suppressant	Hemorrhagic stroke risk; higher risk in ♀ vs ♂; vasoconstriction; ↑ heart rate, hypertension, vasculitis
Dextroamphetamine, methamphetamine, amphetamine	Sympathomimetic amines used as appetite suppressants	Vasoconstriction; ↑ heart rate, BP; micro-aneurysms, necrotizing arteritis, hemorrhagic stroke
Guarana-derived caffeine	Inhibits adenosine-mediated vasodilation; augments release of catecholamines	Additive CNS and CV adverse effects with sympathomimetic amines

BP, blood pressure; CNS, central nervous system; CV, cardiovascular. (Modified according to refs. *2*,*71*,*74–89*.)

2.7. Therapeutic Complications

Bariatrics is the medical field specializing in treating OB-related problems *(71–73)*.

2.7.1. Nonsurgical Complications

Many medications are approved for treatment of OB-related medical conditions in adults with BMI greater than 27, or BMI greater than 30 without related comorbidities. Several weight-modifying drugs, both prescription and nonprescription over-the-counter, carry considerable morbidity and mortality. Table 10 catalogues a few commonly used anorectics and reported complications *(2,74–89)*. Most notably, the combination, fenfluramine–phentermine ("fen-phen") was withdrawn from the US market in 1997 because of probable association with valvular heart disease *(2,74–76)*. Fatal pulmonary hypertension has occurred without valvulopathy *(77)*.

2.7.2. Surgical Complications

Any operation is technically more difficult in OW/OB because excessive adipose tissue prevents the optimal visualization of specific surgical sites. The operations generally last longer and, because of extended anesthesia exposure, represent a greater risk of perioperative complications *(30)*. Any change in metabolic homeostasis in the OB patient (e.g., postoperative fluid and electrolyte shifts, reduced oxygenation, anxiety, physical exertion, and the addition of anesthetics/medications) may promote unpredictable dysrhythmia and sudden cardiac death in absence of any gross cardiac disease *(90)*.

Poor wound healing is increased with OW/OB *(10,91)*. Patients at BMI greater than 34 undergoing abdominal or gynecological procedures experience significantly higher rates of wound infection (11%) compared to normal-weight individuals (4.7%). Incisional hernias occur at 7–10% rate with a BMI greater than 40 *(91)*. There is a higher incidence of thromboembolism after noncardiac surgery in OB *(38)*.

The subspecialty "bariatric surgery" operates to treat morbid OB *(72,73)*. For individuals with a body weight ≥ 45 kg above normal weight, BMI greater than 40, or BMI of 35 and an OB-related comorbidity such as hypertension, bariatric surgical treatments may be indicated for long-term weight loss. Table 11 catalogues common bariatric surgical procedures, including gastric restrictive operations, malabsorptive operations, and liposuction *(72,73,92)*.

3. Pediatric Overweight and Obesity

The prevalence of OW/OB in children and adolescents has more than doubled since 1976, according to two nationwide surveys *(2,53,93)*. One-third of adult OW/OB stems from childhood OW/OB. Revised growth charts and BMI charts for age and gender are available via the CDC website: http://www.cdc.gov/growthcharts/. In adolescents, a BMI of 25 or 30 corresponds to

Table 11
Bariatric Surgery

Treatment	Mechanisms	Complications
Stapled (vertical-banded) gastroplasty	Gastric cardia stapling resulting in a 15–20 mL pouch to the remainder of the digestive tract by a small calibrated stoma outlet	Perioperative mortality <1%. Early (first 30 days) morbidity rate <10%. 80% failure rate at 10 years. 15–20% re-operation for stomal outlet stenosis or severe gastroesophageal reflux disease. Substantial weight gain 3–5 years postoperatively
Gastric banding	A 5.0 cm prosthetic band device partitions the gastric cardia providing an upper 10–15 mL capacity pouch. An inflatable silicone band leads to the lower pouch	Outlet stenosis and gastric wall erosion frequently require re-operation. Less consistent weight loss than reported with banded gastroplasty and gastric bypass
Gastric bypass Roux-En-Y	Upper stomach is completely stapled with only a 20–30 mL capacity reservoir that directly sends contents to Roux limb, a 50–100 cm segment of jejunum stapled to the proximal stomach. The distal stomach with attached duodenum and proximal jejunum remain intact. Distal end of this jejunal loop is approximated to the Roux limb jejunum	Morbidity and mortality rates, <10% and 1%, respectively Venous thrombosis and pulmonary thromboembolism (1–2%), intestinal anastomotic leaks (1–2%) and wound infections (1–5%) Iron and vitamin B_{12} deficiencies (30%). Dumping syndrome (nausea, bloating, diarrhea and colic) .

Table 11
(continued)

Treatment	Mechanisms	Complications
Biliopancreatic bypass "duodenal switch operation"	Fundus is stapled and a 100–200 mL capacity gastric pouch is formed. Functional duodenum and entire jejunum excluded from the digestive continuity. Ileum is anastomosed to the proximal duodenum with the entire jejunum separated. Distal jejunum anastomosed to ileum.	Early complications 10–15%. Overall mortality, 1%. 30% anemia, 30–50% fat-soluble vitamin deficiency, 3–5% hospitalization for treatment of protein-calorie malnutrition.
Nontumescent liposuction	Cosmetic depletion of regional subcutaneous adipose tissue by microcannula fat aspiration	Thrombotic or fat pulmonary emboli
Tumescent liposuction	Additional subcutaneous infusion of a normal saline solution with 500–1000 mg lidocaine, 0.25 to 1.0 mg epinephrine and 12.5 mmol sodium bicarbonate to provide prolonged local anesthesia and minimize blood loss	Pulmonary thromboemboli, hypotension, hypothermia, fluid overload with pulmonary edema, bradycardia, cardiac depression. Lidocaine toxicity (plasma ≥5 mg/L) may cause hypertension and bradycardia in large doses

Modified according to refs. *72*,*73*,*92*.

the CDC BMI growth chart 85th and 95th percentiles for age and gender, respectively. "At risk of OW" children and adolescents fall between these two percentiles and OW children are at or above the 95th percentile. Ten to fifteen percent of US children and adolescents are OW based on CDC criteria *(53)*. Childhood OW, a preventable adverse health condition, results from congeries of various biological, economic, and social factors. Adverse environmental factors include television, childhood video games, childhood inactivity, and high-calorie meals at school and at home *(94,95)*.

Three growth phases place children at higher risk of developing OB that persists to adulthood: prenatal and *in utero* influences, the period of "adiposity" rebound, and adolescence. Prenatal and *in utero* influences stem from maternal risk factors, such as DM. The second phase generally occurs at ages 5–6 years. The greatest risk for adult OB prevails in adolescent OB. Fifty to seventy-five percent of adolescent OB persists into adulthood and correspondingly carries higher risks for subsequent morbidity and mortality *(53)*. Android and gynoid fat distribution develops during adolescence *(25)*. Progressive hyperphagic OB develops in a small number of childhood obese patients who gain weight early and usually surpass a weight gain of 140 kg by age 30 years. It appears that this cohort gains about the same amount of weight every year, necessitating an increase in energy requirements at the same time *(25)*.

Sixty percent of OW children between 5 and 10 years old have at least one additional cardiovascular risk factor: hypertension, hyperlipidemia, and hyperinsulinemia; 25% have two or more of these risk factors *(95–97)*. Other complications of childhood OB include SA, pseudotumor cerebri, and two orthopedic conditions, Blount disease, and slipped femoral capital epiphysis. Blount disease, or bowing of the tibia, is attributed to increased weight stress; slipped femoral capital epiphysis is a surgical emergency. SA occurs in less than 10% of OW children *(53)*. Acanthosis nigricans, thickening and darkening of the skinfolds of the neck, elbows, dorsal interphalangeal spaces, and the axillae, may occur in OW/OB children. The disorder is related to insulin resistance and abates with weight loss. Associated friability of the skin predisposes to an increased risk of fungal and yeast infections *(5)*.

Acknowledgments

Special acknowledgment is given to Carol Bibelhauser for excellent clerical assistance with this manuscript. In loving memory to Victoria, the "Fat Cat," for many graceful moments, who died after 16 wonderful years while this manuscript was being written.

References

1. Chadwick J, Mann WN. Medical works of Hippocrates. Blackwell, Oxford, England, 1950, p. 154.
2. Yanovski SZ, Yanovski JA. Obesity. N Engl J Med 2002;346:591–602.
3. Hamdy RC. Obesity: an epidemic. Southern Med J 2003;96:531,532.
4. Manson JE, Bassuk SS. Obesity in the United States. A fresh look at its high toll. JAMA 2003;289:229,230.
5. Flier JS. Obesity. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. Harrison's Principles of Internal Medicine, 15th ed. McGraw-Hill, New York, San Francisco, Washington DC, 1991, pp. 479–486.
6. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523–1529.
7. Freedman DS, Khan LK, Serdula MK, Galuska DA, Dietz WH. Trends and correlates of class 3 obesity in the United States from 1990 through 2000. JAMA 2002;288:1758–1761.
8. Eckel RH. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003.
9. Sjöström LV. Mortality of severely obese subjects. Am J Clin Nutr 1992;55(Suppl 2):S516–S523.
10. National Task Force on the Prevention and Treatment of Obesity. Overweight and obesity health risk. Arch Intern Med 2000;160:898–904.
11. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. JAMA 2003;289:187–193.
12. Hunter B, French D, Warner J, Remick D. Correlation of body mass index with thoracic and abdominal panniculus. J Forensic Sci 1998;43:427–430.
13. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999;341:427-434.
14. Kuller LH. Concise review: impact of obesity on cardiovascular disease. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. http://www.harrisonsonline.com, 2003.
15. Obesity: preventing and managing the global epidemic of obesity (June 1997) Report of the World Health Organization Consultation of Obesity. Geneva, Switzerland.
16. The practical guide: Identification, Evaluation and Treatment of Overweight and Obesity in Adults (October 2000) National Institutes of Health North American Association for the Study of Obesity (NHLBI) U.S. Department of Health and Human Services (Publication No. 00-4084).
17. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002;346:1623–1630.
18. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes and cardiovascular disease. JAMA 2002;287:2414–2423.
19. Korner J, Leibel RL. To eat or not to eat—how the gut talks to the brain. N Engl J Med 2003;349:926–928.
20. Critster G. Fat Land: How Americans Became the Fattest People in the World. Houghton Mifflin, New York, 2003.

21. Batterham RL, Cohen MA, Ellis SM, et al. Inhibition of food intake and obese subjects by peptide YY3-36. N Engl J Med 2003;349:941–948.
22. Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986–1998. JAMA 2001;286:2845–2848.
23. Yanovski JA, Yanovski SZ, Zovik KN, Nguyen TT, O'Neil PM, Sebring NG. A prospective study of holiday weight gain. N Engl J Med 2000;342:861–867.
24. Adams SA, Der Ananian CA, DuBose KD, Kirtland KA, Ainsworth BE. Physical activity levels among overweight and obese adults in South Carolina. South Med J 2003;96:539–543.
25. Bray GA. Etiology and pathogenesis of obesity. Clinical Cornerstone 1999;2:1–15.
26. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med 2002;162:1182–1189.
27. Huang J, Marin E, Yu H, et al. Prevalence of overweight, obesity, and associated diseases among outpatients in a public hospital. South Med J 2003;96:558–562.
28. Williamson DF. The prevention of obesity (editorial). N Engl J Med 1999;341: 1140,1141.
29. Thompson D, Edelsberg J, Colditz GA, Bird A, Oster G. Lifetime health and economic consequences of obesity. Arch Intern Med 1999;159:2177–2183.
30. Lott JA. The burden of obesity. Advance Lab 2002;1:68–72.
31. Bender R, Jöckel KH, Trautner C, Spraul M, Berger M. Effect of age on excess mortality in obesity. JAMA 1999;281:1498–1504.
32. Eckel RH. Obesity: a disease or a physiologic adaptation from survival? In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 3–30.
33. Becker AE, Grinspoon SK, Klibanski A, Herzog DB. Eating disorders. N Engl J Med 1999;340:1092–1098.
34. Halmi KA. Clinical crossroads. A 24-year-old woman with anorexia nervosa. JAMA 1998;279:1992–1998.
35. Stevens A, Robinson DP, Turpin J, Groshong T, Tobias JD. Sudden cardiac death of an adolescent during dieting. South Med J 2002;95:1047–1049.
36. Poirier P, Eckel RH. The heart and obesity. In: Fuster V, Alexander RW, O'Rourke RA, eds. Hurst's The Heart. McGraw-Hill, New York, St Louis, San Francisco, London, Sydney, 2001, pp. 2289-2303.
37. Duflou J, Virmani R, Rabin I, Burke A, Farb A, Smialek J. Sudden death as a result of heart disease in morbid obesity. Am Heart J 1995;130:306–313.
38. Poirier P, Alpert MA. Heart disease. In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 91-102.
39. Amad KH, Brennan JC, Alexander JK. The cardiac pathology of chronic exogenous obesity. Circulation 1965;32:740–745.
40. Alexander JK, Alpert MA. Cardiac morphology and obesity in man. In: Alexander JK, Alpert MA, eds. The Heart and Lung in Obesity. Futura Publishing, Armonk, NY, 1998, p. 25.

41. Alexander JK, Alpert MA. Hemodynamic alterations with obesity in man. In: Alexander JK, Alpert MA, eds. The Heart and Lung in Obesity. Futura Publishing, Armonk, NY, 1998, p. 45.
42. Alexander JK, Alpert MA. Obesity and ventricular function: systolic function. In: Alexander JK, Alpert MA, eds. The Heart and Lung in Obesity. Futura Publishing, Armonk, NY, 1998, p. 77.
43. Alexander JK, Alpert MA. Obesity and ventricular function: diastolic function. In: Alexander JK, Alpert MA, eds. The Heart and Lung in Obesity. Futura Publishing, Armonk, NY, 1998, p. 57.
44. Benjamin EJ, Levy D. Why is left ventricular hypertrophy so predictive of morbidity and mortality? Am J Med Sci 1999;317:168–175.
45. Lavie CJ, Milani RV, Messerli FH. Obesity and the heart: an ever-growing problem. South Med J 2003;96:535,536.
46. Reisin E, Cook ME. Obesity, hypertension and the heart. In: Alexander JK, Alpert MA, eds. The Heart and Lung in Obesity. Futura Publishing, Armonk, NY, 1998, p. 95.
47. Taegtmeyer H, Wilson CR. Letter to editor. New Engl J Med 2002;347:1887,1888.
48. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:105–113.
49. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci USA 2000;97:1784–1789.
50. Bailey C. The New Fit or Fat. Houghton Mifflin Company, Boston, MA, 1991, p.19.
51. McGill HC, McMahan CA, Herderick EE, et al. Obesity accelerates the progression of coronary atherosclerosis in young men. Circulation 2002;105:2717,2718.
52. Rexrode KM, Carey VJ, Hennekens CH. Abdominal adiposity in coronary heart disease in women. JAMA 1998;280:1843–1848.
53. Dietz WH. Pediatric Obesity. In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 91–102.
54. Kurth T, Gaziano JM, Berger K, et al. Body mass index and the risk of stroke in men. Arch Intern Med 2002;162:2557–2562.
55. Pearson TA, Blair SN, Daniels SR, et al. The American Heart Association (AHA) guidelines for primary prevention of cardiovascular disease and stroke: 2002 update. Circulation 2002;106:388–391.
56. Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. JAMA 1997;277:642–645.
57. Goldhaber SZ, De Rosa M, Visani L. International Cooperative Pulmonary Embolism Registry detects high mortality rate (abstract). Circul 1997;96(Suppl 1):I1–I159.
58. Lakka HM, Laakasonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–2716.
59. Brunzell JD. Dyslipidemia of the metabolic syndrome. In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 378–398.
60. Massie BM. (2002) Obesity and heart failure—risk factor or mechanism? N Engl J Med 2002;347:358,359.
61. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health factors, 2001. JAMA 2003;289:76–79.

62. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the U.S. JAMA 2001;286:1195–1200.
63. Alsup R. Obesity and diabetes continue to rise. KY Epidemiologic Notes Reports 2003;38:1–3.
64. Henry RR, Mudaliar S. Obesity and type II diabetes mellitus. In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 229–272.
65. Colditz GA, Willett WC, Rotnitzk KA, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481–486.
66. Phillipson EA. Sleep apnea. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. Harrison's Principles of Internal Medicine, 15th ed. McGraw-Hill, NY, San Francisco, Washington DC, 1991, pp. 1520–1526.
67. Robinson TD, Grunstein RR. Sleep-disordered breathing. In Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 202–228.
68. Everson GT, Kugelmas M. Hepatobiliary complications of obesity. In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 301–326.
69. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–1638.
70. Heber D. Cancer. In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 327–344.
71. Bray GA. Treatment of obesity with drugs in the new millennium. In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 449–475.
72. Brolin RE. Bariatric surgery a long-term control of morbid obesity. JAMA 2002;288:2793–2796.
73. Latifi R, Sugerman HJ. Surgical treatment of obesity. In: Eckel RH, ed. Obesity, Mechanisms and Clinical Management. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 503–522.
74. From the Centers for Disease Control and Prevention. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services interim public health recommendations, November 1997. JAMA 1997;278:1729–1731.
75. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997;337:581–588.
76. Curfman GD. Diet pills redux. N Engl J Med 1997;337:629–630.
77. Strother J, Fedullo P, Yi ES, Masliah E. Complex vascular lesions at autopsy in a patient with phentermine-fenfluramine use and rapidly progressing pulmonary hypertension. Arch Pathol Lab Med 1999;123:539,540.
78. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 2000;343:1833–1838.

79. Kita DC, Devereaux MW, Chandar K. Intracranial hemorrhages due to phenylpropanolamine. Stroke 1985;16:510–512.
80. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med 2000;343:1826–1832.
81. Fallis RJ, Fisher M. Cerebral vasculitis and hemorrhage associated with phenylpropanolamine. Neurology 1985;35:405–407.
82. Citron BP, Halpern M, McCarron M, et al. Necrotizing angiitis associated with drug abuse. N Engl J Med 1970;283:1003–1011.
83. Wooten MR, Khangure MS, Murphy MJ. Intracerebral hemorrhage and vasculitis related to ephedrine abuse. Ann Neurol 1983;13:37–40.
84. Delaney P, Estes M. Intracranial hemorrhage with amphetamine abuse. Neurology 1980;30:1125–1128.
85. Blanck HM, Khan LK, Serdula MK. Use of nonprescription weight loss products: results from a multistate survey. JAMA 2001;286:930–935.
86. Samenuk D, Link MS, Homoud MK, et al. Adverse cardiovascular events temporally associated with Ma Huang, an herbal source of ephedrine. Mayo Clin Proc 2002; 77:12–16.
87. Nadir A, Agrawal S, King PD, Marshall JB. Acute hepatitis associated with the use of a Chinese herbal product, Ma-huang. Amer J Gastroenterol 1996;91:1436–1438.
88. Zaaccks SM, Klein L, Tan CD. Hypersensitivity myocarditis associated with ephedra use. J Toxicol Clin Toxicol 1999;37:485–489.
89. Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. JAMA 2003;289:1537–1545.
90. Drenick EJ, Fisler JS. Sudden cardiac arrest in morbidly obese surgical patients unexplained after autopsy. Amer J Surg 1988;155:720–726.
91. Roberts JV, Bates T. The use of body mass index and studies of abdominal wound infection. J Hosp Infect 1992;20:217–220.
92. Rama RB, Ely SF, Hoffman RS. Deaths related to liposuction. N Engl J Med 1999;340:1471–1475.
93. NIDDK. Statistics related to overweight and obesity. US Dept. HHS, NIH Pub No. 03-4158. July 2003. Available at: http://www.niddk.nih.gov/health/nutrit/pubs/statobes.htm. Date accessed: August 26, 2004
94. Strauss RS, Pollack HA. Epidemic increases in childhood overweight, 1986–1998. JAMA 2001;286:2845–2848.
95. Lissau I, Overpeck MD, Ruan WJ, et al. Body mass index and overweight in adolescents in 13 European countries, Israel, and the United States. Arch Pediatr Adolesc Med 2004;158:27–33.
96. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 1998;338:1650–1656.
97. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. New Engl J Med 2002;346:802–810.

Child Abuse, Neglect, and Infanticide

5

Infant and Early Childhood Asphyxial Deaths

Diagnostic Issues

Roger W. Byard, MD and Michael Tsokos, MD

Contents

Summary

Acute airway obstruction from a wide variety of causes may result in sudden death in infants and young children. Natural diseases that cause critical narrowing of airways may cause obstruction either on their own, or when there is superimposed plugging by mucopurulent material. Accidental asphyxia may be as a result of inhalation of foreign material or to so-called "sleeping accidents" in which an infant or young child may wedge between a mattress and a bed rail, suffocate in a plastic bag, or hang from a bed rail. Inflicted

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

asphyxia may take the form of strangulation or pressure on the chest causing crush asphyxia. The findings at autopsy will vary depending on the age of the child, but may be minimal in infancy in many cases of accidental or inflicted asphyxia. For this reason, such cases require extensive investigation, with evaluation of the family history and examination and documentation of the death scene by trained personnel. Although asphyxial deaths caused by different underlying mechanisms appear generally nonspecific, careful documentation of the findings observed at autopsy with full histological examination may become relevant in a specific case in later stages of the investigation.

Key Words: Asphyxia; suffocation, strangulation; choking; foreign body impaction.

1. Introduction

A wide range of accidental, inflicted, and natural conditions or diseases may cause fatal asphyxia in infants and young children *(1)*. The diagnosis of asphyxia may, however, be difficult in young victims as a result of the absence, or relative paucity, of physical signs on external examination of the body and at autopsy, and the failure to carefully examine the upper aerodigestive tract for certain rare conditions. This chapter provides an overview of the types of natural and unnatural conditions that may be associated with fatal asphyxia in young age groups with discussion of particular difficulties that may arise at external examination and autopsy.

2. Mechanisms

Asphyxia occurs when there is a decrease in the amount of oxygen reaching the tissues, resulting in impaired respiration. Asphyxia can be caused by a variety of mechanisms ranging from deprivation of environmental oxygen to interference with oxygen use at the cellular level by chemicals such as cyanide *(2)*. Asphyxia has been classified in a variety of ways. Extrinsic causes include traumatic asphyxia and reduced environmental oxygen, whereas intrinsic causes include airway obstruction from mucus, foreign bodies, or tumors. It is more usual to divide asphyxial deaths into those resulting from suffocation, in which oxygen does not reach the blood; strangulation, in which blood vessels and/or air passages are obstructed by pressure on the neck; and chemical asphyxia from interference with the uptake or utilization of oxygen at the cellular level. Examples of suffocation include situations in which inert gases replace oxygen in the atmosphere or atmospheric oxygen is depleted during entrapment in an airtight space, and circumstances such as smothering,

in which there is blockage of the nose and mouth, choking from obstruction within the airways, and mechanical asphyxia, in which pressure on the chest prevents breathing. Strangulation involves pressure on the neck from a ligature or the hands of an assailant, or hanging, in which the weight of the body is suspended from a ligature around the neck *(1,3)*.

3. General Remarks on Death as a Result of Asphyxia in Infants and Young Children

3.1. Death Scene and External Examination of the Body

Inspection of the death scene may reveal an obvious cause of an asphyxial death, such as a defective crib that has resulted in wedging, or a curtain cord or parts of clothing wrapped around a neck causing hanging *(4,5*; Fig. 1A,B). A detailed reconstruction of the death scene should be undertaken in each case. In specific cases, the use of a doll is useful in demonstrating the position in which the victim was found. Usually present in hanging cases is a thin parchment hanging mark that runs circumferentially around the neck, upward and backward to the point of suspension (Fig. 1C).

Smothering from blockage of the external air passages by a hand may lead to cutaneous abrasions on the child's chin, nose, lips, and around the mouth, especially when the child is old enough to offer a certain degree of resistance (Fig. 2).

Unfortunately the pathological findings in wedging cases are usually more subtle, with minimal evidence of asphyxia as death results from a combination of smothering from covering of the face and from positional/mechanical asphyxia.

Generally, other features at autopsy that suggest asphyxia include conjunctival and facial petechiae (Fig. 3A,B), facial congestion, and scleral hemorrhages. Serosanguinous secretions from the nose and mouth are often seen in infant deaths, but are not specific for any type of condition, merely reflecting agonal pulmonary congestion and edema. However, if frank blood is present within the nose, an explanation is required, as this may suggest a small vessel hemorrhage from asphyxiation *(6,7)*. Other possibilities include local trauma from attempted resuscitation, or bleeding from an intranasal vascular malformation, tumor, infection, or hemangioma. For this reason, detailed description of resuscitative efforts is required in all sudden and unexpected infant and childhood deaths along with otoscopic examination of the nasal passages at autopsy.

Fig. 1. Accidental hanging of a 2-year-old boy caused by entanglement of the cord of his anorak at the top of a slide. **(A,B)** Death scene. **(C)** Circumferential ligature mark passing back to the nape of the neck.

Fig. 1. *Continued*

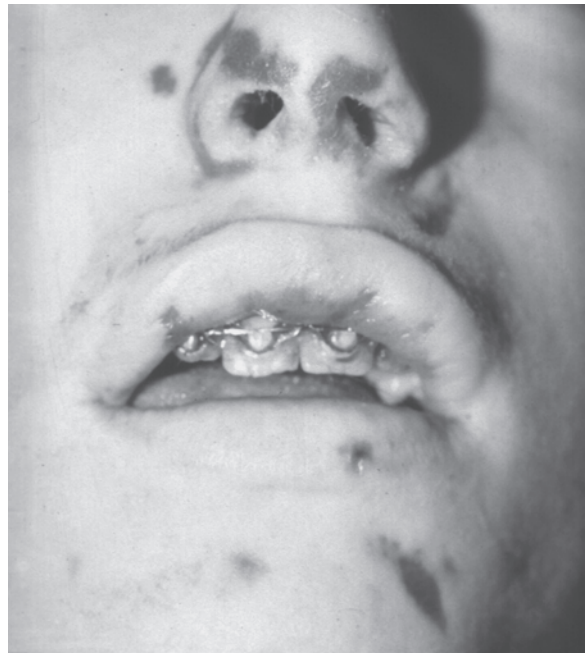

Fig. 2. Cutaneous abrasions on the chin, lips, and around the nostrils as a result of smothering of an 11-year-old boy by his stepfather.

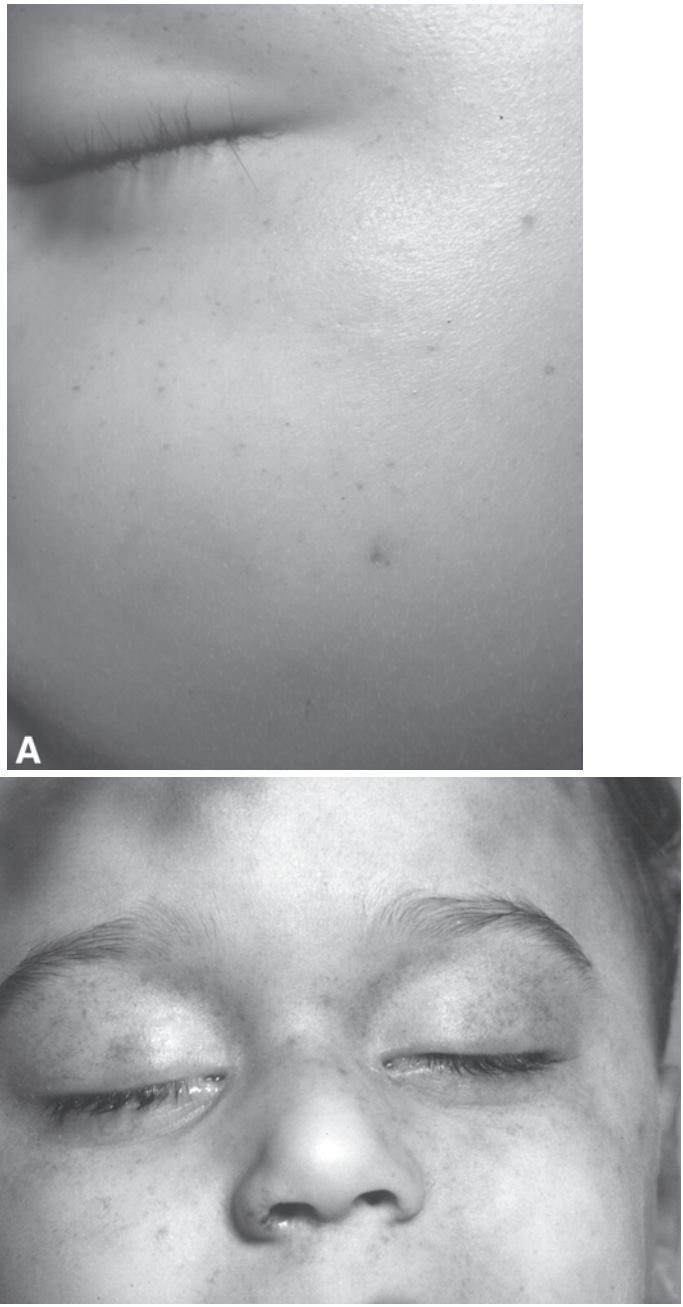

Fig. 3. Petechiae in childhood asphyxial deaths. **(A)** Discrete facial petechiae. **(B)** Marked petechial hemorrhages in the skin of the eyelids.

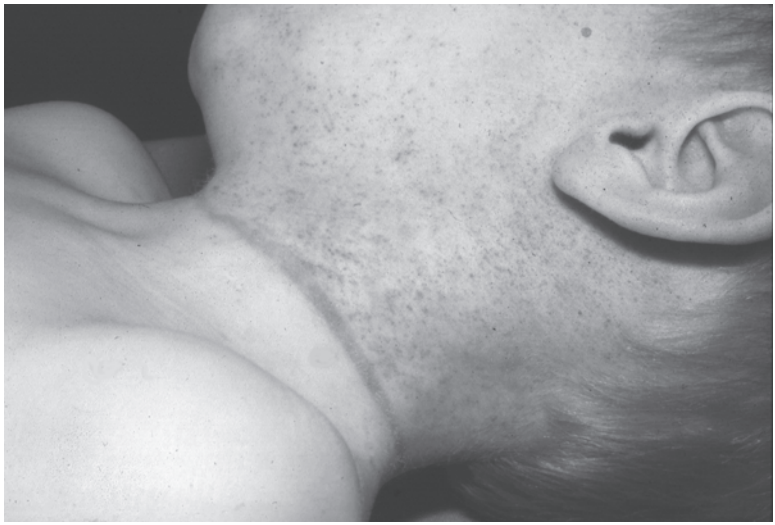

Fig. 4. Horizontal ligature mark and marked congestion of the face with numerous cutaneous petechiae in a 4-year-old boy who was strangled with a ligature by his mother.

Facial and conjunctival petechiae are not infrequent findings in adults who have asphyxiated, but are relatively uncommon in infants. They are not a feature of sudden infant death syndrome (SIDS) cases and, when present, suggest that there has been obstruction to venous return involving vessels of the face and neck. This may be from forceful coughing or vomiting or possibly an epileptic fit *(8)*. Such petechiae may also occur if there has been strangulation with pressure applied to the neck (Fig. 4), or if there has been mechanical compression of the chest, as occurs when an infant is being pressed face down into a soft mattress or compressed under a pillow. The authors have not seen convincing facial or conjunctival petechiae in infants or young children attributable to attempted resuscitation. In adults, cutaneous petechiae may readily develop in dependent areas and have been documented as a postmortem phenomenon *(9)*.

Petechiae and cutaneous hemorrhages may also occur in disseminated infections such as meningococcal disease *(10)*, however, generalized distribution is not a marker of asphyxiation. A difficulty may arise in children with darkly pigmented skin as generalized petechiae and cutaneous hemorrhages may not be discernable, with petechiae only visible in the conjunctivae, giving a misleading appearance of their geographic distribution. Other difficulties may arise when only one or two suspected petechiae are noted. This

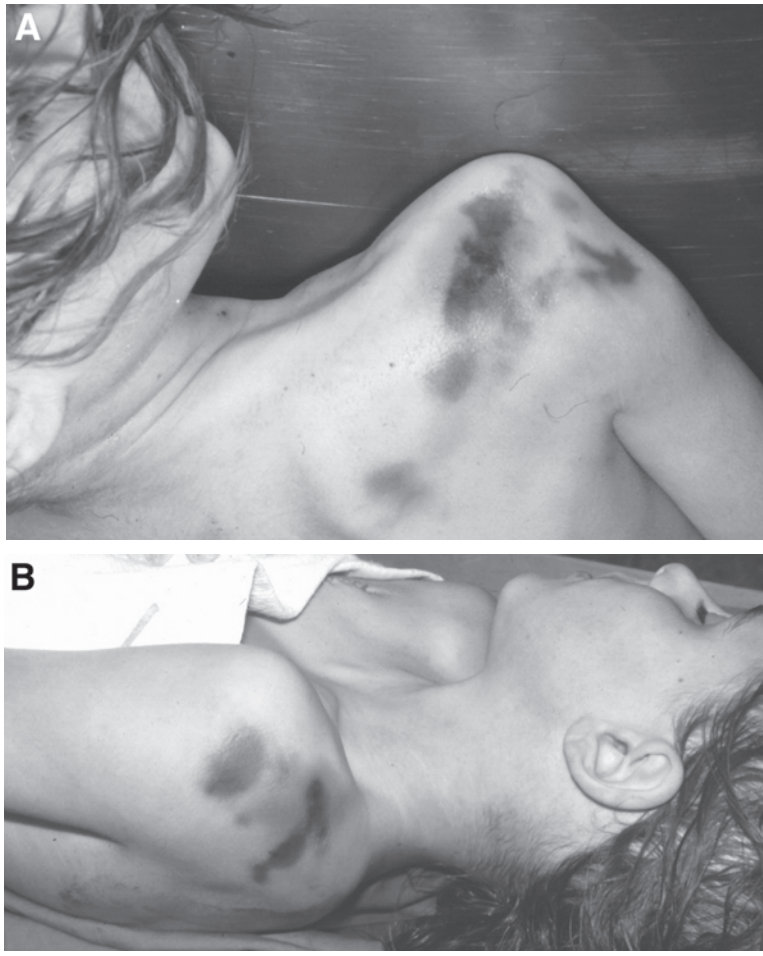

Fig. 5. (A,B) Cutaneous abrasions over the shoulders of a 7-year-old girl who accidentally locked herself in a box and died of suffocation.

contrasts with the florid finding of so-called "masque ecchymotique" in which the face is covered with petechiae *(11)*. Cautious interpretation is required in the presence of only a few petechiae.

Examination of the skin may reveal abrasions that could, if found on the neck, represent adult fingernail marks in cases of manual strangulation. Cutaneous abrasions may also represent signs of self-rescue attempts prior to death, for example, when a child is accidentally or intentionally locked in small self-contained spaces, such as a box (Fig. 5A,B). There may also be rounded areas of bruising from fingertip pressure in the skin, subcutaneous tissues, and

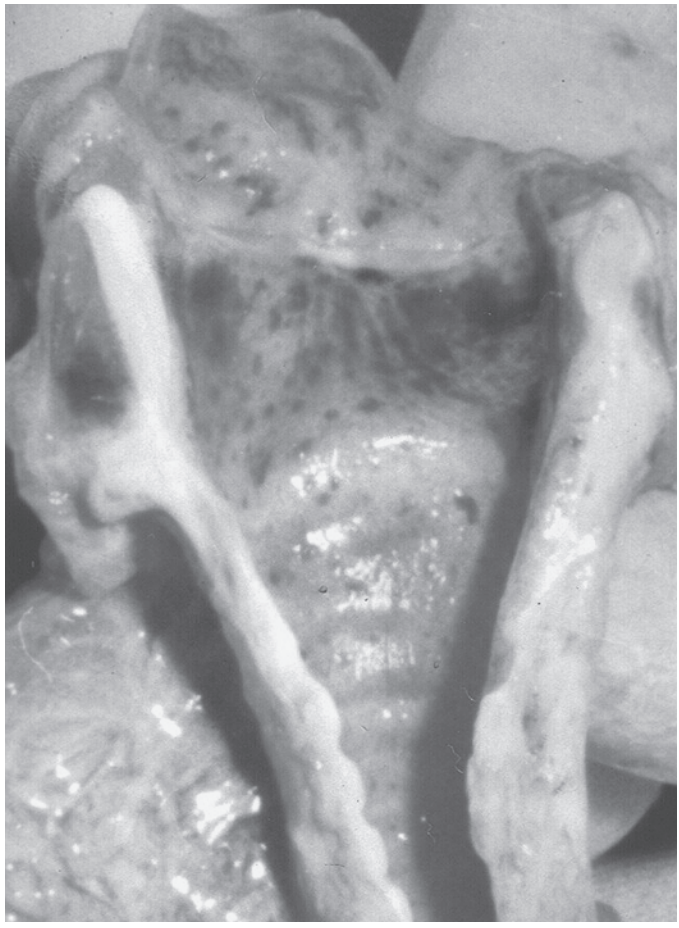

Fig. 6. Petechial and more confluent hemorrhages on the mucosal surface of the interior of the larynx in a 4-year-old boy (same case as Fig. 4).

underlying strap muscles. For this reason, autopsy examination requires a full neck dissection once the brain has been removed to drain blood from the area.

3.2. Autopsy Findings

In cases of fatal asphyxia, objective autopsy findings are usually scanty or absent and it is now widely accepted that there are no classical signs of asphyxia. Both the fluidity of blood and dilatation of the ventricle and atrium of the right heart are sometimes mentioned as indicative of asphyxia, but unfortunately they are not.

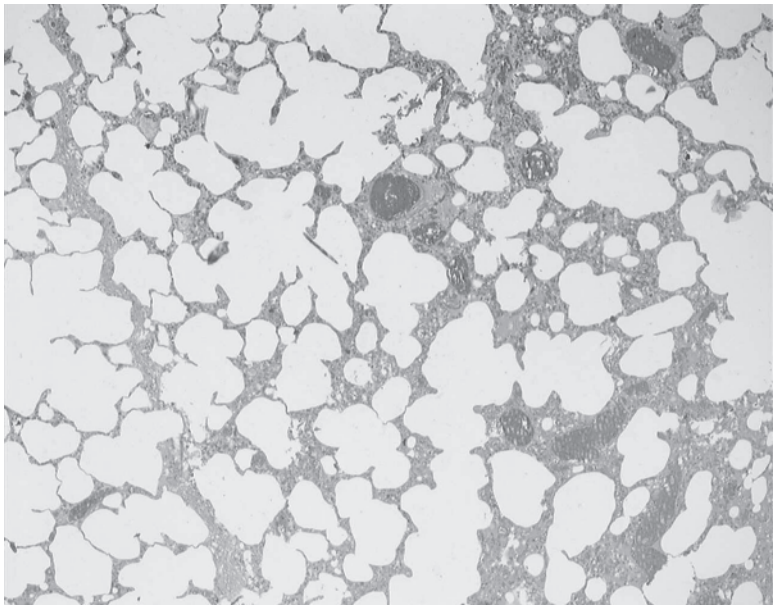

Fig. 7. Alveolar overdistension accompanied by alveolar ruptures in a case of fatal ligature strangulation in a 4-year-old boy (same case as Fig. 4).

Tardieu's spots, petechiae of the visceral pleura, are a frequent finding but are also not pathognomonic *per se* for asphyxia. Petechial or more confluent hemorrhages may also be apparent on the mucosal surface of the interior of the larynx but one has to differentiate carefully whether they are there mainly as a result of direct trauma (Fig. 6).

As a result of the extreme pliability of the thyroid cartilage and hyoid bone in infancy and childhood, these structures are less often damaged than in older adults who have suffered forceful neck pressure.

3.3. Histopathology

Asphyxial deaths caused by different underlying mechanisms demonstrate changes at autopsy that are also seen frequently in a broad variety of natural or violent causes of death in forensic pathological practice.

Histopathological findings observed in the lungs in cases of fatal asphyxia can be summarized as follows: alveolar overdistension accompanied by alveolar rupture, and enlargement of alveolar spaces (Fig. 7), atelectasis, focal as well as more circumscribed intra-alveolar hemorrhage with or without edema (Fig. 8A,B), pulmonary congestion with swelling of pneumocytes, microthromboses, and leukocyte margination within the pulmonary microvasculature, collapse

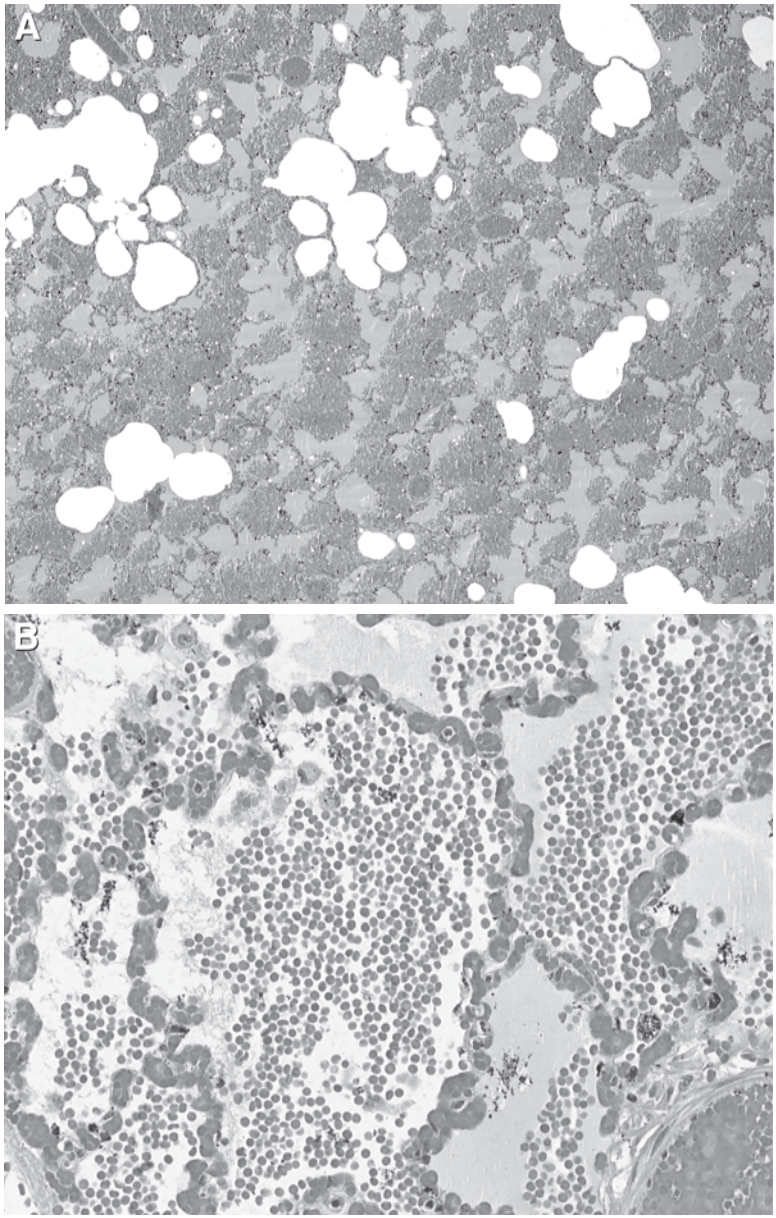

Fig. 8. Suicidal hanging of a 16-year-old girl. **(A)** Intra-alveolar hemorrhage with alveolar edema. **(B)** High-power view of intra-alveolar hemorrhage, congestion of alveolar capillaries, and swelling of pneumocytes.

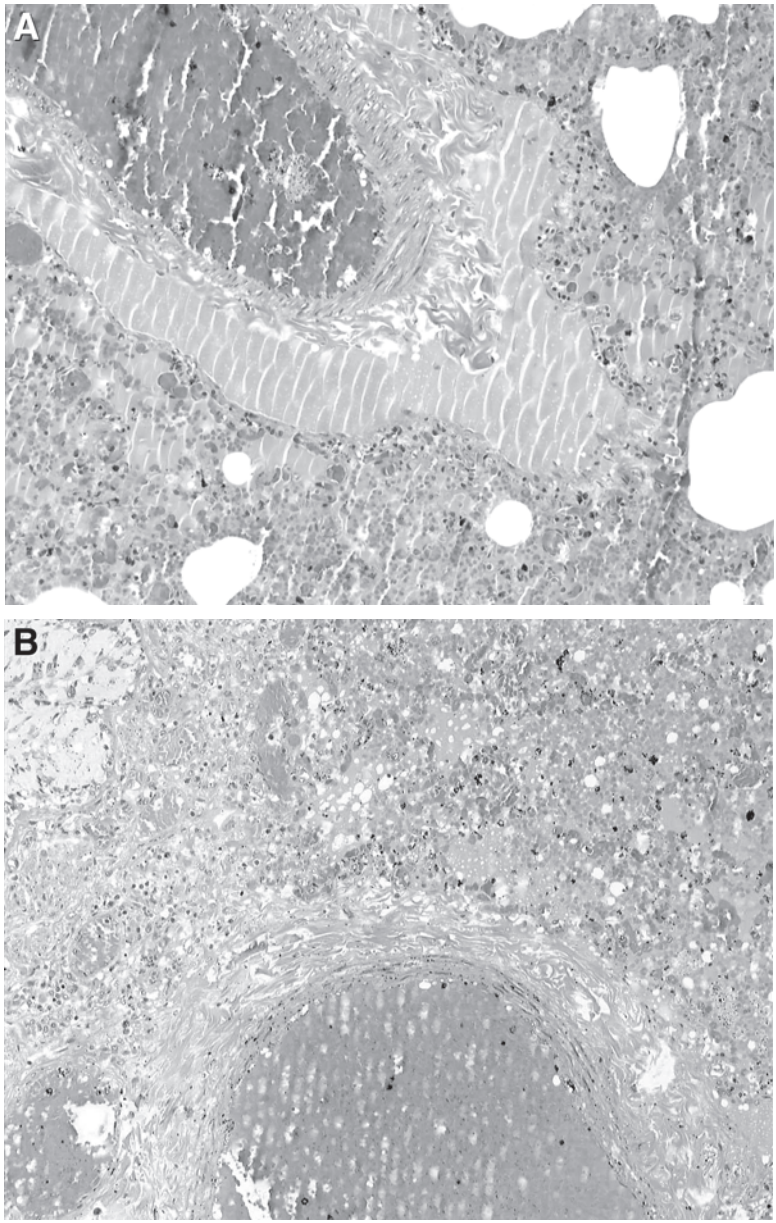

Fig. 9. (A,B) Features of perivascular, cuff-like edema around larger and medium-sized pulmonary artery branches in a 4-year-old boy (same case as Fig. 4).

of bronchi, and occasionally a marked perivascular, cuff-like edema around larger and medium-sized pulmonary artery branches (Fig. 9A,B).

Although intra-alveolar hemorrhage was proposed as a marker of airway obstruction *(12)*, one has to be aware that bleeding into the airways may be influenced by a number of independent factors including length of attempted resuscitation prior to death and a broad variety of preexisting illnesses that may lead to diffuse intra-alveolar bleeding such as Goodpasture's syndrome or idiopathic pulmonary hemosiderosis. Additionally, intra-alveolar hemorrhage may be caused by internal hypostasis in dependent areas of the lungs, influenced by the position of the body after death; gravitational movement of the blood after cessation of circulation leads to dependent areas becoming engorged with blood thus resulting in intra-alveolar and interstitial hemorrhage from leaking vessels *(13,14)*. This finding is therefore highly dependent on the area of the lung that is sampled.

It has also been suggested that hemosiderin-containing macrophages within alveoli are the result of previous asphyxial episodes with iron-containing pigments deriving from the breakdown of intra-alveolar blood *(15)*. Again, although previous apneic episodes or episodes of obstructed respiration may result in hemosiderin within alveolar macrophages, this finding is not specific for asphyxiation and may be found in infants with no suspicious histories. Hemosiderin within the interstitial tissues of the lung in infants whose deaths are attributed to SIDS is not uncommon *(16)*.

Although the aforementioned histopathological features are *per se* of no pathognomonic value in diagnosing fatal asphyxia, a careful histological examination and documentation of the findings observed may become relevant in a specific case in later stages of the death investigation.

4. Pathological Features of Death as a Result of Asphyxia in Infants and Young Children: Specific Circumstances

4.1. Asphyxia as a Result of Upper Airway Obstruction From Natural Diseases

There are many rare causes of airway narrowing in infants and children that should be checked for at autopsy. Although not all of these conditions have been reported as causes of sudden death, it is likely that any condition that results in significant narrowing of the upper airway may predispose to obstruction, particularly if there is coincidental or related upper airway infec-

Table 1
Conditions Associated With Upper Airway Obstruction and Sudden Death in Infancy and Childhood

1.	Choanal atresia
2.	Nasopharyngeal tumors
3.	Posterior lingual masses (e.g., thyroglossal duct cysts)
4.	Macroglossia
5.	Micrognathic syndromes (e.g., Pierre-Robin, Goldenhar, Treacher-Collins, Apert, Crouzon)
6.	Heterotopic tissues
7.	Upper airway infections
8.	Structural airway defects (e.g., tracheomalacia, bronchomalacia)
9.	Tracheal stenosis
10.	Vascular rings
11.	Upper mediastinal tumors
12.	Miscellaneous

Modified according to ref. *17*.

tion with tenacious mucus in the airways. Conditions causing airway narrowing in infants and young children have been summarized earlier *([17]* Table 1).

Obstruction may occur at the level of the nasal choanae and may involve soft tissue or bone membranes. Complete obstruction will cause respiratory distress at birth, whereas infants with partial obstruction may not have problems until later. Manifestations usually occur during feeding and are associated with posterior movement of the tongue. Obstruction at the level of the choanae may also be functional and so an anatomical blockage may not always be demonstrable at autopsy.

Tumors and abnormalities, such as teratomas and encephaloceles, may significantly narrow the upper airway. Congenital cervical teratomas usually manifest soon after delivery as a result of tracheal compression or deviation. Adenoidal and tonsillar hypertrophy may cause airway blockage and chronic hypoxia in affected infants. Choristomas, which are heterotopic tissues, may also occur in the airways causing narrowing. Examples include heterotopic thymus in the trachea and gastric mucosa in the hypopharynx. Hemangiomas and cystic hygromas may also involve the airways, and significant narrowing may result from laryngeal papillomatosis *(18)*.

Tumors or swellings at the base of the tongue may produce critical narrowing of airways. This may occur in cases of lingual thyroglossal duct cysts in which a remnant of thyroid tissue in the back of the tongue at the foramen cecum produces a cystic swelling that can cause inspiratory stridor, especially in infants lying on their backs, and also occasionally fatal airway obstruction

(19). Lingual tonsils or posterior lingual abscesses may have a similar effect *(20)*.

Disproportion between the size of the tongue and the mandible may result in posterior displacement of the tongue and occlusion of the upper airway at the glottis. This is most commonly seen in syndromes such as Pierre-Robin anomalad in which there is micrognathism. Mandibular hypoplasia may also be associated with an array of other congenital deformities and occurs in Joubert, Brachman de Lange, Mobius, Treacher-Collins, Goldenhar, and Stickler syndromes *(17,21)*. Maxillary hypoplasia in Apert and Crouzon syndromes may also cause acute upper airway obstruction. Consultation with a medical geneticist/dysmorphologist may provide useful information on what types of abnormalities may be present prior to commencing an autopsy in such a case. Significant macroglossia (e.g., in Down's syndrome) may also obstruct the oropharynx.

Upper airway infections may result in critical swelling of tissues with airway compromise. The classic example is acute epiglottitis in which the epiglottis becomes swollen and edematous as a result of infection with *Hemophilus influenzae* type B and plugs the glottis causing acute respiratory embarrassment. These cases are now rarely seen in communities where immunization programs against *Hemophilus* have been introduced. Other focal areas of sepsis with acute inflammation may also compromise the airway including tonsillitis and peritonsillar abscess, lingual tonsillitis and posterior lingual abscess, and retropharyngeal abscess *(22)*.

Anatomical abnormalities of the airways resulting from deficiencies in cartilage may also cause narrowing when there is loss of structural support in cases of laryngo-, tracheo-, and bronchomalacia. Weakening of the walls of the upper airway results in collapse with stridor and possible respiratory arrest/recurrent apneas. However, cases of infant death have only rarely been reported. Tracheomalacia may be primary or secondary in cases of tracheo-esophageal fistulas and vascular rings, Larsen and Ehlers-Danlos syndromes, polychondritis, and congenital chondromalacia. Tracheal stenosis may also result in critical upper airway narrowing. This may also be primary or secondary to tracheo-esophageal fistula repair. Congenital subglottic stenosis as a result of cartilaginous or soft tissue narrowing of the subglottic space is associated with Down's syndrome and may cause significant airway obstruction *(17)*.

As many of the conditions mentioned here are exceedingly rare, they may not be suspected prior to autopsy. Postmortem detection requires removal of the entire upper aerodigestive tract, including the soft palate and uvula for careful examination and documentation of abnormalities. Suboptimal dissection of the upper airways may result in failure to detect all cases. As there may

be an inherited component to certain syndromes associated with upper airway compromise, genetic counseling may be warranted.

4.2. Foreign Body Impaction

Young children are at particular risk of accidental asphyxia from inhalation of foreign material, with the greatest incidence occurring between 2 and 3 years of age, although choking on inhaled material may also occur in young infants and older children. Food and parts of toys are the most common inhaled materials, thus parents and caregivers must ensure that only food that is appropriate for the child's level of dental and developmental maturity is provided, and that toys do not have small detachable parts. Foods that most often cause choking episodes in children vary among communities but include round, firm foods such as hot dogs, nuts, candy, vegetables like carrots, and fruit such as grapes. In addition to parts of toys, plastic pen caps, metal screws, and balloons have all caused fatal upper airway occlusion in children *(4,5,23)*.

The autopsy investigation of these cases may be difficult if the obstructing foreign body has already been removed and there is no clear description of events leading up to the fatal collapse, as physical findings are very nonspecific. The foreign body should ideally accompany the body to the mortuary for photography, measurements, and comparison with airway caliber. Obstructing material usually lodges in the pharynx or tracheobronchial tree and causes coughing, choking, gagging, or complete airway obstruction and collapse. Symptoms may not have been present, however, if the material was in the mouth prior to a toddler going to sleep, or if the material has passed deeper into a bronchus.

Food inhalation is a particular problem in toddlers who are able to bite off portions of firm food before they can effectively masticate, as incisor teeth erupt at 10 months to 2 years before the second molars at 20 to 30 months. Venues such as social gatherings, parties, or child-care centers may have increased risks because toddlers often encounter food to which they have not previously been exposed *(24)*. Rarely, material may lodge in the esophagus and subsequently cause airway obstruction by a combination of direct pressure on the trachea and local inflammatory swelling. Such material may also erode through the wall of the esophagus and cause fatal hemorrhage, cardiac tamponade, or sepsis *(25)*. The feeding of inappropriate material to infants and younger children may indicate neglect or inflicted injury.

4.3. Asphyxia Occurring in Cribs and Beds

Infants and young children who are placed to sleep in certain situations may be at risk of accidental asphyxial death. This may occur if an infant slides

or rolls into a gap, or if clothing is caught and causes pressure around the neck *(4,5)*.

Wedging deaths occur when an infant has slipped into a narrow space between a crib mattress and side, or between an adult mattress and a wall. An infant who slips into a crevice suffers respiratory compromise from pressure on the chest and/or covering of the mouth and nose. A variety of sleeping situations are known to have an increased risk of asphyxial death and these include mesh-sided portable cribs in which the sides of the crib are distensible, enabling an infant to slip down beside the mattress. The recoil of the elastic mesh then holds the infant in place, preventing escape *(26)*. Sofas are not safe, as infants may roll backward and slip between cushions and the back. If an adult is also sleeping on a sofa with an infant there is always an increased risk of overlaying *(27)*. Broken cribs may have bars or slats missing, which increases the risk of wedging. Drop-sided cribs may also have gaps into which infants can slide. Children with severe developmental delay are at increased risk of asphyxiating in bed at older ages than are other children, as a result of devices used to prevent them from rolling out of bed *(28)*. As noted previously, autopsy findings in cases of wedging may be minimal unless there has been pressure from railings or bars in the crib.

Hanging may occur when an infant slips down in restraints or when a toddler stands and catches clothing on projections inside a crib, causing the weight of the body to be suspended from webbing or clothing around the neck. Curtain cords around the neck have also caused hanging deaths once balance has been lost and a young child has become suspended. It is important during the investigation of such cases to determine whether an infant was supervised at the time of death, as hanging deaths in seats with restraints often occur when an infant has been left unattended for some time.

Suffocation may occur in infants put to sleep face down on partially filled waterbeds because the weight of the head pushes the infant's face into a depression in the mattress. The mattress then molds around the infant's face, blocking air entry. V-shaped pillows have also been reported as a cause of infant suffocation when an infant is propped up in a pillow that has been wedged into a crib. The infant may slide into the depths of the cushion and smother *(29)*. Deaths have occurred in infants who have been left lying on polystyrene-filled cushions. Studies have demonstrated a significantly elevated level of carbon dioxide in experimental animals placed in similar situations *(30)*. Plastic bags or sheeting used to protect mattresses and pillows have caused smothering when infants have become entangled in the plastic.

4.4. Inflicted Asphyxia

Intentional asphyxiation of infants is not technically difficult as the small size and weakness of the victim means that death may occur from airway obstruction with the use of only minor force by an assailant. Additionally, certain infants are unusually susceptible to the effects of even transient airway occlusion. For this reason there are often no signs of asphyxia at the time of autopsy. Fragments of lint or material from a towel, blanket, or pillow that has been used to asphyxiate an infant may be found on the face unless deliberately removed by a perpetrator or inadvertently dislodged during attempted resuscitation.

Infants may be intentionally asphyxiated for diverse reasons. An infant may be covered by a pillow merely to silence crying, or the intention from the outset may be to end the infant's life. Serial deaths in families have occurred when a mother has been part of a Münchausen syndrome by proxy situation in which she has been intentionally suffocating children to the point of unconsciousness to achieve family and medical attention. Miscalculation of the amount of time required to achieve loss of consciousness, or a genuine intent to murder infants, has resulted in several widely publicized cases of multiple deaths over a number of years *(31–33)*. Homicidal hangings in infancy are rare. Plastic bags or wrap have also been used to smother infants, and again there would not be expected to be significant findings at autopsy. If the plastic that was used can be found there may be impressions of the infant's mouth and/or recoverable DNA from the infant's face and the perpetrator's hands.

4.5. SIDS and Asphyxia

SIDS has been defined as "the sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene and review of the clinical history" *(34)*. The etiology of SIDS is still not understood, however, it appears likely that the additive effects of environmental and intrinsic factors in certain infants at a susceptible time of life may cause unexpected deaths. One of the many theories of SIDS proposes that at-risk infants have upper airway narrowing with large tongues and that this constellation of anatomical factors predisposes to asphyxia from obstructive apnea. However, although these features may certainly increase the risk of unexpected death, there are undoubtedly many other contributing factors involving both individual susceptibilities and environmental risk factors *(35,36)*.

Although the risk of SIDS increases in infants who sleep prone, this is not simple asphyxiation from smothering, as only a small percentage of infants in this position succumb. Other factors undoubtedly involve defective central

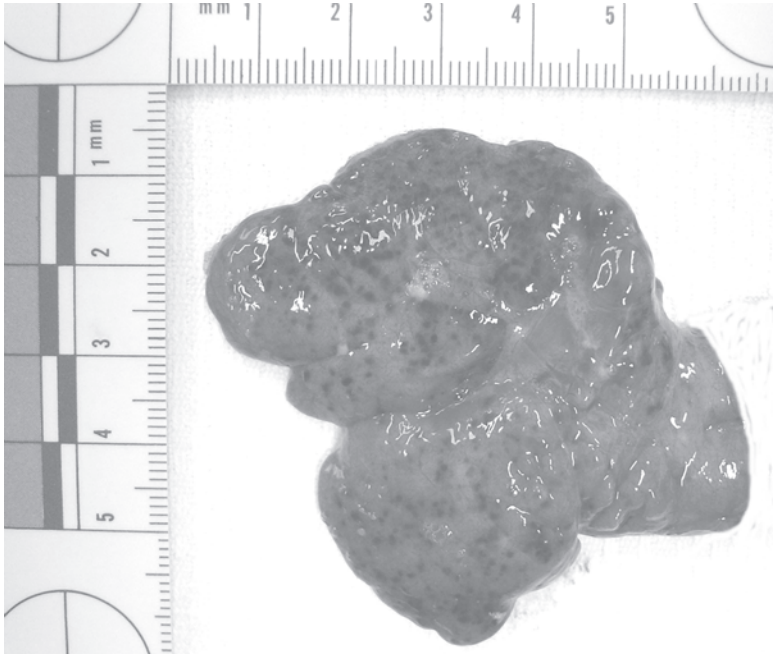

Fig. 10. Petechiae of the thymus gland in a case of SIDS.

autonomic control, overheating, carbon dioxide rebreathing, and diaphragmatic splinting, in addition to possible airway occlusion, in an infant with inherent vulnerabilities *(37)*.

Intrathoracic petechiae have been cited as evidence of upper airway obstruction in SIDS infants (Fig. 10), however, it is likely that these represent a terminal phenomenon related to agonal gasping. There may be an obstructed glottis at this stage but this is probably a result of the underlying physiological disruption, rather than a cause. The paucity of petechiae in the posterior intracervical portion of the thymus gland (Beckwith's sign) is supportive of agonal gasping as the underlying mechanism, with portions of thymus above the innominate vein being protected from the effects of increased negative intrathoracic pressure *(8)*.

4.6. Overlaying and Wedging

Overlaying, or the accidental or deliberate suffocation of an infant sleeping in the same bed as an adult, was once considered the most common cause of unexpected infant death. Overlaying in recent times has become an issue of heated debate. The supporters of shared sleeping point out that this has been

an adaptive mechanism over millennia that has served to protect infants from environmental dangers. Breastfeeding is also enhanced when there is shared sleeping, and certain studies have shown increased arousals which, it has been suggested, will decrease the risk of SIDS *(38–40)*. On the other hand, there are dangers associated with small infants sleeping in adult beds. Certain infants will not survive this environment with increased risks of asphyxia occurring when parents are obese, fatigued, sedated, or intoxicated, and are sleeping on soft mattresses with heavy coverings, with the infant between them *(41,42)*. In some circumstances, there may be a number of other individuals also sleeping in the same bed. Other cases have also occurred in which infants have asphyxiated while being breastfed *(43)*. A distracted or sleeping mother has been unaware that her breast was obstructing the infant's mouth and nose. In rare cases, infants have been nearly fatally strangled by long maternal hair.

Findings at the death scene are usually unhelpful as there has been disturbance of the scene with movement of the infant's body. Serosanguinous fluid staining of a parent's nightwear from an infant's mouth and nose may confirm that contact between the adult and infant occurred at some time during the night. Autopsy findings in these cases are usually unremarkable *(44)*.

4.7. Miscellaneous Causes of Asphyxia

A variety of other rare causes of asphyxia may be encountered in early childhood as curious children develop the mobility to explore their world without a concomitant understanding of potential dangers. Entrapment, particularly in airtight freezer may cause suffocation as a result of a lack of environmental oxygen. Traumatic asphyxia may occur if young children tip furniture over on to themselves *(45)*, or if they get caught under electric garage doors (Fig. 11). Open car windows may leave a gap in which toddlers or young children may wedge their necks and hang *(46)*. Cases have also been reported in which young children have been caught by car power windows.

5. *Conclusions*

A number of problems arise in the assessment of possible asphyxia in infancy, not the least of which is the absence of diagnostic autopsy findings and the difficulty in distinguishing these cases from SIDS fatalities. Following the introduction of detailed death scene and autopsy protocols, however, there has been an increase in the number of cases of deaths as a result of asphyxia being identified *(47)*. Intrinsic lesions of the upper airway causing fatal obstruction are rare but must always be considered, as must the possibility of foreign body aspiration, even in the absence of a history of respiratory

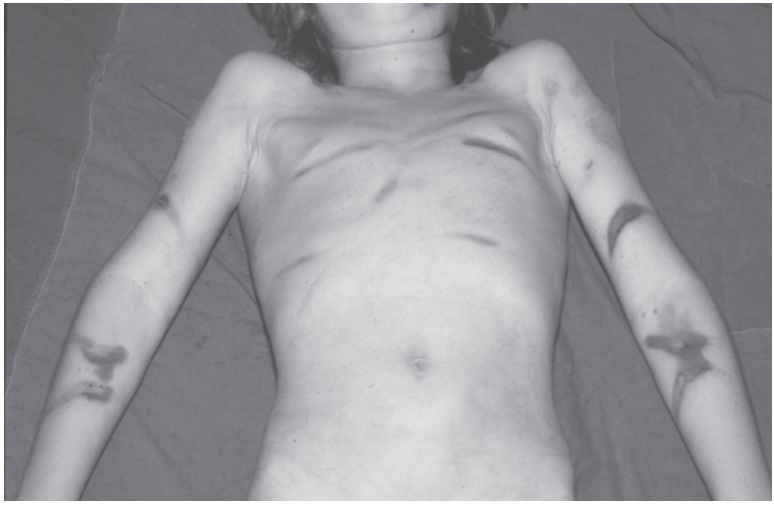

Fig. 11. Dried dermal abrasions in a 9-year-old girl who was accidentally caught under an electric garage door and died of traumatic asphyxia as a result of thoracic compression.

problems. Cases of inflicted asphyxia are particularly difficult and the investigation and prosecution usually cannot depend on pathological findings to either confirm or refute this possibility.

References

1. Byard RW. Sudden Death in Infancy, Childhood and Adolescence, 2nd ed. Cambridge University Press, Cambridge, 2004.
2. Byard RW, Cohle SD. Accidents. In: Byard RW, ed. Sudden Death in Infancy, Childhood and Adolescence, 2nd ed. Cambridge University Press, Cambridge, 2004, pp. 11–73.
3. DiMaio DJ, DiMaio VJM. Forensic Pathology. CRC Press, Boca Raton, 1993.
4. Byard RW. Hazardous infant and early childhood sleeping environments and death scene examination. J Clin Forensic Med 1996;3:115–122.
5. Byard RW, Beal S, Bourne AJ. Potentially dangerous sleeping environments and accidental asphyxia in infancy and early childhood. Arch Dis Child 1994;71:497–500.
6. Krous HF, Nadeau JM, Byard RW, Blackbourne B. Oronasal blood in sudden infant death. Am J Forensic Med Pathol 2001;22:346–351.
7. Becroft DM, Thompson JM, Mitchell EA. Nasal and intrapulmonary hemorrhage in sudden infant death syndrome. Arch Dis Child 2001;85:116–120.
8. Byard RW, Krous HF. Petechial hemorrhage and unexpected infant deaths. Legal Med 1999;1:193–197.

9. Knight B. Forensic Pathology. 2nd ed. Arnold, London, 1996.
10. Sperhake JP, Tsokos M. Pathological features of Waterhouse-Friderichsen syndrome in infancy and childhood. In: Tsokos M, ed. Forensic Pathology Reviews, Vol. 1. Humana Press Inc., Totowa, NJ, 2004, pp. 219–231.
11. Perrot LJ. Masque echymotique. Specific or nonspecific indicator for abuse. Am J Forensic Med Pathol 1989;10:95–97.
12. Yukawa N, Carter N, Rutty G, Green MA. Intra-alveolar haemorrhage in sudden infant death syndrome: a cause for concern? J Clin Pathol 1999;52:581–587.
13. Hanzlick R. Pulmonary hemorrhage in deceased infants. Baseline data for further study of infant mortality. Am J Forensic Med Pathol 2001;22:188–192.
14. Berry PJ. Intra-alveolar haemorrhage in sudden infant death syndrome: a cause for concern? J Clin Pathol 1999;52:553,554.
15. Becroft DM, Lockett BK. Intra-alveolar pulmonary siderophages in sudden infant death: a marker for previous imposed suffocation. Pathology 1997;29:60–63.
16. Byard RW, Stewart WA, Telfer S, Beal SM. Assessment of pulmonary and intrathymic hemosiderin deposition in sudden infant death syndrome. Pediatr Pathol Lab Med 1997;17:275–282.
17. Byard RW. Respiratory conditions. In: Byard RW. Sudden Death in Infancy, Childhood and Adolescence, 2nd ed. Cambridge University Press, Cambridge, 2004, pp. 328–349.
18. Byard RW, Burrows PE, Izakawa T, Silver MM. Diffuse infantile haemangiomatosis: clinicopathological features and management problems in five fatal cases. Eur J Pediatr 1991;150:224–227.
19. Byard RW, Bourne AJ, Silver MM. The association of lingual thyroglossal duct remnants with sudden death in infancy. Int J Pediatr Otolaryngol 1990;20:107–112.
20. Byard RW, Silver MM. Sudden infant death and acute posterior lingual inflammation. Int J Pediatr Otorhinolaryngol 1993;28:77–81.
21. Byard RW, Kennedy JD. Diagnostic difficulties in cases of sudden death in infants with mandibular hypoplasia. Am J Forensic Med Pathol 1996;17:255–259.
22. Byard RW. Unexpected infant and childhood death. In: Payne-James J, Busuttil A, Smock, W, eds. Forensic Medicine: Clinical and Pathological Aspects. Greenwich Medical Media, London, 2003, pp. 231–245.
23. Nixon JW, Kemp AM, Levene S, Sibert JR. Suffocation, choking, and strangulation in childhood in England and Wales: epidemiology and prevention. Arch Dis Child 1995;72:6–10.
24. Byard RW, Gallard V, Johnson A, Barbour J, Bonython-Wright B, Bonython-Wright D. Safe feeding practices for infants and young children. J Paediatr Child Health 1996;32:327–329.
25. Byard RW. Mechanisms of unexpected death in infants and young children following foreign body ingestion. J Forensic Sci 1996;41:438–441.
26. Byard RW, Bourne AJ, Beal SM. Mesh-sided cots—yet another potentially dangerous infant sleeping environment. Forensic Sci Int 1996;83:105–109.
27. Byard RW, Beal S, Blackbourne B, Nadeau JM, Krous HF. Specific dangers associated with infants sleeping on sofas. J Paediatr Child Health 2001;37:476–478.
28. Amanuel B, Byard RW. Accidental asphyxia in bed in severely disabled children. J Paediatr Child Health 2000;36:66–68.

29. Byard RW, Beal SM. V-shaped pillows and unsafe infant sleeping. J Paediatr Child Health 1997;33:171–173.
30. Kemp JS, Thach BT. Sudden death in infants sleeping on polystyrene filled cushions. N Engl J Med 1991;324:1858–1864.
31. Byard RW, Beal SM. Munchausen syndrome by proxy: repetitive infantile apnoea and homicide. J Paediatr Child Health 1993;29:77–79.
32. Meadow R. Suffocation, recurrent apnea, and sudden infant death. J Pediatr 1990;117:351–357.
33. Meadow R. Unnatural sudden infant death. Arch Dis Child 1999;80:7–14.
34. Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. Pediatr Pathol 1991;11:677–684.
35. Byard RW, Krous HF. Sudden infant death syndrome—overview and update. Pediatr Develop Pathol 2003;6:112–127.
36. Byard RW, Krous HF. Sudden Infant Death Syndrome. Problems, Progress and Possibilities. Arnold, London, 2001.
37. Stanley FJ, Byard RW. The association between the prone sleeping position and sudden infant death syndrome (SIDS): an editorial overview. J Paediatr Child Health 1991;27:325–328.
38. McKenna JJ, Mosko S. Mother-infant cosleeping: toward a new scientific beginning. In: Byard RW, Krous HF, eds. Sudden Infant Death Syndrome. Problems, Progress and Possibilities. Arnold, London, 2001, pp. 258–274.
39. McKenna JJ, Mosko SS, Richard CA. Bedsharing promotes breastfeeding. Pediatrics 1997;100:214–219.
40. McKenna JJ, Mosko S, Richard C, et al. Experimental studies of infant-parent cosleeping: mutual physiologic and behavioral influences and their relevance to SIDS (sudden infant death syndrome). Early Hum Dev 1994;38:187–201.
41. Byard RW. Is co-sleeping in infancy a desirable or dangerous practice? J Paediatr Child Health 1994;30:198,199.
42. Byard RW, Hilton J. Overlaying, accidental suffocation and sudden infant death. J SIDS Infant Mort 1997;2:161–165.
43. Byard RW. Is breast feeding in bed always a safe practice? J Paediatr Child Health 1998;34:418,419.
44. Mitchell E, Krous HF, Byard RW. Pathological findings in overlaying. J Clin Forensic Med 2002;9:133–135.
45. Byard RW, Hanson K, James RA. Fatal unintentional traumatic asphyxia in childhood. J Paediatr Child Health 2003;39:31,32.
46. Byard RW, James RA. Car window entrapment and accidental childhood asphyxia. J Paediatr Child Health 2001;37:201,202.
47. Mitchell E, Krous HF, Donald T, Byard RW. Changing trends in the diagnosis of sudden infant death. Am J Forensic Med Pathol 2000;21:311–314.

Suicide

6

Complex Suicides

Michael Bohnert, MD

Contents

Summary

The term "complex suicide" refers to suicides in which more than one suicide method is applied. In this context, a distinction can be made between planned and unplanned complex suicides. In planned complex suicides, two or more methods are employed simultaneously in order to make sure that death will occur even if one method fails. In unplanned complex suicides, several other methods of suicide are tried after the first method chosen failed to gain one's end or when it proved to be too painful. In planned complex suicides, typically two of the generally common methods of suicide (e.g., ingestion of hypnotics or other medicaments, hanging, use of firearms, drowning, jumping from a height) are combined. However, unusual combinations have been described also, such as the simultaneous firing of several guns, self-immolation, jumping from a height, or shooting oneself while driving a car. In unplanned complex suicides, injuries by sharp force, especially cutting the wrists, are often found as the primary act of suicide. In some cases, the suicidal changes

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

from the infliction of cut wounds to the infliction of stab wounds (most often located in the heart region). Other frequently used methods after failure of the first method are hanging and jumping from a height. A further characteristic feature of unplanned complex suicides is the application of more than two methods of suicide. The literature has reported the use of up to five suicide methods applied one after the other. From the criminological point of view, the presence of several injuries of different origin strongly suggests infliction by another person. Differentiation is possible only if autopsy including toxicological analysis is performed and the traces at the death scene are thoroughly investigated, so that the sequel of events can be reconstructed.

Key Words: Planned complex suicide; unplanned complex suicide; primary combined suicide; secondary combined suicide.

1. Introduction

The term "complex suicide" refers to suicides in which more than one suicide method is applied. On the one hand, this refers to those cases in which the simultaneous combination of several methods of suicide is employed to guarantee one will at least succeed. The purpose of the second suicide method employed—and any further method that may be employed, too—is to serve as a safeguard in case that the first method fails. However, the term "complex suicide" is also used for those cases in which the methods of suicide are not applied simultaneously, but one after the other. This may be the case if the first method chosen did not cause death, if death occurs too slowly, or this method causes too much pain. Contrary to the aforementioned cases, those suicides have to be distinguished in which the suicidal individual uses the same tool several times successively, because the first injury did not cause death immediately or at least did not induce immediate incapacitation. This may be the case especially when firearms *(1–5)* or sharp tools are used *(6–11)* to commit suicide.

For a better differentiation, it has been suggested to distinguish between primary combined or planned complex suicides and secondary combined or unplanned complex suicides *(12–14)*. Pollak called those suicides in which "the success is to be guaranteed by a planned coincidence or mutual acceleration of two or more methods of suicide" primary combined suicides. In contrast to the aforementioned group, secondary combined suicides are those in which the suicidal individual uses one or several other forms of inflicting damage to him or herself directly after the unintentional failure of a first attempt in one and the same course of action *(14)*. Hofmann and Herber recommended

using the term "prolonged suicide" instead of "secondary combined suicide," as one cannot speak of a combination of different methods of suicide in the proper sense of the word *(15)*. In the American literature, the emphasis is put more on the dichotomy of planned complex vs unplanned complex instead of primary combined vs secondary combined. Here, the distinction between simple and complex suicides that was first made by Marcinkowski is preferred, with the latter group being subdivided again into planned and unplanned suicides *(16)*.

During the last 25 years, numerous reports have dealt with complex suicides. Almost all of them are case reports *(14,15,17–58)* and accordingly systematic investigations concerning the frequency of complex suicides are rare *(12,14,15,41,59)*. In many publications on the epidemiology of suicide, complex suicides are not mentioned at all or only on the fringe *(60–65)*. According to the literature, complex suicides account for 1.5 to 5% of all completed ("successful") suicides *(12,14,15,41,59,66,67)*.

From the criminological point of view, the presence of several different injuries found on a deceased are especially suspicious for homicide. Careful inspection of the death scene, a thorough investigation of the surroundings of the deceased, and a full autopsy are necessary to elucidate the correct mode of death in such cases. Additionally, the objective of these investigations must be to allow a precise reconstruction of the sequel of events prior to death.

2. Planned Complex Suicides

2.1. General

The most obvious reasons why several methods of suicide are applied simultaneously are to guarantee death, accelerate death, or cause less pain to the suicidal individual by a planned combination of methods. The latter is especially true when hypnotics or other sedative medications are taken. According to Pollak, the combination of different methods may also be designed in such a way that the second method is only activated when the first method has failed, but then automatically *(14)*.

The individual methods used for complex suicides do not differ from those used in "simple" suicides (in the sense of employing only one suicide method). An international comparison shows at best the typical, regionally different frequencies in the use of the various methods of suicide. For example, firearms are used more frequently in the United States than in European countries. Accordingly, reports on complex suicides using firearms are more often published by US authors *(17,18,20,24,31,32,38,45,54)*.

There is hardly any combination of suicide methods that is not imaginable. However, certain combinations are seen more often than others, which are only rarely employed. For example, sharp-force injuries are relatively rarely seen in planned complex suicides. They are seen more frequently in unplanned complex suicides in which they are the suicide method of first choice but then given up in favor of another method. Since the mid-1990s, numerous reports have been published concerning the combination of ingesting toxic substances and then putting a plastic bag over one's head, mainly in connection with assisted suicide. To what extent all these cases were categorized correctly remains questionable. The number of unrecorded cases of assisted suicide is probably very high.

2.2. Typical Combinations of Methods Applied to Planned Complex Suicides

A typical feature of primary complex suicides is the simultaneous application of two methods of suicide. Since the early 1980s, only one case report on a planned complex double suicide in which more than two methods were applied at the same time has appeared *(41)*. Common combinations are ingestion of hypnotics or other medicaments and hanging, ingestion of hypnotics or other medications and drowning, ingestion of hypnotics or other medications and suffocation by a plastic bag put over the head, use of firearms and hanging (Fig. 1A,B), and use of firearms and drowning *(14)*.

The methods used for committing a planned complex suicide reflect the spectrum of the classical methods of suicide. That the ingestion of hypnotics or other sedative drugs is so common in planned complex suicides seems to be attributable to the fact that this continues to be one of the most frequently used methods of suicide in general *(14,63,66,67)*. One motive for the use of hypnotics or other sedative drugs in primary complex suicides may be the suicidal person's intention to avoid painful suffering as soon as the second method is activated. This appears plausible from the suicidal individual's point of view especially when so-called "hard" methods of suicide (e.g., use of firearms, hanging, jumping from a height) are combined as second method. On the other hand, it seems also worth discussing whether, especially in combination with drowning or suffocation in a plastic bag, the primary intention may have been even death by intoxication *per se*, with the second method serving merely as a safeguard in case that the first method has failed.

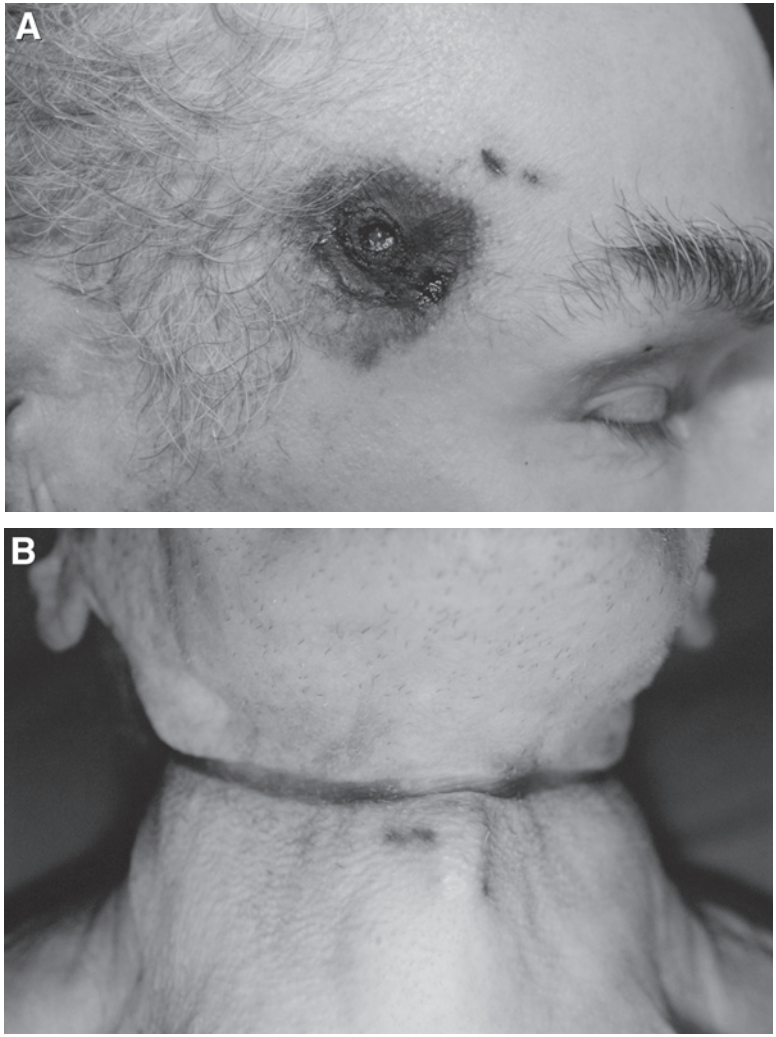

Fig. 1. Planned complex suicide of a 72-year-old man by shot to the head with a modified blank cartridge revolver and hanging. **(A)** Entrance wound on right temple. **(B)** Hanging mark.

In deaths resulting from suffocation by use of a plastic bag, the combination with previous intake of drugs that affect the central nervous system (CNS) is the most common variation in general *(68,69)*. This method of suicide was and still is often recommended by organizations for assisted suicide *(35,47,51,53,68,70,71)*. Especially in the United States, but also in Switzer-

land, a considerable rise in the number of suicides committed in this way has been reported *(68,71,72)*.

Firearms are used almost exclusively by males, both as sole method of suicide *(73–77)* and in combination with other methods *(17,19–21,23,25,26,31–33,38,46,49,54,78)*. Apart from firearms (in the strict sense of this term), several cases of complex suicides using slaughterer's guns have been reported *(14,15,52,56,79–83)*. In the majority of cases, the shot was fired against the head. Typically, this method is often combined with another hard method of suicide such as hanging, traffic accidents, or jumping from a height *(83)*.

3. Atypical Combinations of Methods Applied to Planned Complex Suicides

Atypical planned complex suicides represent not only rare combinations of means of suicide, but also the simultaneous use of more than two suicide methods. The case reports published so far focus mainly on atypical constellations. A survey of the cases published since the early 1980s, with partly unusual combinations of the methods applied, is presented in Table 1.

Those cases in which suicidal individuals inflicted injuries on themselves by firing several firearms at the same time are worth mentioning *(17,20,21,24–26,32,33,54)*. In such cases, the postmortem examination of the deceased must be performed with special attention to the attribution of every single gunshot wound to one of the weapons involved. Moreover, the weapons and the hands firing the shots and, if necessary, also the firing devices specifically constructed, have to be investigated in order to allow reconstruction of the sequel of events.

Another rare combination includes self-incineration. Publications of cases of self-incineration are of more recent date *(27,39,49,52,56,58);* in the earlier literature no information is presented on this subject.

Complex suicides in road traffic also seem to be very rare *(19,31,38,41,80,82,84)*. Although injuries caused by an additional mechanical blunt impact will normally be detected at autopsy, it might be very difficult or even impossible to distinguish especially the fatal combination of ingestion of drugs and trauma in traffic accidents from real accidents. Anyway, it has to be assumed that a high number of suicides in road traffic remains undetected *(85)*.

Table 1
Case Reports Dealing With Planned Complex Suicides Published Since the 1980s

Applied methods	Number of cases	References
Simultaneous shots to the head and/or chest with two different hand guns	*n* = 9	*17,20,21,23,25,26,32,33*
Inhalation of gases (ether, carbon monoxide, chloroform, propane) and suffocation in a plastic bag	*n* = 8	*29,35,40,43,51,94*
Oral ingestion of medicaments and drowning in a bathtub	*n* = 8	*37,48,57*
Gunshot while driving a car	*n* = 7	*19,31,38*
Oral ingestion of medicaments or poisons, respectively, and suffocation in a plastic bag	*n* = 5	*36,53,94,95*
Shot to the head with slaughterer's gun and hanging	*n* = 5	*15,57,79–81*
Self-immolation and jump from a height	*n* = 4	*27,56*
Shot to the head and hanging	*n* = 3	*44,46,49*
Ingestion of hypnotics or drugs, respectively, and strangulation/traffic accident	*n* = 2	*41*
Shot to the head and self-immolation	*n* = 2	*58*
Carbon monoxide poisoning and hanging	*n* = 1	*15*
Carbon monoxide poisoning and ligature strangulation	*n* = 1	*15*
Cut wounds to the neck and self-immolation	*n* = 1	*39*
Explosion of hand grenade and drowning	*n* = 1	*30*
Hanging and electroshock	*n* = 1	*16*
Injection of barbital and oral ingestion of arsenic	*n* = 1	*22*
Ligature strangulation and drowning in a bathtub	*n* = 1	*96*
Ligature-strangulation while driving a car	*n* = 1	*84*
Oral ingestion of medicaments and self-gagging	*n* = 1	*57*
Rectal application of medicines and drowning	*n* = 1	*42*
Self-immolation and hanging	*n* = 1	*49*
Shot to the head and drowning	*n* = 1	*49*

Table 1
(continued)

Applied methods	Number of cases	References
Shot to the head with slaughterer's gun and drowning	$n = 1$	*81*
Shot to the head with slaughterer's gun and self-immolation	$n = 1$	*52,56*
Shot to the head with slaughterer's gun while driving a car	$n = 1$	*80,82*
Stab to the chest and drowning	$n = 1$	*57*
Stab to the chest and hanging	$n = 1$	*57*
	total: $n = 70$	

4. Unplanned Complex Suicides

4.1. General Perspectives

Hofmann and Herber recommended using the term "prolonged suicide" instead of "secondary complex suicide" *(15)*, but this recommendation has not become generally accepted. In fact, unplanned complex suicides do not represent a combined use or a planned combination of several methods, but rather a switch to another suicide method after the first method chosen failed to gain one's end. The reasons for this may be complete failure of the method of first choice, or pain associated with an injury slowly causing death while the suicidal individual is still conscious and able to act. The choice of the alternative method depends more on the concrete availability of the means of suicide than was the case when the suicidal individual chose the initial suicide method. First, the physical capability and the radius of movement may be impaired by the first insufficient suicide attempt, and second, the suicidal person may get under "pressure to succeed" because of the pain and/or the experience of failure. Between the individual's suicide attempts there may also be longer spaces of time. In some cases, the individual may really wreak havoc against his or her own person after the first suicide attempt fails *(15,28,86)*.

In such cases, the forensic pathologist performing the autopsy will also have to answer questions regarding the chronological order of the appearance of injuries as well as how long and to what extent the suicidal individual was capable to act after he or she sustained the injuries.

4.2. Methods of Suicide

Secondary complex suicides are characterized by the primary choice of an inappropriate method of suicide that failed in the first place. This is mostly the case when sharp instruments are used to inflict cuts or stabs. The changes from the infliction of cut wounds to the infliction of stab wounds with the same sharp instrument means a change in the method *(14)*. For this constellation, the change from the often insufficient, nonfatal cuts (in decreasing order of occurrence extremities, neck, head, and trunk) to the infliction of stab wounds that are usually localized in the region of the heart, is typical. In case reports, cuts are described more often than is to be expected according to the theory of probabilities (Table 2). Most of them are wrist cuts. Unsuccessful attempts of hanging as the primary method of suicide can be shown less often. Under forensic aspects, this is possible only if a hanging mark can be demonstrated on the neck. At the death scene, a torn ligature or broken anchorage may point to a preceding attempt of hanging.

In the end, the suicide is committed with an appropriate method. In the study by Pollak, hanging accounted for 37.8% of suicides and was the method most often used *(14)*. Jumping from a height (Fig. 2A,B) was also reported quite often *(14,15,28,34)*.

Unplanned and planned complex suicides often differ in the number of methods used to commit suicide. Among the 19 case reports on secondary complex suicides that have been published in the literature since the 1980s (Table 2), 10 reports describe three or more methods that were chosen and applied one after the other. The highest number of methods used was five *(14,28)*.

4.3. Chronological Order of the Methods Applied

The chronological order of the methods applied can be reconstructed only if all information available on the given case is taken into consideration. Apart from the outcome of autopsy, all traces found at the death scene, as well as the statements of witnesses concerning the sequel of events, if available, are of particular importance in this context. Solely based on autopsy findings a sufficient reconstruction is rarely possible (i.e., in such cases in which there are only two injuries and one of them was nonfatal). As an example, the frequently found wrist cuts, which are mostly located only superficially and rarely deep enough to really open the arteries, may be mentioned. In complex injury patterns, especially if more than three methods of suicide were applied, this may not be possible. In such cases, reconstruction of the sequel of events on the basis of the traces found on the scene is much more promising.

Table 2
Case Reports Dealing With Unplanned Complex Suicides Published Since the 1980s

Number of methods	Methods	Number of cases	References
2	(Attempted) hanging and carbon monoxide poisoning	*n* = 1	*15*
2	Ingestion of acetic acid and ligature strangulation	*n* = 3	*50*
2	Shot to the head and hanging	*n* = 1	*15*
2	Wrist cuts and alcohol intoxication	*n* = 1	*57*
2	Wrist cuts and drowning in a bathtub	*n* = 1	*48*
2	Wrist cuts and shot to the head	*n* = 1	*57*
2	Wrist cuts and shot to the head with a slaughterer's gun	*n* = 1	*80,82*
3	Blows with a blunt object against the head, cuts to the neck, and hanging	*n* = 1	*57*
3	Wrist cuts, attempted hanging, and fall from a height	*n* = 2	*15*
3	Wrist cuts, cuts to the neck, and stab wounds to the chest, the abdomen, and the head	*n* = 1	*15*
3	Wrist cuts, ingestion of hydrochloric acid, and "traffic accident" with a car	*n* = 1	*86*
3	Wrist cuts, shot to the head with blank cartridge pistol, and self-immolation	*n* = 1	*56*
4	Stab wounds to the chest and the head, ingestion of petrol, and jump from a height	*n* = 1	*28*
4	Stabs to the chest, cuts to the neck, (attempted) ligature strangulation, and fall from a height	*n* = 1	*34*
5	"Traffic accident" with a car, wrist cuts, stabs to the chest and neck, ingestion of medicines, and jump from a height	*n* = 1	*28*
5	Attempted hanging, ingestion of medicaments, wrist cuts, stabs to the heart region, and fall from a height	*n* = 1	*14*
		total: *n* = 19	

Fig. 2. Unplanned complex suicide of a 28-year-old woman who jumped from a height after cutting her left wrist. Cause of death was a blunt-force injury to the head. **(A)** Finding situation. **(B)** Superficial hesitation marks and a deeper cut wound on the left wrist.

Table 3
Classification of the Ability to Act

Grade 1	Complex, carefully directed actions that require full consciousness
Grade 2	Instinctive actions that are appropriate to the situation
Grade 3	Reflexes and automatisms also appearing in the unconscious
Grade 4	Incoherent, rapidly exhaustible sequences of movements such as extension spasms

Based on ref. *89.*

As the suicide act is usually performed within a narrow time frame, the usual methods of determining the wound age *(87)* will, in most instances, not provide any additional information regarding the chronological differentiation in the sequel of origin of the wounds.

4.4. Ability to Act

Regarding the ability to act, Petersohn *(88),* as well as Staak and König *(89),* distinguish four grades (Table 3). Immediate incapacitation is to be expected only if central regulatory centers are injured or if blunt trauma to the head leads to loss of consciousness. On the other hand, injuries to the heart, the lungs, or larger vessels in the vicinity of the heart do by no means always result in immediate incapacitation, even if the injuries are eventually fatal. In their retrospective analysis of 37 deaths caused by sharp force, Zimmer et al. observed deaths resulting from exsanguination after sharp-force injury to the heart in which the victim was still able to act (grade 1 to 2) for a mean of 10 to 15 minutes *(11)*. Other authors also reported that the ability to act was partly maintained over prolonged periods of time after sustaining injuries to the heart or brain *(1–4,7,9,89,90)*. If blood loss continues, the ability to act deteriorates more or less slowly until death occurs. There are reports that wounds to the heart were survived for several hours, thus especially in cases in which the left ventricle was penetrated not in its full thickness but for only a few millimeters *(10,91,92)*.

After oral ingestion of larger doses of medicaments or substances that affect the CNS, the ability to act may maintain for quite some time as a result of delayed absorption. Even after the ingestion of poisons with a high efficiency and a rapid onset of action, such as cyanide, there are occasional single reports describing a continued ability to act of up to 10 minutes *(93)*.

References

1. Karger B. Penetrating gunshots to the head and lack of immediate incapacitation. II. Review of case reports. Int J Legal Med 1995;108:117–126.
2. Karger B. Penetrating gunshots to the head and lack of immediate incapacitation. I. Wound ballistics and mechanisms of incapacitation. Int J Legal Med 1995;108:53–61.
3. Karger B, Banaschak S, Brinkmann B. Erhaltene Handlungsfähigkeit bei Gehirnschußverletzung. Arch Kriminol 1997;199:159–166.
4. Karger B, Brinkmann B. Multiple gunshot suicides: potential for physical activity and medicolegal aspects. Int J Legal Med 1997;110:188–192.
5. Missliwetz J. Phänomenologie von Selbsttötungen mit mehrfachen Schußverletzungen. Arch Kriminol 1983;171:143–150.
6. Bohnert M, Ropohl D, Pollak S. Suizidale Stichbeibringung durch die Kleidung. Arch Kriminol 1997;200:31–38.
7. Karger B, Niemeyer J, Brinkmann B. Physical activity following fatal injury from sharp pointed weapons. Int J Legal Med 1999;112:188–191.
8. Lieske K, Püschel K, Bußmann E. Suizid durch 120 Bruststichverletzungen? Arch Kriminol 1987;180:143–149.
9. Thoresen SO, Rognum TO. Survival time and acting capability after fatal injury by sharp weapons. Forensic Sci Int 1986;31:181–187.
10. Wiese J, Maxeiner H. Zweifacher suizidaler Herzstich mit Koronarverletzung. In: Schütz H, Kaatsch H-J, Thomsen H, eds. Medizinrecht—Psychopathologie—Rechtsmedizin. Springer, Berlin, Heidelberg, 1991, pp. 631–639.
11. Zimmer G, Miltner E, Mattern R. Zur Handlungsfähigkeit nach Stich- und Schnittverletzung. Arch Kriminol 1994;194:95–104.
12. Schwarz F. Der aussergewöhnliche Todesfall. Erste Feststellungen am Ort des Geschehens. Enke, Stuttgart, 1970.
13. Holzer FJ. Der kombinierte Selbstmord. In: Schäfer H, ed. Grundlagen der Kriminalistik. Steintor, Hamburg, 1971, pp. 321–352.
14. Pollak S. Statistik und Phänomenologie kombinierter Selbsttötungen und anderer suizidaler Mehrfachschädigungen im urbanen Bereich. Arch Kriminol 1978;161:20–30, 68–81.
15. Hofmann V, Herber F. Über kombinierte und protrahierte Suizide. Kriminal forens Wiss 1984;53/54:83–88.
16. Marcinkowski T, Pukacka-Sokolowska L, Wojciechowski T. Planned complex suicide. Forensic Sci 1974;3:95–100.
17. Fatteh A, Gore SB, Mann GT, Garvin K. Suicide with two guns: a unique case. J Forensic Sci 1980;25:883–885.
18. Hudson P. Multishot firearm suicide. Am J Forensic Med Pathol 1981;2:239–242.
19. Lutz FU, Lins G. Kombinierter Suizid—Zwei Falldarstellungen. Z Rechtsmed 1981;86:145–148.
20. Hudson P. Suicide with two guns fired simultaneously. J Forensic Sci 1982;27:6,7.
21. Lunghi F. Un caso eccezionale di suicidio con due armi da fuoco. Quad Med Leg 1982;4:109–117.

22. Graham MA, Poklis A, Mackell MA, Gantner GE. A case of suicide involving the concomitant intravenous injection of barbital and oral ingestion of arsenic. J Forensic Sci 1983;28:251–254.
23. Marchiori A. Eccezionale caso di suicidio mediante il contemporaneo uso di due pistole. Zacchia 1983;56:409–414.
24. Danto BL, Taff ML, Mirchandani HG. Cases of self-destructive behavior involving multiple methods during a single episode. Am J Forensic Psych 1985;6:38–45.
25. Lucchini G. Su di un caso di suicido mediante due colpi d'arma da fuoco al capo, esplosi da armi diverse. Arch Med Leg Assoc 1985;7:22–28.
26. Lunetta Q, Chiarelli G. Suicidio per esplosione contemporanea di due colpi d' arma da fuoco (con armi diverse) alle regioni temporali. Riv Ital Med Leg 1985;7:1268–1272.
27. Lignitz E, Strauch H. Kombinierter Suizid durch Verbrennen und Sturz aus der Höhe. Arch Kriminol 1986;178:51–53.
28. Markwalder C, Bänziger F. Der protrahierte Suizid als kriminalistisches Problem. Arch Kriminol 1987;180:79–87.
29. Wehr K, Schäfer A. Eine ungewöhnliche Kohlenmonoxid-Intoxikation. Arch Kriminol 1987;180:155–160.
30. Gerling I, Pribilla O. Ungewöhnlicher Tod im Wasser. Arch Kriminol 1989;183:163–167.
31. Murphy GK. Suicide by gunshot while driving an automobile. Am J Forensic Med Pathol 1989;10:285–288.
32. Rogers DR. Simultaneous temporal and frontal suicidal gunshots. Am J Forensic Med Pathol 1989;10:338,339.
33. Gentilomo A, Bogoni A. Duplice colpo d' arma da fuoco al capo. Arch Med Leg Assoc 1991;13:1–6.
34. Schmidt P, Haarhoff K, Hoffmann E. Sekundär kombinierter Suizid unter den Augen der Ehefrau. Arch Kriminol 1991;188:65–71.
35. Avis SP, Archibald JT. Asphyxial suicide by propane inhalation and plastic bag suffocation. J Forensic Sci 1994;39:253–256.
36. Cina SJ, Raso DS, Conradi SE. Suicidal cyanide ingestion as detailed in Final Exit. J Forensic Sci 1994;39:1568–1570.
37. Lichtenwalner M, Tully R. A fatality involving zolpidem. J Anal Toxicol 1997;21:567–569.
38. Murphy GK. Suicide by gunshot while driving a motor vehicle. Two additional cases. Am J Forensic Med Pathol 1997;18:295–298.
39. Grimm U, Sigrist T. Verbrennen im Freien. Arch Kriminol 1998;201:137–145.
40. Kernbach-Wighton G, Pohlmann K, Sprung R. Zur Phänomenologie bei Ether-Applikation. Arch Kriminol 1998;202:87–94.
41. Lasczkowski G, Röhrich J, Bratzke H. Suizidexzeß—Darstellung eines ungewöhnlichen Falles. Arch Kriminol 1998;202:100–108.
42. Musshoff F, Dettmeyer R, Madea B. Tod in der Badewanne—Rektale Medikamentenbeibringung. Arch Kriminol 1998;201:80–86.
43. Nadjem H, Logemann E. Zur Kasuistik der suizidalen Chloroformintoxikation. Arch Kriminol 1998;202:29–37.

44. Pollak S. Zur Typologie der Suizide mit mehr als einer Schußverletzung. In: Strauch H, Pragst F, eds. Rechtsmedizin. Festschrift für Gunther Geserick anläßlich seines 60. Geburtstags. Verlag Dr. Dieter Helm, Heppenheim, 1998, pp. 102–120.
45. Taff ML, Boglioli LR, Danto BL. Planned complex suicide [comment]. Am J Forensic Med Pathol 1998;19:194.
46. Blanco-Pampin JM, Suarez-Penaranda JM, Rico-Boquete R, Concheiro-Carro L. Planned complex suicide. An unusual suicide by hanging and gunshot. Am J Forensic Med Pathol 1999;18:104–106.
47. Giroud C, Augsburger M, Horisberger B, Lucchini P, Rivier L, Mangin P. Exit association-mediated suicide: toxicological and forensic aspects. Am J Forensic Med Pathol 1999;20:40–44.
48. Nowers MP. Suicide by drowning in the bath. Med Sci Law 1999;39:349–353.
49. Cingolani M, Tsakri D. Planned complex suicide. Report of three cases. Am J Forensic Med Pathol 2000;21:255–260.
50. Faller-Marquardt M, Bohnert M, Logemann E, Pollak S. Kombinierte Suizide durch Einnahme von Essigsäure mit nachfolgendem Erhängen. Arch Kriminol 2000;206:140–149.
51. Athanaselis S, Stefanidou M, Karakoukis N, Koutselinis A. Asphyxial death by ether inhalation and plastic-bag suffocation instructed by the press and the Internet. J Med Internet Res 2002;4:E18.
52. Bohnert M, Schmidt U, Große Perdekamp M, Pollak S. Diagnosis of a captive-bolt injury in a skull extremely destroyed by fire. Forensic Sci Int 2002;127:192–197.
53. Grellner W, Anders S, Tsokos M, Wilske J. Suizide mit EXIT Bags: Umstände und besondere Problemlagen bei Sterbebegleitung. Arch Kriminol 2002;209:65–75.
54. Parroni E, Caringi C, Ciallella C. Suicide with two guns represents a special type of combined suicide. Am J Forensic Med Pathol 2002;23:329–333.
55. Schmidt P, Driever F, Lock M, Madea B. Zur Bewertung atypischer Stich- und Schnittverletzungen bei einem kombinierten Suizid. Arch Kriminol 2002;210:28–38.
56. Bohnert M, Rothschild MA. Complex suicides by self-incineration. Forensic Sci Int 2003;131:197–201.
57. Pollak S, Saukko PJ. Atlas of Forensic Medicine. CD-ROM, Elsevier, Amsterdam, 2003.
58. Türk EE, Anders S, Tsokos M. Planned complex suicide. Report of two autopsy cases of suicidal shot injury and subsequent self-immolation. Forensic Sci Int 2003;139:35–38.
59. Dotzauer G, Goebels H, Legewie H. Selbstmord und Selbstmordversuch. MMW 1963;105:973–975.
60. Lindeman SM, Hirvonen JI, Hakko HH, Lonnqvist JK. Use of the National Register of medico-legal autopsies in epidemiological suicide research. Int J Legal Med 1995;107:306–309.
61. Rogde S, Hougen HP, Poulsen K. Suicides in two Scandinavian capitals—a comparative study. Forensic Sci Int 1996;80:211–219.
62. Osuna E, Perez-Carceles MD, Conejero J, Abenza JM, Luna A. Epidemiology of suicide in elderly people in Madrid, Spain (1990–1994). Forensic Sci Int 1997;87:73–80.

63. Grellner W, Kukuk M, Glenewinkel F. Zur Suizidmethode von Ärzten, medizinischem Personal und verwandten Berufsgruppen. Arch Kriminol 1998;201:65–72.
64. Lee CJ, Collins KA, Burgess SE. Suicide under the age of eighteen: a 10-year retrospective study. Am J Forensic Med Pathol 1999;20:27–30.
65. Bennett AT, Collins KA. Suicide: a ten-year retrospective study. J Forensic Sci 2000;45:1256–1258.
66. Fieguth A, Grimm U, Kleemann WJ, Tröger H-D. Suizidmethoden im Sektionsgut des Instituts für Rechtsmedizin der Medizinischen Hochschule Hannover. Arch Kriminol 1997;199:13–20.
67. Scheib K. Kriminologie des Suizids. Selbstverlag, Groß-Gerau, 2000.
68. Haddix TL, Harruff RC, Reay DT, Haglund WD. Asphyxial suicides using plastic bags. Am J Forensic Med Pathol 1996;17:308–311.
69. Bullock MJ, Diniz D. Suffocation using plastic bags: a retrospective study of suicides in Ontario, Canada. J Forensic Sci 2000;45:608–613.
70. Humphry D. Final exit. The practicalities of self-deliverance and assisted suicides using plastic bags. Bantam Doubleday, New York 1991.
71. Marzuk PM, Tardiff K, Hirsch CS, et al. Increase in suicide by asphyxiation in New York City after the publication of Final Exit. N Engl J Med 1993;329:1508–1510.
72. Bosshard G, Ulrich E, Bär W. 748 cases of suicide assisted by a Swiss right-to-die organisation. Swiss Medical Weekly 2003;133:310–317.
73. Druid H. Site of entrance wound and direction of bullet path in firearm fatalities as indicators of homicide versus suicide. Forensic Sci Int 1997;88:147–162.
74. Eisele JW, Reay DT, Cook A. Sites of suicidal gunshot wounds. J Forensic Sci 1981;26:480–485.
75. Koops E, Flüs K, Lockemann U, Püschel K. Tödliche Schußverletzungen in Hamburg 1966–1991. Arch Kriminol 1994;193:14–22.
76. Ropohl D, Koberne F. Tödlicher Schußwaffengebrauch in Friedenszeiten. Beitr Gerichtl Med 1990;48:339–348.
77. Schmeling A, Strauch H, Rothschild MA. Female suicides in Berlin with the use of firearms. Forensic Sci Int 2001;124:178–181.
78. Müller E. Verkehrsunfall und Selbstmord. Arch Kriminol 1965;135:61–69.
79. Wirth E, Markert K, Strauch H. Ungewöhnliche Suicide mit Viehbetäubungsapparaten. Z Rechtsmed 1983;90:53–59.
80. Koops E, Püschel K, Kleiber M, Janssen W, Möller MR. Todesfälle durch sogenannte Bolzenschußgeräte. Beitr Gerichtl Med 1987;45:103–107.
81. Pollak S, Maurer H. Zur klinischen Bedeutung der Imprimate bei Verletzungen durch Schlachtschußapparate. Acta Chir Austriaca 1987;19:29–37.
82. Lignitz E, Koops E, Püschel K. Tod durch Bolzenschußgeräte—eine retrospektive Analyse von 34 Fällen aus Berlin und Hamburg. Arch Kriminol 1988;182:83–93.
83. Nadjem H, Pollak S. Kombinierte Suizide unter Verwendung von Viehbetäubungsapparaten. Med Sachverst 1993;89:29–33.
84. Watanabe-Suzuki K, Suzuki O, Kosugi I, Seno H, Ishii A. A curious autopsy case of a car crash in which self-strangulation and lung collapse were found: a case report. Med Sci Law 2002;42:261–264.

85. Ohberg A, Penttilä A, Lonnqvist J. Driver suicides. Brit J Psychiat 1997;171:468–472.
86. Canale M. L' impiego dell' automobile come mezzo suicidario; considerazioni su un caso singolare di suicidio combinato. Zbl Rechtsmed 1971;2:348.
87. Betz P. Immunohistochemical parameters for the age estimation of human skin wounds. Am J Forensic Med Pathol 1995;16:203–209.
88. Petersohn E. Über die Aktions- und Handlungsfähigkeit bei schweren Schädeltraumen. Dtsch Z ges Gerichtl Med 1967;59:259–270.
89. Staak M, König HG. Handlungsfähigkeit und Verletzungsmuster bei Opfern von tödlichen Schuß- und Stichverletzungen. Beitr Gerichtl Med 1976;35:273–280.
90. Missliwetz J. Ungewöhnliche Handlungsfähigkeit bei Herzdurchschuß durch Schrotgarbe. Arch Kriminol 1990;185:129–135.
91. Große Perdekamp M, Riede UN, Pollak S. Penetrierende Herzstichverletzung mit ungewöhnlich langer Überlebenszeit. Arch Kriminol 2000;206:102–109.
92. Kampmann H, Bode G. Traumatischer Infarkt nach Stichverletzung des Herzens. Z Rechtsmed 1982;88:159–164.
93. Vock R, Magerl H, Lange O, et al. Handlungsfähigkeit bei tödlichen oralen Intoxikationen mit Cyan-Verbindungen. Rechtsmedizin 1999;9:56–61.
94. Lignitz E, Strauch H. Tod durch Plastbeutel—Beitrag zum akzidentellen und suizidalen Ersticken. Kriminal forens Wiss 1986;63:36–49.
95. Große Perdekamp M, Nadjem H, Weinmann W, Pollak S. Plastikbeutel als Mittel der Selbst- und Fremdtötung. Arch Kriminol 2001;207:33–41.
96. Schmidt V, Guggolz M, du Bois R. Ertrinken in der Badewanne nach Drosseln: Fremdtötung, Unfall oder Suizid? Arch Kriminol 1991;187:163–172.

7

Occupation-Related Suicides

Peter H. Schmidt, MD, Stephan A. Padosch, MD, and Burkhard Madea, MD

Contents

Summary

This chapter focuses on occupation-related peculiarities of suicides. It is intended to elucidate problems that may arise in occupation-related suicides and to provide approaches and solutions for practical forensic casework. A number of suicides with outstanding occupation-related features observed by the authors are presented and compared with analogous observations reported in the literature. Several common characteristic features related to the respective occupational background can be derived from those case reports. Among others, characteristic features comprise availability and easy access to the used tools (e.g., drugs, poisons, special equipment, self-constructed machinery). Furthermore, special knowledge and skills provided by the suicidal individual's occupational background and practice are applied (e.g., injection and dissec-

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

tion techniques as seen in physicians and related professions or the use of extraordinary self-constructed weapons by technicians). As for adequate interpretation of autopsy findings, patterns of injury initially not in line with criteria of self-infliction often can be interpreted correctly when taking occupation-related modification of an usual suicide method into consideration. With special regard to outcome of toxicology, appropriate consideration of the suicidal individual's profession may focus attention on rare and uncommon toxic agents that are usually not taken into account and that are not detected when only routine toxicological screening methods are employed. Suicides with occupation-related backgrounds usually present with highly individual and uncommon modes of commitment and peculiar forensic pathological findings that are difficult to recognize and assess. Supplementing the experience by case reports provided in the literature is an indispensable prerequisite to handling cases of occupation-related suicides in a professional and competent way.

Key Words: Suicide; occupation; modus operandi, intoxication; self-infliction; bolt gun; nail gun; suicidal explosions; anesthetics; incision of blood vessels; electrocution; electric current; death scene investigation; combined suicides; injury pattern; cyanide; insulin; guillotine; professional knowledge; self-constructed shooting device.

1. Introduction

Typical examples of occupation-related suicide methods have already been mentioned in earlier medicolegal textbooks, with special emphasis on the tools employed as well as the modes of commitment. Such knowledge can provide valuable tools for practical casework in terms of the reconstruction of suicides and correctly determining the mode of death.

In his renowned German textbook of forensic medicine, Mueller described 20 occupation-related kinds of knots used in cases of suicidal hanging, for example, "fisherman's knot" and others *(1)*. The criminological importance of "occupation-specific knots" is reflected by their contribution to the forensic reconstruction of the implementation of suicide *(2,3)*. Prokop published examples of occupation-specific anatomic localizations and the transection of blood vessels in suicides that were committed by physicians as well as the usage of bolt guns in agricultural workers *(4)*. Moreover, it has been repeatedly emphasized that health care professionals, especially, commit peculiar kinds of suicide by using highly efficient therapeutical drugs or substances,

which, in many cases, cannot be detected by routine toxicological methods. In these cases, the key for a successful elucidation of the used method of suicide lies in a meticulous investigation of the death scene and other circumstantial evidence with special regard to a possible occupation-related background *(5–8)*.

This chapter provides an overview of case reports on occupation-related suicide methods, focusing on modus operandi and characteristic forensic pathological findings. To begin with, case reports of occupation-related suicides that were encountered at the Institute of Legal Medicine, University of Bonn, Germany, are presented. In these cases a careful evaluation of the decedents' occupation or previous professional career markedly contributed to the final diagnosis and solving of the cases in question. Furthermore, an overview of the earlier and current literature on the subject is provided. Finally, common characteristics of the presented cases in the light of the literature are summarized. As a matter of fact, a large collection of well-documented case reports is a basic requirement for a competent and well-founded analysis of such peculiar cases in practical casework.

2. Case Reports

2.1. Case 1

A 38-year-old goldsmith was found dead by his wife in his workshop's bathroom. He was lying between the door and the toilet bowl in a left-sided prone position. A puddle of blood was found around his head. The physician who was called for the certification of death diagnosed a lethal head injury resulting from a fall. At autopsy, injuries of the skull and brain were excluded. A massive hemorrhagic edema of the lungs was determined as the origin of the puddle of blood. Further police investigations disclosed that a half-emptied small box labeled "Gilding bath 2000—toxic" was found in the deceased's jacket. Furthermore, the man had a previous history of a psychiatric disorder. The weekend before his death, he had moved out of a conjoint domicile. Toxicological investigations revealed that the small box contained pure cyanide, rather than any gilding substance. Analysis of samples obtained at autopsy confirmed a lethal cyanide intoxication with a blood cyanide concentration of 80.9 mg/L. Thus, a fatality initially assumed to be an accident was actually proven to be a suicide.

2.2. Case 2

A 23-year-old female botany student and a 19-year-old male had prepared a tea from yew needles (*Taxus baccata*) to commit suicide. In a police report that described the findings at the death scene, cups with remnants of the needles were mentioned. At autopsy, particles of green, needle-shaped leaves were noted in the mouth and the esophagus of the deceased. Applying gas chromatography/mass spectroscopy methods, taxicatin and its agylcon phloroglucinedimethylether (3,5-dimethoxyphenol) were detected in autopsy blood samples, confirming a lethal suicidal ingestion *(9,10)*.

2.3. Case 3

A 34-year-old gardener was found by relatives dead on his bed. At investigation of the death scene, bluish-purplish marks were noticed on the edge of the bed. Additionally, a flasket with a bluish content was found on a table. At autopsy, approx 100 mL of a bluish-greenish liquid were found in the man's stomach and bluish particles were present in his duodenum and jejunum. The mucosa of the upper lip was cauterized. Apart from a blood ethanol concentration of 217 mg/dL, gastric contents and blood were shown to be positive for organophosphates, namely the insecticide parathion; the characteristic parathion metabolite *p*-nitro phenol was detected in urine samples. A fatal suicidal parathion ingestion was determined as the cause of death.

2.4. Case 4

A 26-year-old intensive care unit (ICU) male nurse was found dead by his girlfriend, lying in his bed in a prone position. According to police investigations, he had abused diazepam previously, which he had stolen from the ICU until one year ago. He was reported to have consumed marihuana occasionally. In one pocket of the deceased's trousers an empty flasket of tramadol was found. In the following, tramadol was detected in peripheral venous blood (9.6 mg/l). An intoxication as a result of this opiate derivative was stated as the cause of death.

2.5. Case 5

A 21-year-old pediatric nurse was found dead in her parents' bathtub. Her nostrils were above the water level and there were no hints toward possible electric conductors, nor were there any signs of current marks or of other external violence. At autopsy, a white-waxy material was found in the perianal region and up to 5 cm deep within the rectum. Toxicological analysis

revealed that this paste was a mixture of diazepam, tetrazepam, and phenobarbital, administered by a rectal mode of application. Accordingly, these substances and their metabolites were detected in femoral venous blood (diazepam 500 ng/mL, nordazepam 65 ng/mL, tetrazepam 180 ng/mL, and phenobarbital 9.4 mg/L). As severe complications of the drug intoxication, agonal bilateral pneumonia and cardiac failure had developed *(11)*.

2.6. Case 6

A 56-year-old "skilled craftsman" who had attempted to commit suicide several times before was found dead in his car. The upper part of his body was leaning at the door next to the front passenger's seat. In the foot well, a metal construction consisting of tension springs and a 14-cm long tube was found (Fig. 1A,B). Blood spatters were present on the inner side of the front windowshield and on the dashboard. A projectile was recovered from the seat. Autopsy revealed a lethal gunshot wound to the chest. The entrance wound had an uncharacteristic morphological appearance with a secondary laceration-like enlargement. Moreover, a patterned abrasion ring that corresponded to the diameter of the metal tube was detected (Fig. 1C *[12]*).

3. Further Case Reports and Larger Series of Occupation-Related Suicides Reported in the Literature

As for occupation-related suicidal intoxications, the use of thiopentone has repeatedly been reported *(13–16)*. Thiopentone is a short-acting barbiturate, which is administered intravenously to produce complete anesthesia of short duration or to induce general anesthesia. The suicidal individuals in these cases included anestheologists *(13,15)*, surgeons *(15)*, nurses *(14,15)*, and fire-rescue paramedics *(16)*. As a rule, thiopentone was self-administered intravenously via infusion and the intravenous catheter was professionally held in position by a strip of adhesive strapping *(13,15,16)*. A particular morphological finding was the adhesion of multiple white, star-shaped crystals to the endothelium of the right ventricle, which was attributed to the high concentration of thiopentone in the infusion *(16)*. Lesions of the endothelium were considered as cytotoxic side effects and were most prominent after circulatory arrest in the agonal and supravital period with high concentrations of thiopentone damaging the endothelium *(17)*. Additionally, several case reports of suicides by intravenous self-administration of neuromuscular blocking agents by physicians or nurses who were professionals in the clinical discipline of anesthesia have been published *(18–20)*.

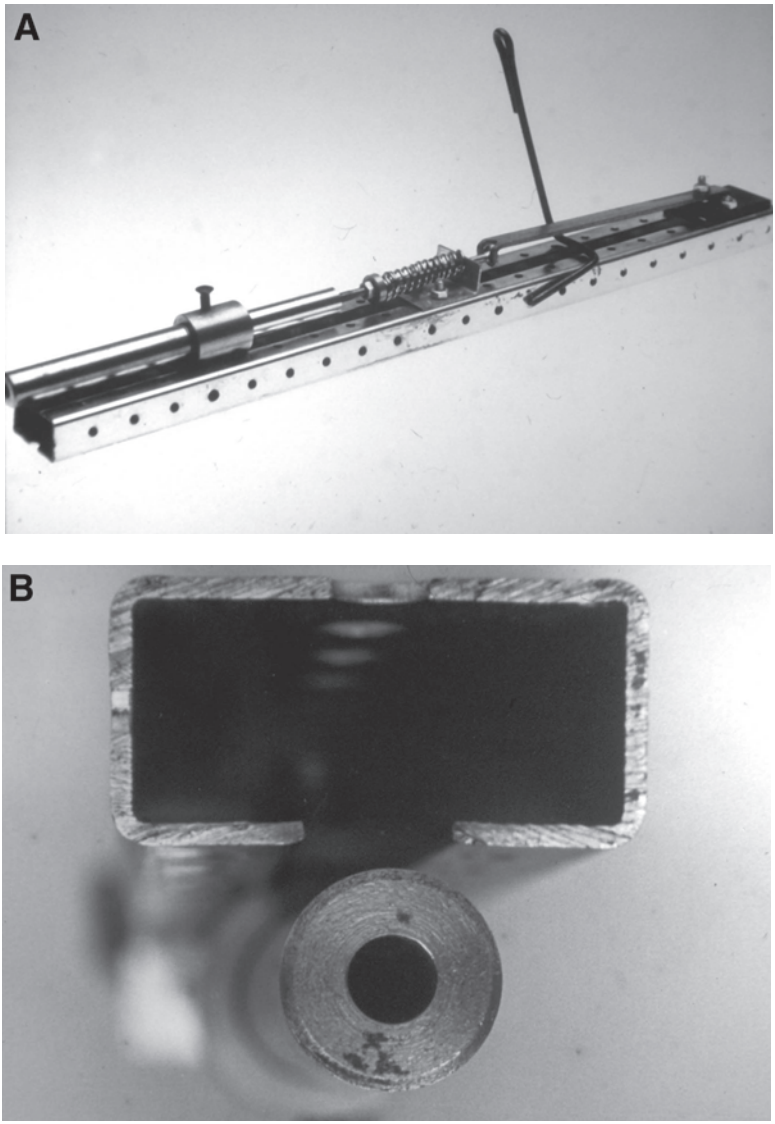

Fig. 1. Suicide of a craftsman. **(A)** Self-made peculiar shooting device using commercially available components arranged on a light metal bar. **(B)** Characteristic appearance of the muzzle of the self-constructed shooting device. **(C)** Entrance wound on the chest. Patterned abrasion corresponding to the self-constructed shooting device's muzzle imprint.

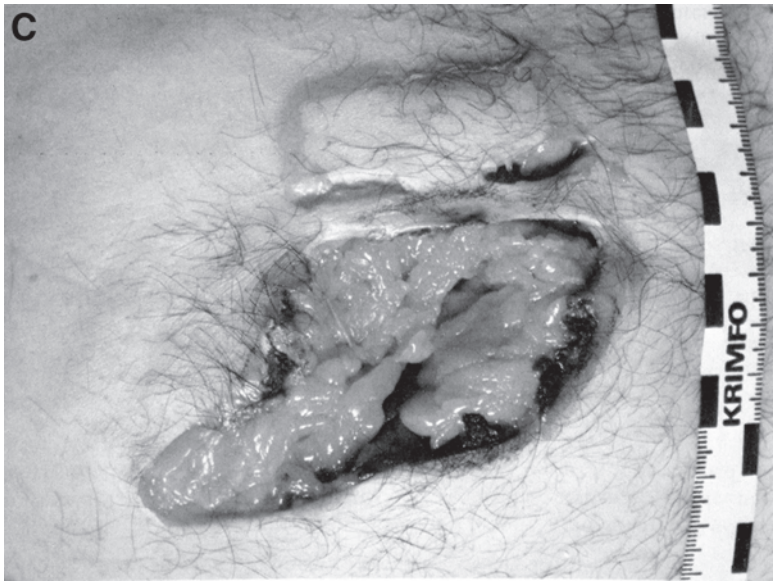

Fig. 1. *Continued*

More recently introduced agents for anesthesia have also been used for suicide, for example, propofol (Diprivan®), a highly lipophilic intravenous sedative-hypnotic agent with fast onset. Adverse reactions resulting from overdosage may include respiratory depression, hypotension, and convulsions. One of the first fatalities associated with self-administration of propofol reported in the literature involved a female hospital radiographer who had injected the agent into a vein in the dorsum of her right foot. Using high-performance liquid chromatography, a postmortem concentration of 0.22 mg/L propofol was detected in femoral blood. The coroner in charge considered this fatality to be an accidental overdosage *(21)*. In the following, the suicides of an anestheologist and a surgeon by infusion of propofol were reported *(22)*. In comparison with the accidental fatality mentioned previously, substantially higher levels of 3.9 and 9.7 mg/L propofol, respectively, were found in femoral blood. Likewise, pharmacists and nurses have access to agents, such as insulin, that exert regulative effects on metabolism, and thus they can employ these substances to commit suicide *(23,24)*. When exogenous insulin administration is used to commit suicide, the postmortem examination has to include the following: (a) investigation of a tissue sample from the injection site using immunohistochemistry or a radioimmunoassay, (b) determination of the concentration of insulin in relation to the concentration of C-peptide to prove an

exogenous route of administration, and (c) analysis of Hb-A_{1c} and fructosamine to exclude a preexisting diabetes mellitus.

The side effects of overdosage of therapeutical drugs may also be used to commit suicide. A 20-year-old female doctor's assistant secretly ingested approx 20 tablets (containing 300 mg each) of the class Ic antiarrythmic drug propafenone. Following ingestion, she remained under the supervision of the physician with whom she worked. She developed electrocardiographic abnormalities, loss of consciousness, and cardiac failure and died about 6 hours later *(25)*.

Case reports *(26)* and the retrospective analysis of lethal cyanide concentrations covering a period of 40 years *(27)* indicate that the intoxicated victims are mostly adults who had professional access to various cyanogenic compounds (65% of the cases) and had ingested them with the intention to commit suicide. The professions encountered included chemical workers, scientists, chemists, pharmacists, goldsmiths, photographers, glassblowers, and disinfectors. Nine percent of the suicidal individuals were found dead at their workplace. Besides unspecific findings of an underlying intoxication, about 15% of the deceased showed injuries attributable to an agonal fall.

Veterinarians and their laboratory assistants have been reported to commit suicide by infusion of veterinary euthanasia agents, that is, "lethal" (ingredients: amobarbital, pentobarbital, isopropanol, and polyethylene glycol-200) (*28*) or embutramid, an active substance of "T-61" *(8)*.

Further peculiarities related to the occupation of the victim comprise the ingestion of metallic arsenic by a chemistry student *(29)*, the ingestion of sodium azide by a laboratory assistant *(30)*, the intravenous injection of salad oil (resulting in fat embolism) by a nurse *(31)*, and self-poisoning with carbon monoxide by a process engineering student who employed a self-constructed apparatus producing carbon monoxide by the reactions of formic acid and sulfuric acid *(32)*. A 57-year-old psychiatrist performed suicide by insufflating a powder from a chemical fire extinguisher into his respiratory and gastrointestinal tract, inducing death not by mechanical asphyxia but by vagally mediated asystole *(33)*.

In a case series of six suicidal intoxications clearly related to the occupational background of the victim, the decedents included a veterinarian, three nursing personnel members of a hospital, and two laboratory assistants *(34)*. The substances applied comprised the narcotics thiopentone (Trapanal®, Pentothal®) and ketamine (Ketanest®), the neuromuscular-blocking agent succinylcholine, insulin, a veterinary euthanasia agent, and finally numerous toxic chemicals for laboratory use (sodium azide, acrylamide, etc.). These substances would not have been detected during routine toxicological analysis but were

identified on the basis of taking into account the occupations of the deceased. As a result, additional toxicological analyses were performed. The toxic agents were administered via an intravenous route of application in two cases and via infusion in a further case in which the syringe inserted at an anatomically unusual location, namely into a vein on the dorsum of a foot *(34)*.

Retrospective analysis of the autopsy cases of the Institute of Legal Medicine in Munich, Germany, over the time period 1976–1994 regarding suicides by self-injection of toxic agents revealed 36 respective cases involving physicians, nurses, and other health care professionals in 78% of the fatalities *(35)*. Anesthetics and related drugs, like benzodiazepines or barbiturates, were most commonly used in this series. The injection marks were predominantly localized above veins in the cubital fossa or the forearm, but in four cases the drugs were injected into the subcutaneous adipose tissue.

When compared to controls, in a series of 31 suicides committed by physicians, medical personnel, and related professions, infusions and injections (anesthestetists) and cyanide poisoning (chemical personnel) were overrepresented *(36)*. Another rare, but characteristic mode of suicide employed by physicians in this study was the incision of blood vessels. As illustrated by brief case reports, physicians in particular used local anesthetics and heparin to reduce the pain associated with the incision and to prevent clotting of the blood, respectively. The authors concluded that the tendency to apply a method related to the occupation increased with the individual's degree of professional specialization, most probably as a result of a more detailed knowledge and easier access to "appropriate" drugs, xenobiotics, and other substances *(36)*.

As early as 1923, the Austrian Haberda published a report dealing with the suicide of a physician who had opened his rigid and meandering temporal arteries, in addition to his cubital vessels *(37)*. Moreover, this author reported on another physician who committed suicide by cutting his right femoral vessels with a sharp scalpel. Four cases of surgeons who incised their femoral arteries for suicidal purposes showed common features, culminating in the case of a surgeon who administered local anesthetics to both his groins, then dissected both his femoral arteries and incised one, before he finally put an inhalation anesthetic-soaked dabber on his face and died *(38)*.

In a similar manner, a former autopsy assistant administered a local anesthetic subcutaneously into both his groins and inflicted cuts there. Finally, he committed suicide by cutting his left radial artery without previous local anesthesia *(39)*. Such an incision of radial arteries is another interesting feature of suicide committed by medical personnel. Usually, during the respective surgical procedures, the radial arteries are opened in a transverse direction. However, on lengthwise opening the chances for life-threatening injuries

increase and, in addition, blood loss is not subject to physiological self-limitation as a result of rolling of the intima, as it is often the case after transverse cuts *(6,39)*.

In this context, another interesting observation merits mentioning: a medical student performed lengthwise cuts of both forearms in the proximity of the radial arteries, finally cutting through both vessels in a transverse direction. Signs of prior local anesthesia were obvious. Several injection marks were noted in the proximity of the above-mentioned lesions. Moreover, disposable syringes, needles, and an empty box of the local anesthetic Impletol® (procaine hydrochloride) were found at the scene *(40)*. In another case, a 30-year-old nurse carried out suicide by opening one of her radial arteries that was located in an anatomical superficial variant as a result of an iatrogenic damage that occurred during surgery 1 year before *(41)*.

Another important group of occupation-related suicides is represented by technical professionals using self-constructed shooting devices. A plumber committed suicide in the course of a psychiatric disorder with a self-constructed shooting device that was made of an 84-cm long copper tube that was closed on one side and ignited by the heat of an oven *(42)*. A 34-year-old engine fitter shot himself with a self-constructed front loader. He plugged one end of a water pipe, used a cylindrical lead shot, special black powder (about 4 g of a powder that he had obtained from fire-crackers with admixture of aluminum), and ignited the weapon in front of his chest. He died immediately of the shot injury. The missile retained in the chest and the weapon "flew away like a rocket." Unused projectiles and powder as well as the undamaged pipe allowed the reconstruction of the modus operandi in this case *(43)*.

The dangers of signal-pistols and their ammunition in an occupation-related context is illustrated by the unusual suicide of a ship owner. He shot a signal cartridge to his head, which penetrated the skull and then entered the brain. The burning-out of the signal-set took about 10 seconds, subsequently causing burning of the flat *(44)*.

As a matter of fact, in practical casework, more complex self-constructed devices or bizarre usage of common tools are often encountered. A 50-year-old plumber performed suicide in his car by self-inflicting a contact shot to his left chest with a nail gun. The nail gun caused a peculiar slit-like entrance wound and a penetrating myocardial injury. The characteristic morphological features included an outer "muzzle imprint," corresponding to the front side of the nail gun, and an inner "muzzle imprint" caused by the nail itself *(45)*.

A 21-year-old unemployed mechanic committed suicide with a self-constructed "guillotine." He had manufactured a metal construction according to his own technical plans in a locksmithery, allegedly a sporting device. In the

following, he installed a blade with attached weights. Cause of death was exsanguination from the individual's injured right carotid artery *(46)*. Such suicidal decapitations are only observed rarely as a result of the fact that the complex construction of appropriate tools (e.g., a guillotine) demands specific skills and at least a certain space of time for the construction, which bears danger of discovery.

Eyewitnessed suicides of workers in carpenter's workshops who used bandsaws to saw off the superior part of the skull directly above the ears or to transect the neck have been reported as well *(47)*. The choice of this bizarre mode of suicide was supposed to be related to the professional knowledge of the danger associated with the operation of these machines.

Suicides of miners, workers in quarries, and blasters working in civil engineering who employed explosives to commit suicide have been reported repeatedly. Usually, the explosives were put into the oral cavity or located close to the head by the suicidal when ignition took place *(48–53)*. In general, in suicidal deaths caused by explosives the modus operandi reflects familiarity and proficiency, or at least a certain degree of specialized technical knowledge, with the use of explosive devices *(53)*. Determining whether the mode of death is suicide, homicide, or accident in explosion-related fatalities can present an especially difficult task for the forensic pathologist. In a case report from the former Hungarian Democratic People's Republic, a 21-year-old army sergeant blew up his car with a self-constructed detonator and TNT (2,4,6,-trinitrotoluol) which he had stolen from a military shooting range *(54)*.

Suicidal self-application of electric current (electrocution) can be regarded as one of the most rarely used methods of suicide *(55–58)*. The frequency is reported to be about less than 1% *(59)*. Among other things, the reasons for this might include a pseudo-mystic dread of a "mysterious power" *(55,58)*. Conversely, sources of electric current are often localized in restricted areas, giving rise to concerns of the suicidal person being discovered or having unwanted observers *(55)*. The rare usage of direct current (DC; 220 V) can be explained by the fact, that its lethal effects are almost unknown to laymen unfamiliar with electrotechnical matters *(56)*. In principle, four ways of commitment of suicidal electrocution can be distinguished *(55,57,58)*:

1. The individual climbs up a pylon and subsequently touches the high-voltage power line with both hands.
2. The individual fastens a wire around his or her wrist. The loose end, aggrieved with any heavy object, is thrown over the high-voltage power line.
3. The individual connects him or herself to a regular power supply system with two wires.

4. The suicide is atypically committed with outstanding bestiality or applying a highly sophisticated method.

The latter two methods are regarded as expression of at least a certain degree of special knowledge and proficiency with electrotechnical matters. Therefore, suicide by electrocution is widely regarded as a characteristic example for an occupation-related suicide, except when performed in the bathtub *(58–60)*. However, retrospective analyses have shown a previous occupational relationship to electricity in about 20% of the victims *(56,57)*. Nevertheless, in the remainder a remarkable private interest in electricity and electrotechnical issues was recognized *(56,61–63)*. The following typical features were observed: for the most part DC (220 V) or low-voltage alternating current (50 Hz) were used *(59,60)*; typical sources were power outlets, sockets, or otherwise modified electrical devices *(56)*.

In many cases, keys, coins, self-constructed electrodes, or similar objects serve as subtle conductors. Alternatively, electric cables are attached to the extremities or other peculiar localizations, like the neck *(58,60,63)*. In one case, the conductors were connected to metallic buckets filled with water and the suicide victim put his hands into the water *(62)*. Electrodes are usually attached in proximity to the heart or on the extremities, thus to ensure a direct impact of the current flow on the myocardium *(58–60,63,64)*. Complex circuits including clocks and time switches can be employed to ensure a fast and painless death *(63,64)*. Furthermore, a long-acting current with subsequent overcoming of the cutaneous resistance is often applied to guarantee fatal outcome *(58)*.

Sometimes, even special precautions are taken to enable the suicidal to switch on the current from a certain distance *(59)* or to prevent fuses from blowing and short circuiting, respectively *(58)*. Therefore, complex findings at the death scene often provide valuable hints toward the cause of death. In the majority of cases of suicidal electrocutions, a thorough scene investigation will enable the death investigator to definitively differentiate between a suicidal and an accidental mode of death *(56,59,64)*. Further relevant criteria comprise witness reports, farewell letters, the finding of the deceased in a remote place (no disturbance, late discovery), specialized technical skills of the deceased, comprehensive preparations *(60)*, and a resolute modus operandi *(57)*.

Regarding suicidal usage of bolt guns, controversial theories exist in the literature. According to earlier theories, such devices are used predominantly by male individuals who are used to handling them at their workplace. These individuals would include butchers, farmers, veterinarians, and others in related

occupations *(65–67)*. Accordingly, in a larger series of suicides carried out with bolt guns, 14 cases involved butchers and 7 involved individuals who were working in the building trade *(68)*. Contrary to that, it is often argued that these devices are freely available and easy to handle and therefore, the employment of bolt guns to commit suicide is also encountered in persons who are not professionally used to such devices *(69)*.

Typical injuries caused by bolt guns are characterized by a punched cutaneous defect corresponding to the diameter of the captive bolt pistol, symmetrically localized powder burns as a result of propellant gas-outlets, and the lack of an exit wound *(67,70)*. However, atypical injuries can be found especially in cases involving manipulated livestock stunners *(69)*, devices that are intended to cause unconsciousness and analgesia of livestock. Removal of the spiral spring that is responsible for retraction of the bolt may result in the remaining of the anterior part of the bolt within the skull cavity *(69,71)* and elongation of the bullet track *(72)*. In such cases, the entry wound is usually found in the center of the forehead *(73)*. More rare localizations of the entry wound include the right temple, the pariteal region *(74)*, the left temple, and the back of the head *(73),* as well as the heart *(75)*. Possible reasons for these preferentially chosen localizations include the practical handling of bolt guns requiring both hands *(75)*. Besides, individuals used to the professional employment of livestock stunners may aim at these effects when committing suicide *(73,75,76)*.

Suicides with multiple entry wounds as a result of bolt guns and livestock stunners have been reported *(67,77,78)*. Determining the mode of death as "suicide" unequivocally requires maintenance of capacity to act after infliction of the first injury, especially when the weapon has to be reloaded. This may be possible especially in cases in which at first only the frontal lobes of the brain are injured *(67,73,78)*. Additionally, combined suicides including bolt gun injuries have been reported, most frequently in combination with hanging *(73,75)*. Rarities comprise a butcher's suicide with a livestock stunner following the unsuccessful attempt to dissect his radial arteries *(79)*. In another case, the use of a bolt gun was combined with final drowning *(80)*.

Vehicles used for professional purposes have also been reported to be used for suicide. A 23-year-old unemployed pilot approached the airport with his plane without the landing gear down, crossed over the runway at an acute angle, and leveled out at a height of 5 m before crashing into the office of an airline company. Shortly before the crash, he had been noted to sing hymns and having said "it is better to die with honor than live with dishonor." Regarding the personality of the pilot, a history of aggression, an impulsive way of acting and intolerance of frustration was reported. His personality was markedly

determined by fantasies adopted from a cinematic caricature of a World War II tactical aircraft pilot *(81)*.

4. Discussion

Particularly suicides committed by ingestion of toxic agents are highly related to the individual's professional background *(34)*. A number of case reports have established that especially in cases of sudden, unexpected deaths of health care professionals, extraordinary modes of committing suicide, in particular the use of highly toxic drugs, must be taken into consideration, too *(6–8,22,25)*. Several characteristic features related to the respective occupational background can be derived from these case reports. At first sight, the fact that the occupation renders the suicidal individual to gain access to drugs, chemicals, or other toxic substances, which are not usually available, appears rather trivial. However, in practical forensic casework, the appropriate consideration of the individual's occupation may focus attention on rare (toxic) agents, which are usually not taken into account at first sight and would not be detected when routine toxicological screening methods are applied only. Thus, in cases with a high index of suspicion of an underlying intoxication with an unusual substance, routine toxicology screening methods have to be supplemented by additional more specific methods for the detection of such specific substances *(9,10,34)*. Additionally, such suicides involving health care professionals are characterized by a distinct knowledge of the (most often rapid) onset of action, efficiency, and active principles of the respective substances. Accordingly, two groups of suicidal individuals can be distinguished *(34)*. The first group comprises laboratory assistants, technicians, and related professions choosing toxic substances without any further subtle pharmacological knowledge beyond the sole fact of "toxicity" of the substance. The second group comprises individuals with a much more sophisticated expertise on pharmacodynamics and pharmacokinetics, choosing a "suicidal concept" that guarantees fatal outcome.

Given these considerations, the observed prevalence of certain substance groups seems comprehensible. In particular, the following aspects merit special emphasis. Physicians, especially anestheologists, have repeatedly been reported to use anesthetics and muscle relaxants for suicidal purposes. Moreover, physicians may avail professional knowledge of harmful side effects, whereas the knowledge of medical laymen is usually restricted to the sole therapeutic benefit of these substances. Finally, metabolically active substances and hormones such as insulin are sometimes used by health care professionals with suicidal intention *(6,22,25,35,36)*.

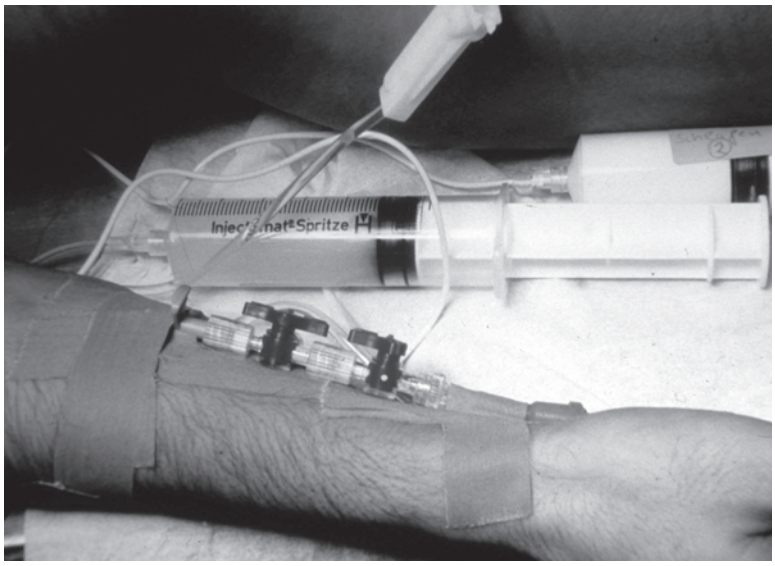

Fig. 2. Suicide of an anestheologist. Death scene findings. Intravenous access to right cubital vein and professional infusion set including two three-way stopcocks and syringes (note the upper syringe containing milky propofol emulsion).

Besides influences on the choice of highly potent (toxic and efficient) substances, professional knowledge and skills also determine extraordinary routes of administration, for example, rectal application *(11)* and other modes of application such as intramuscular injections or intravenous injections into veins at the dorsum of the foot. Furthermore, the usage of infusion sets *(6,8,15,22,34–36)*, or self-constructed application devices (Fig. 2) has been observed occasionally in the death investigator's practice *(32)*.

In analogy, frequently used modes of carrying out suicide may be modified in association with occupation-specific knowledge and skills (e.g., transsection of arteries). Here, special knowledge of anatomy and surgical practice enables the suicidal victim to inflict him or herself highly efficient injuries at surgery-specific locations *(6,38,39,41)*, in some cases combined with the administration of local anesthetics prior to the incision *(38–40)*. Interestingly, patterns of injury, which are, at first sight, not in line with the criteria of self-infliction (Fig. 3), can sometimes be interpreted correctly in a later stage of death investigation when evaluated under aspects of occupation-related modifications of a usual suicide method *(40)*. As a matter of fact, specialized sophisticated knowledge is often encountered regarding peculiar

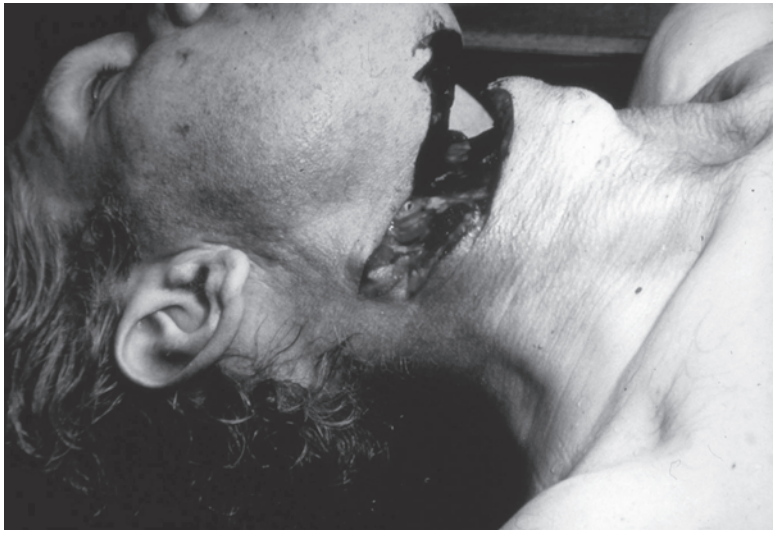

Fig. 3. Suicide of a sheperd by inflicting a large-incised wound to the neck, initially raising suspicion of homicide. Note the lack of hesitation marks. The deep incised wound resulted in incision of the right common carotid artery. This way of cutting is a common slaughtering technique for sheep, killing them by exsanguination.

shooting devices constructed by technicians and related professions *(12,42,43)*. In analogy, similar considerations should be taken into account when dealing with self-constructed devices for suicidal electrocution in electricians and related occupations (Fig. 4).

In conclusion, practical forensic casework demands the following:

- Adequate evaluation and interpretation of findings at the death scene potentially providing relevant links for further considerations *(8,12,32,35,42)*.
- Sophisticated reconstruction of the case in question *(42,43)*.
- Appropriate assessment of atypical injury patterns *(12,40)*.
- Application of a thorough toxicological analysis *(9,10)*, if necessary.

A proven association between professional abilities and peculiarities of carrying out a suicide offers the chance to determine the mode of death as suicide beyond any reasonable doubt. In suicides with a highly specialized occupation-related background, often outstanding finesse and subtlety of the chosen modus operandi are encountered, each representing a great challenge for forensic pathologists and other death investigators. Therefore, the com-

Fig. 4. Suicidal electrocution. For the application of current an unusual self-constructed power source was used in this case.

prehensive assessment and understanding of a particular case demands an adequate intellectual approach as well as detailed expertise and knowledge of the features in which occupation-related suicides may present.

References

1. Mueller B. Erstickung. In: Mueller B, ed. Gerichtliche Medizin, Vol. 1, 2nd ed. Springer Verlag, Berlin, Heidelberg, New York, 1975, pp. 439–468.
2. Püschel K, Holtz W, Hildebrand E, Naeve W, Brinkmann B. Erhängen: Suizid oder Tötungsdelikt? Arch Kriminol 1984;174:141–153.
3. Hausmann R, Schellmann B. Suizidales Erhängen oder Tötungsdelikt? Arch Kriminol 1995;196:12–17.
4. Prokop O, Radam G. Atlas der gerichtlichen Medizin. VEB Volk und Gesundheit, Berlin, 1987, pp. 290, 512.
5. Junge M, Tsokos M, Püschel K. Suicide by insulin injection in combination with beta-blocker application. Forensic Sci Int 2000;113:457–460.
6. Schneider V, Klug E. Suizid durch Muskelrelaxantien. Beitr Gerichtl Med 1979;37:230–233.
7. Schneider V. "Hand an sich legen..." Suizid—Selbstmord, Selbsttötung, Freitod. Kriminalistik 1979;8:350–356.
8. Wagner K, Schneider V. Suizid mit einem Tiertötungsmittel. In: Bauer G, ed. Gerichtsmedizin. Festschrift für Wilhelm Holzcabek. Deuticke, Wien, 1988, pp. 245–248.

9. Jacob B, Mußhoff F, Plenge B, Demme U, Fowinkel C, Daldrup T. Demonstration of 3,5-dimethoxyphenol as marker for an intoxication with Taxus baccata ingredients in a case of suicidal yew leave ingestion. In: Jacob B, Bonte W, Daldrup T, Heller H, Mußhoff F, eds. Advances in Forensic Sciences, Vol. 5. Verlag Dr. Köster, Berlin, 1995, pp. 86–89.
10. Mußhoff F, Jacob B, Fowinkel C, Daldrup T. Suicidal yew leave ingestion—Phloroglucindimethylether (3,5-dimethoxyphenol) as a marker for poisoning from Taxus baccata. Int J Legal Med 1993;106:45–50.
11. Mußhoff F, Dettmeyer R, Madea B. Tod in der Badewanne—Rektale Medikamentenbeibringung. Arch Kriminol 1998;201:80–86.
12. Seehafer K, Madea B, Heinze U. Suizid mit einem selbstgebauten Schußapparat. Beitr Gerichtl Med 1991;49:201–209.
13. Bruce AM, Oliver JS, Smith H. A suicide by thiopentone injection. Forensic Sci 1977;9:205–207.
14. Noirfalise A. Fatal intoxication by thiopental. Forensic Sci 1987;11:167.
15. Nováková E, Vecerková J. Über den Thiopentalnachweis in biologischem Material. Arch Toxicol 1974;32:313–320.
16. Schneider V, Klug E. Auskristallisiertes Thiopental im rechten Herzen bei suizidaler Vergiftung. Arch Kriminol 1979;164:89–92.
17. Lieske K, Püschel K, Schmoldt A. Ungewöhnliche Intima- und Endokardschädigung nach suizidaler Infusion von Thiobutabarbital. Z Rechtsmed 1987;99:197–203.
18. Pommerenk, U. Selbstmorde mit Suxamethoniumchlorid. Arch Kriminol 1978;162:167–169.
19. Kintz P, Tracqui A, Ludes B. The distribution of laudanosine in tissues after death from atracurium injection. Int J Legal Med 2000;114:93–95.
20. Varga M, Somogyi G. A suicide with neuromuscular blocker. Z Rechtsmed 1988;100:223–226.
21. Drummer OH. A fatality due to propofol poisoning. J Forensic Sci 1992;37:1186–1189.
22. Riesselmann B, Roscher S, Tenczer J. Suizide von Medizinalpersonal - Häufung von Todesfällen nach Propofol-Applikation. In: Püschel K, Wischhusen F, eds. Referate der 8. Frühjahrstagung - Region Nord - der Deutschen Gesellschaft für Rechtsmedizin. Eigendruck, Hamburg, 1999, p. 65.
23. Logemann E, Pollak S, Khalaf AN, Petersen KG. Zur postmortalen Diagnostik der exogenen Insulin-Applikation. Arch Kriminol 1993;191:28–36.
24. Schneider V, Dulce HJ. Suizidale Vergiftungen mit Insulin und ihr Nachweis an der Leiche (Radioimmunassay). Arch Kriminol 1979;164:142–152.
25. Maxeiner H, Klug E. Lethal suicidal intoxication with propafenone, after a history of self-inflicted injuries. Forensic Sci Int 1997;89:1,2.
26. Winek CL, Fusia E, Collom WD, Shanor SP. Cyanide poisoning as a mode of suicide. Forensic Sci 1978;11:51–55.
27. Pasi A, Morath M, Hartmann H. Die Zyanvergiftung: Forensisch-toxikologische Beobachtungen bei der Untersuchung von 54 Fällen tödlicher Intoxikation. Z Rechtsmed 1985;95:35–43.

28. Clark MA, Jones JW. Suicide by intravenous injection of a veterinary euthanasia agent: report of a case and toxicologic studies. J Forensic Sci 1979;24:762–767.
29. Logemann E, Krützfeldt B, Pollak S. Suizidale Einnahme von elementarem Arsen. Arch Kriminol 1990;185:80–88.
30. Klug E, Schneider V. Suizid mit Natriumazid. Z Rechtsmed 1987;98:129–132.
31. Schneider V, Klug E, Helwing HP, Bartsch G. Tödliche Fettembolie nach Selbst-Injektion von Speiseöl. Z Rechtsmed 1971;69:197–209.
32. Wehr K, Schäfer A. Eine ungewöhnliche suizidale Kohlenmonoxid-Intoxikation. Arch Kriminol 1987;180:155–160.
33. Dirnhofer R, Sigrist T. Außergewöhnlicher Suizid eines Arztes. Z Rechtsmed 1978;81:227–235.
34. Magerl H, Vock R, Schwerd W. Die berufsbezogene suizidale Intoxikation. In: Bauer G, ed. Gerichtsmedizin. Festschrift für Wilhelm Holzcabek. Deuticke, Wien, 1988, pp. 227–229.
35. Peschel O, Betz P, Eisenmenger W. Injection of toxic agents: an unusual cause of death. Forensic Sci Int 1995;75:95–100.
36. Grellner W, Kukuk M, Glenewinkel F. Zur Suizidmethode von Ärzten, medizinischem Personal und verwandten Berufsgruppen. Arch Kriminol 1998;201:65–72.
37. Haberda A. Eduard R. v. Hofmanns Lehrbuch der gerichtlichen Medizin. Urban und Schwarzenberg, Berlin, Wien, 1923.
38. Hübner O. Selbstmord durch Schnittverletzung der Oberschenkelblutader. Kriminalistik 1954;8:314–316.
39. Iten PX, Zollinger U. Suicid durch Eröffnen von Gefäßen unter Lokalanästhesie: risikoarme Extraktion von HIV-infiziertem Gewebe mittels Stomacher. Arch Kriminol 1991;188:47–53.
40. Faller-Marquardt M, Hellerich U, Pollak S. Berufsbezogene Vorgangsweise bei Selbstverletzung im Rahmen eines fingierten Überfalls. Arch Kriminol 1999;203:129–137.
41. Baur C. Selbstmord unter Nutzung postoperativer Gegebenheiten. Arch Kriminol 1977;160:148–150.
42. Reh H. Selbsttötung mit einem primitiven Schießgerät. Arch Kriminol 1979;163:100–104.
43. Maxeiner H, Horn W, Beyer W. Rekonstruktion eines Suizides mit einer selbstgefertigten Schußwaffe. Arch Kriminol 1986;177:19–28.
44. Kellermann ST, Koops E, Kleiber M, Kulle KJ, Püschel K. Ungewöhnlicher Suizid durch Kopfschuss mit einer Signalpistole. Arch Kriminol 1994;194:71–77.
45. Karger B, Teige K. Suizid mit einem Bolzensetzwerkzeug: Wundballistik und Einschussmorphologie. Arch Kriminol 1995;195:153–158.
46. Nowak R, Seidl S. Suizid mit einer Guillotine. Arch Kriminol 1994;193:147–152.
47. Härtel V, Petkovits TH, Brinkmann B. Ungewöhnliche Suizide mit Bandsägen. Arch Kriminol 1989;184:168–174.
48. Weimann W. Zur Explosionswirkung von Mundschüssen. Arch Kriminol 1931;88:208,209.

49. Weimann W. Nahexplosion. Arch Kriminol 1932;91:70–71.
50. Elbel H. Selbstmord mit Zündpatrone. Dtsch Z ges Gerichtl Med 1942;35:164,165.
51. Greiner H. Selbstmord mit einer Zündkapsel. Arch Kriminol 1974;153:141–143.
52. Orthner H. Selbstmord durch Entzünden einer Sprengkapsel im Mund. Dtsch Z ges Gerichtl Med 1939/40;32:336,337.
53. Tsokos M, Türk EE, Madea B, et al. Pathologic features of suicidal deaths caused by explosives. Am J Forensic Med Pathol 2003;24:55–63.
54. Mojzes L, Antal A, Kupecz I, Földes V, Farkas Z. Ein ungewöhnlicher Selbstmord - Selbstsprengung im Kraftfahrzeug. Arch Kriminol 1983;172:21–28.
55. Buhtz G. Selbstmord mit dem Strom der Lichtleitung. Dtsch Z ges Gerichtl Med 1930;14:443–448.
56. Munck W. Selbstmord durch Gleichstrom von 220 Volt. Dtsch Z ges Gerichtl Med 1934;23:97–109.
57. Somogyi E, Orovecz B, Irányi J. Angaben zu dem Problem der durch elektrischen Strom begangenen Selbstmorde. Dtsch Z ges Gerichtl Med 1961;52:52–59.
58. Lafrenz M, Rötzscher K. Suicid durch elektrischen Gebrauchsstrom. Arch Kriminol 1966;138:172–178.
59. Leygraf E. Suizidale Stromtodesfälle außerhalb der Badewanne. Beitr Gerichtl Med 1990;48:551–559.
60. Földes V, Lászik A. Ein besonderer Fall des Selbstmordes durch elektrischen Strom. Arch Kriminol 1992;189:140–144.
61. Nippe M. Beiträge zur Frage nach Mord, Selbstmord oder Unfall. Vierteljahrsschr Gerichtl Med Öffentl Sanitätswesen 1921;61:204–215.
62. Nippe M. Etwas eigenartiger elektrischer Selbstmord? Dtsch Z ges Gerichtl Med 1942;36:307–310.
63. Weimann W. Selbsttötungen nach der Uhrzeit. Arch Kriminol 1961;127:127–136.
64. Anders S, Matschke J, Tsokos M. Internal current mark in a case of suicide by electrocution. Am J Forensic Med Pathol 2001;22:370–373.
65. Fritz E. Merkwürdiger Befund nach Tötung eines Menschen mittels eines Bolzenschuß-Tiertötungsapparates. Arch Kriminol 1942;111:25–29.
66. Gehrke T. Morde und Selbstmorde mit Viehschussmasken. Arch Kriminol 1942;111:19–24.
67. Grellner W, Buhmann D, Wilske J. Suizid durch zweimalige Bolzenschussverletzung des Kopfes: Fallbericht und Literaturübersicht. Arch Kriminol 2000;205:163–168.
68. Lignitz E, Koops E, Püschel K. Tod durch Bolzenschussgeräte. Eine retrospektive Analyse von 34 Fällen aus Berlin und Hamburg. Arch Kriminol 1988;182:83–93.
69. Pollak S, Reiter C. Über die Entstehung von "Bolzengeschossen" bei Verwendung präparierter Viehbetäubungsapparate. Z Rechtsmed 1981;87:279–285.
70. Czursiedel H. Ein Selbstmord mittels eines Bolzenschussapparates. Zeitschr Gerichtl Medizin 1937;28:132,133.
71. Fieguth A, Gunther D, Schroeder G, Tröger HD. Tödliche "Bolzengeschoss"-Verletzung bei Verwendung eines manipulierten Viehbetäubungsapparates. Arch Kriminol 2002;210:39–44.
72. Liebegott G. Seltener kombinierter Selbstmord und seine versicherungsrechtliche Auswirkung. Zeitschr Gerichtl Medizin 1948/1949;39:351–355.

73. Wirth I, Markert K, Strauch H. Ungewöhnliche Suizide mit Viehbetäubungsgeräten. Z Rechtsmed 1983;90:53–59.
74. Wallbaum F. Über einen eigenartigen Fall von Selbstmord vermittels eines Tiertötungsapparates. Zeitschr Gerichtl Medizin 1931;16:174–179.
75. Schollmeyer W, Disse M. Sechs Selbstmorde und ein Mord mittels Bolzenschussapparats. Arch Kriminol 1961;127:85–96.
76. Pollak S. Zur Morphologie der Bolzenschussverletzung. Z Rechtsmed 1977;80:153–165.
77. Schiermeyer H. Suicid durch zweimaligen Bolzenschuß in den Kopf. Arch Kriminol 1973;151:87–90.
78. Wolff F, Laufer M. Über Bolzenschussverletzungen. Deutsche Zeitschr Gerichtl Medizin 1965;56:87–96.
79. Riemann H. Kasuistische Beiträge zum Suizid mittels Bolzenschussapparates. Dt Gesundh-Wesen 1959;14:1952–1956.
80. Maurer H. Verletzungen durch Schussapparate. Beitr Gerichtl Med 1961;21:48–66.
81. Goldney R. Homicide and suicide by aircraft. Forensic Sci Int 1983;21:161–163.

Infectious Diseases

8

Sudden, Unexpected Death Related to Viral Myocarditis

A Survey of Histological, Immunohistochemical, and Molecularpathological Methods for the Postmortem Diagnosis

Reinhard Dettmeyer, MD and Burkhard Madea, MD

Contents

Summary

Sudden, unexpected deaths of previously healthy individuals without establishment of a definitive acute lethal event at autopsy represent a substantial proportion of forensic autopsy cases. It is well established that viral myocarditis can be associated with sudden, unexpected manifestation of death. Nevertheless, this diagnosis may present difficulties when there are no relevant histological findings using conventional histological stains. When applying a comprehensive combination of molecularpathological and immunohistochemical techniques, obviously a higher prevalence of viral myocarditis can be detected with regard to forensic pathological autopsy cases.

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

Immunohistochemical methods include qualification and quantification of interstitial leukocytes including macrophages, T-lymphocytes, and the expression of adhesion molecules and cytokines as well as major histocompatibility complex class I and II molecules. Conventional histology may provide, when supplemented by immunohistochemistry, important clues regarding the underlying etiology of myocarditis. The actual demonstration of microorganisms in the myocardium or the elucidation of a previous administration of drugs or exposure to toxic substances are the only reliable means of establishing an etiological diagnosis of myocarditis. Molecularpathological techniques should be employed particularly for the detection of viral genome in the myocardium by reverse transcriptase polymerase chain reaction (rt-PCR) as already established regarding the investigation of endomyocardial biopsies. In combination with histological, immunohistochemical, and *in situ* hybridization, these techniques will enable the forensic pathologist or medical examiner, respectively, to clarify the cause of death in a higher number of cases of sudden, unexpected death that present otherwise without any relevant morphological findings.

Key Words: Sudden death; myocarditis; immunohistochemistry; molecularpathology; polymerase chain reaction (PCR); forensic pathology.

1. Introduction

Myocarditis is clinically defined as an inflammation of the myocardium. First introduced into the medical literature at the beginning of the 19th century, the term "myocarditis" was initially used to describe diseases of the myocardium not associated with valvular abnormalities *(1)*. On the one hand, bacterial myocarditis characterized by a granulocytic infiltration accompanied by myocytolysis appears to be rare, but on the other hand, viruses have been isolated from the myocardium of both adults and infants with acute and/or chronic inflammatory heart muscle disease *(2)*. Postmortem studies suggest that myocarditis is a major cause of sudden, unexpected death (accounting for approx 20% of cases) in adults less than 40 years of age *(3,4)*, and also affects young athletes *(5)*. Many infectious agents, including viruses, bacteria, protozoa, and even fungi and worms can cause a clinical symptomatic myocarditis. Although most viruses have the potential to cause this disease, serological and *in situ* hybridization studies, as well as molecularpathological investigations, indicate that enteroviruses of the Picornaviridae family are involved in more than 50% of cases *(6,7)*. At least 70 serotypes that cause infection in humans have been identified so far including the polioviruses (three serotypes), coxsackievirus group A (CVA, 23 serotypes), and more recently

recognized serotypes simply named enterovirus types 68–72. Meanwhile, echovirus type 22 has also been found to be an atypical enterovirus *(8)*. Further evidence comes from reports of an elevated incidence of sudden cardiac deaths as a result of myocarditis, for example, during enterovirus epidemics, particularly with coxsackievirus B3 *(9,10)*.

Nevertheless, almost any viral infection may be accompanied by clinical evidence of heart involvement, most frequently abnormal formation and conduction of cardiac impulses or abnormal repolarization *(11)*. It is not always easy to find the cause-and-effect relationship between the viruses identified and the obvious clinical symptoms, but it is now widely accepted that myocarditis is caused by viral infections more frequently than it has been assumed in the past. In a number of cases, viral myocarditis may be responsible for fatal outcome, for example, in cases of sudden death of neonates *(12)*, in cases of suspected sudden infant death syndrome (SIDS; *[13–17]*), as well as in childhood *(18)*. Recent clinical reports and case studies, some using molecularbiological techniques to detect the genome sequences of the viruses, have shown evidence of different viruses in such cases, for example, enteroviruses *(19)*, adenoviruses *(20)*, Epstein-Barr virus *(21)*, influenza viruses *(22)*, cytomegaloviruses *(23)*, and parvovirus B19 *(24,25)* in clinical biopsy samples and autopsy specimens, respectively. Immunohistochemical and molecularpathological techniques have improved the diagnosis of myocarditis compared to conventional histological staining techniques that are carried out according to the Dallas criteria of myocarditis *(26,27)*. Regarding the clinical course of virus-induced myocarditis, it is hypothized that most cases present without any relevant clinical symptoms, persist only for a short time, and will not lead to pathological late sequelae like inflammatory cardiomyopathy at all. Single cases resulting in fatal outcome are considered to be a result of involvement of the cardiac conduction system.

2. *Sudden, Unexpected Death and Myocarditis*

The term "sudden, unexpected death" refers to the unforeseen death of a previously healthy individual without establishment of a definitive acute lethal event at autopsy *(28)*. Such fatalities, mostly occurring outside hospitals, represent a substantial proportion of forensic autopsy cases *(29)*. In some of these cases, it may be difficult to establish the definite cause of death at the autopsy table. Regarding the seasonal accumulation of virus infections *(30)* and sudden, unexpected deaths related to viral myocarditis, a clear correlation has been established especially when referring to enteroviral epidemics *(9,10,31,32)*.

2.1. Gross Pathology

Usually, viral myocarditis is a chronic disease. It is associated with end-stage heart failure that is actually classified as a specific cardiomyopathy. Marked dilatation of all four cardiac chambers, although not pathognomonic, is the diagnostic hallmark of myocarditis at gross examination of the heart. In cases of acute myocarditis, the myocardium appears flabby. Focal hemorrhages are occasionally observed throughout the heart. According to the World Health Organization/International Society and Federation of Cardiology classification from 1995, the term "specific cardiomyopathy" refers to a group of diseases of the myocardium that are associated with specific cardiac or systemic disorders. To characterize cases of chronic myocarditis with dilatation of the ventricles and muscular hypertrophy of the ventricular walls, virus-induced myocarditis is described as dilated cardiomyopathy with inflammation (DCMi), a myocarditis associated with cardiac dysfunction. In the latter cases, the heart is enlarged and dilated with diffuse and focal fibrosis of the endocardium and a heart weight of up to 750 g and more. Enteroviruses, adenoviruses, and cytomegaloviruses were identified as responsible agents within the myocardium in cases of DCMi (*33*,*34*). Virus-induced myocarditis presents not only as a diffuse inflammatory process, but also as a sole micro*focal* infiltration. Therefore, it is essential to examine a large number of postmortem myocardial samples because *focal* inflammatory processes will be detectable only in a limited number out of all these samples ("sampling error"). Accordingly, it is necessary to obtain a representative number of samples from different myocardial regions at autopsy. In the first instance, it is suggested to take one sample (babies, infants) or two samples (adults) from the regions listed in Table 1. If there are no pathological findings, the diagnosis of myocarditis by conventional histological stains can be excluded. If there are single microfocal infiltrates of leukocytes, single necroses of cardiomyocytes, and/or distinct interstitial or perivascular fibrosis, it is mandatory to examine more samples from the respective heart detained on the whole.

2.2. Conventional Histopathology

Myocarditis is a purely descriptive term meaning, in clinico-pathological terms, inflammation of the myocardium. In this broad sense, this term does not imply either the underlying etiology or pathogenesis, respectively. When using histology with conventional stains, myocarditis is characterized by an inflammatory infiltrate in the myocardium associated with myocyte damage in the absence of coronary artery disease. In cases of virus-induced inflammatory alterations of the myocardium, the infiltrates consist predomi-

Table 1
Suggested Regions for Myocardial Samples in Cases With a High Index of Suspicion of Myocarditis (One Sample From Each Region in Young Age Groups, Two Samples From Hearts of Adults)

1.	Right ventricle, anterior
2.	Right ventricle, posterior
3.	Septum interventricular, cranial
4.	Septum interventricular, caudal
5.	Left ventricle, anterior wall, cranial
6.	Left ventricle, anterior wall, caudal
7.	Left ventricle, posterior wall, cranial
8.	Left ventricle, posterior wall, caudal

Table 2
Dallas Criteria of Myocarditis (Histological Criteria)

1. Active myocarditis: cellular infiltrate in close contact to myofibers; myocytolysis with or without interstitial edema
2. Ongoing myocarditis (as in point 1)
3. Resolving (healing) myocarditis: sparse infiltrate mostly in the interstitial space; no or very sparse myocytolysis in a second biopsy specimen
4. Resolved myocarditis: focal (or diffuse) interstitial fibrosis which may be rich in cells (mostly fibroblasts)

Based on refs. *1,26,35*.

nantly of lymphocytes and macrophages. The infiltrates can be classified as diffuse or focal and graded semiquantitavely as mild, moderate, or severe. Myocyte damage may consist of necrosis with myocyte debris or vacuolization and disruption of the cell in association with infiltration of inflammatory cells.

In 1986, the Dallas criteria for the histological diagnosis of active myocarditis were introduced (Table 2 *[35]*). When examining endomyocardial biopsies by using light microscopy and conventional histological stains, infiltrating lymphocytes and myocytolysis were considered to reflect the diagnosis of an active (acute) myocarditis. Without myocytolysis, a borderline or ongoing myocarditis should be diagnosed despite lymphocytic infiltration. These Dallas criteria probably underestimate the true incidence of myocarditis *(1)* and the degree of interobserver variability is large (*36*). As mentioned

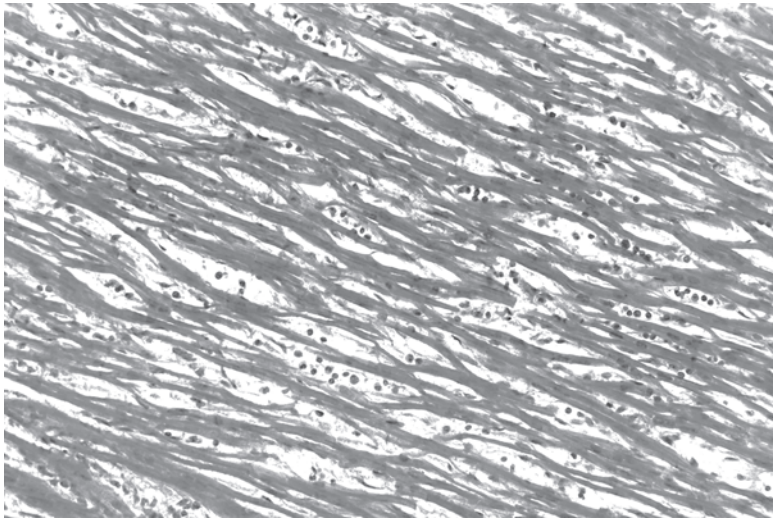

Fig. 1. Diffuse lympho-monocytic infiltration of the myocardial interstice with necroses of cardiomyocytes and interstitial edema: active myocarditis according to the Dallas criteria. 24-year-old male (hematoxylin & eosin, original magnification x250).

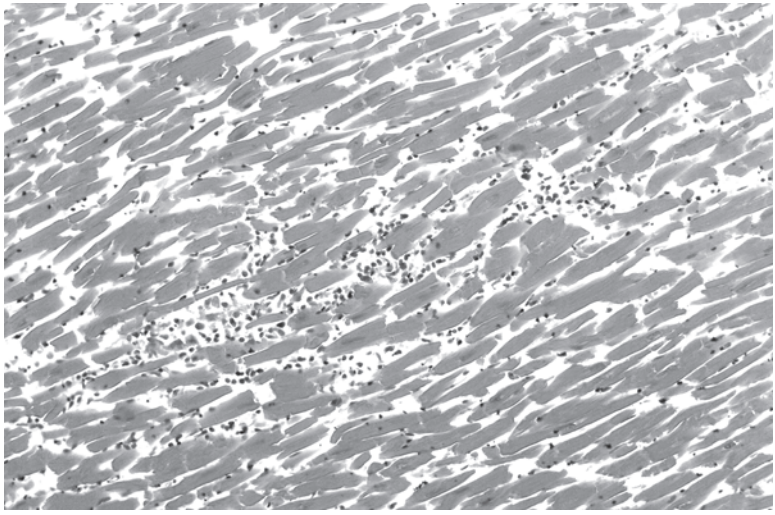

Fig. 2. Focal active myocarditis with lympho-monocytic infiltrates. This 42-year-old male was found lifeless in his bed in hospital where he was admitted to clarify the cause of a severe diarrhea (hematoxylin & eosin, original magnification x125).

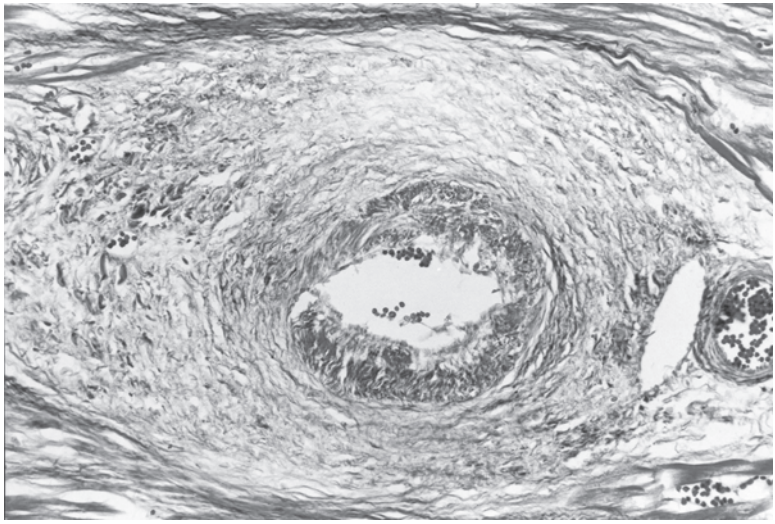

Fig. 3. Severe perivascular fibrosis in the myocardium of a 4-month-old boy who was found lifeless in bed in a prone position by his mother. This case was first regarded as sudden infant death syndrome (Mallory-stain, original magnification x400).

before, myocarditis can present as a pure focal inflammatory process. Therefore, a considerable number of myocardial specimens must be obtained at autopsy to avoid a "sampling error" (*37*).

Nevertheless, conventional histological stains can reveal a virus-induced lympho-monocytic myocarditis when there are diffuse interstitial infiltrates, myocytolysis, and interstitial edema (Fig. 1). There are also cases in which only 1 or 2 of 10 or more myocardial samples show focal lympho-monocytic infiltration (Fig. 2). Diffuse and perivascular interstitial fibrosis (Fig. 3), and single foci of only a few leukocytes, predominantly macrophages, are described in cases of chronic myocarditis (chronic inflammatory DCMi). This disease is diagnosable by conventional histological stains like hematoxylin and eosion, Mallory-stain, elastica-van-Gieson, luxol-fast-blue, or siriusred.

Studies of viral myocarditis in mice revealed, in a first-phase postinfection, a time course without any signs of myocarditis according to the Dallas criteria, although viral infections resulted in fatal outcome (*1*). Early phase-dependent viral lesions can only be detected by electron microscopy *(38)*. Immunohistochemical signs of myocarditis appear prior to the conventional histological signs of myocarditis according to the Dallas criteria. Recent

studies that dealt with the time course of experimental viral myocarditis in mice described an interval of up to 4 days before the infiltration of mononuclear cells became diagnosable. During this early phase of viremia, cytokine expression and activation of macrophages (corresponding to acute myocarditis) can be found although the following development, 4 to 14 days postinfection, with cellular infiltration is regarded as *subacute myocarditis* and the phase of viral clearing (*1*). Cell-mediated immunity has an important role in viral clearing with a variety of host defense mechanisms able to limit cardiac injury after a viral infection (*1*).

2.3. Immunohistochemical Techniques

The use of immunohistochemical methods for the diagnosis of acute myocarditis has been described in previous studies *(27,39,40),* mainly concerning endomyocardial biopsies from adults *(41–44)*. The *de novo* expression of antigens of the major histocompatibility complex (MHC), coded on the sixth chromosome, may indicate the activation of the immune system as a result of lympho-monocytic viral myocarditis associated with an increased number of LCA^+-leucocytes, $CD68^+$-macrophages and $CD45R0^+$-T-lymphocytes *(45)*. An increased expression of the MHC class I + II antigens is found on endothelial and interstitial cells in cases of myocarditis as well as on the endocardium (Fig. 4) in comparison to control samples *(46–48)*. T-lymphocytes are known to react with foreign antigens when presented on cell surfaces in conjunction with MHC antigens *(49)*. Additionally, the expression of cell adhesion molecules like E-selectin (Fig. 5), vascular cell adhesion molecule-1, and intercellular adhesion molecule-1, as well as cytokines (e.g., interleukin [IL]-1, IL-2, tumor necrosis factor [TNF], interferon-γ, perforin) is increased in cases of acute and chronic viral myocarditis *(50–53)*. Enteroviral antigen is detectable by an immunohistochemical staining technique using an enterovirus group-specific antibody to viral capsid protein VP1 *(54,55)*.

In the past, by means of examining histological slides stained with conventional techniques, the finding of a mean value of more than five T-lymphocytes per high-power field (HPF), when investigating 20 visual fields at 400-fold magnification, has been regarded as a sign of active myocarditis in adults *(56)*. Some authors suggested an upper normal limit of at least more than 10 T-lymphocytes and macrophages per HPF for this diagnosis *(57,58)*.

Concerning babies and infants, mean values are not yet established. In the younger age groups, in contrast to criteria for analysis of adult samples, more rigorous criteria should be applied. The finding of more than 10 T-lymphocytes per HPF should be interpreted as a reliable sign of active myocardi-

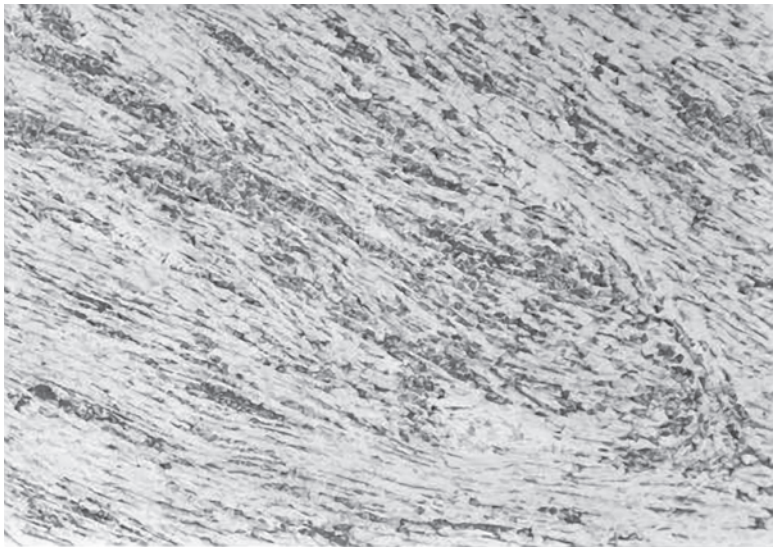

Fig. 4. Highly enhanced expression of major histocompatibility complex class II molecules on inflammatory cells in a case of enteroviral myocarditis (original magnification x125).

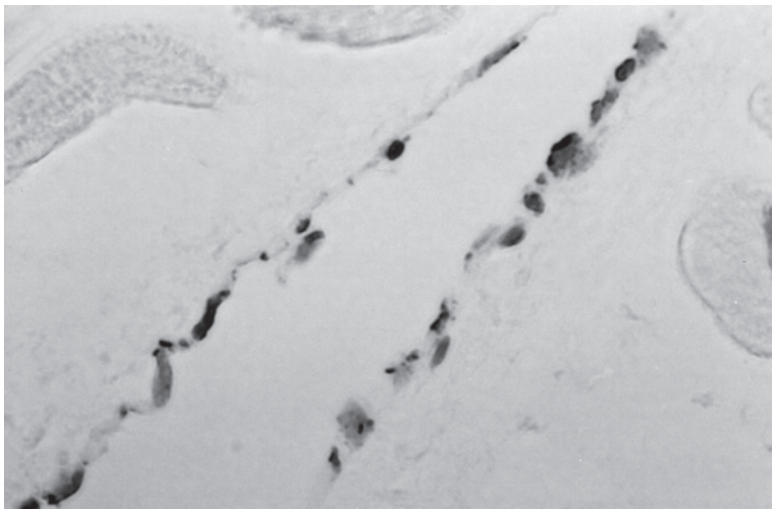

Fig. 5. Myocardium with increased expression of E-selectin in the endothelium of small vessels. This 34-year-old woman died suddenly during the third trimester of pregnancy. Molecular-pathological investigations revealed viremia as a result of hepatitis B virus and parvovirus B19-PVB19 (original magnification x1000).

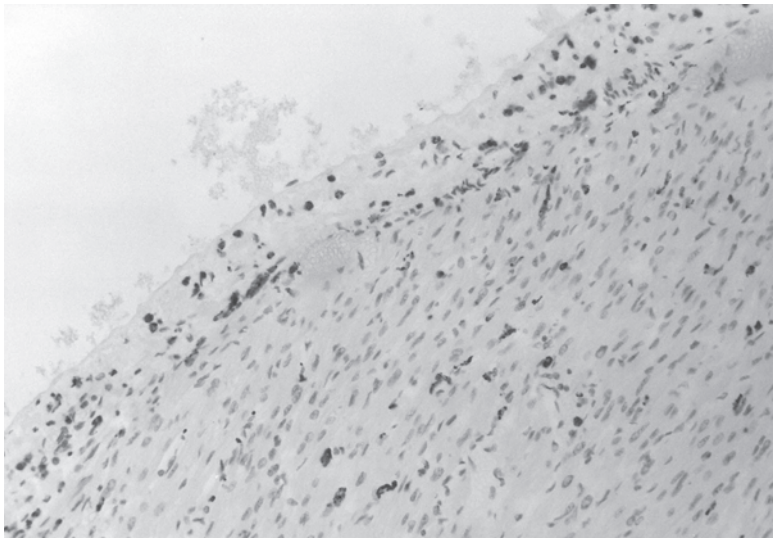

Fig. 6. Numerous CD68^{+}-macrophages infiltrating the epicardium and the myocardium in a case of coxsackievirus B3-induced myocarditis. Four-month-old girl (original magnification x250).

tis. Furthermore, cases showing more than 15 T-lymphocytes and macrophages per HPF should also be diagnosed as "active myocarditis" in younger age groups. Cases with 5 to 10 T-lymphocytes per HPF should be regarded as "suspicious," as should cases with more than 10 macrophages per HPF accompanied by less than 5 T-lymphocytes, resulting in less than 15 cells. Cases with an increased number of macrophages (Fig. 6) remain unclear at the moment, however, it may indicate a late inflammatory process (e.g., resolving myocarditis) and for such instances the term "macrophage-rich inflammatory process" should be used. Cases with less than 5 T-lymphocytes or 10 macrophages should be assessed as "without pathological findings" (Table 3). Qualification and quantification of interstitial leukocytes, T-lymphocytes, and macrophages can help to identify cases with a high index of suspicion of myocarditis (Fig. 7). Such samples should be investigated additionally by molecularpathological methods. Expression of MHC class II molecules can also give valuable hints toward virus-induced myocarditis in the early phase when there are no histological findings detectable according to the Dallas criteria of myocarditis (Fig. 8).

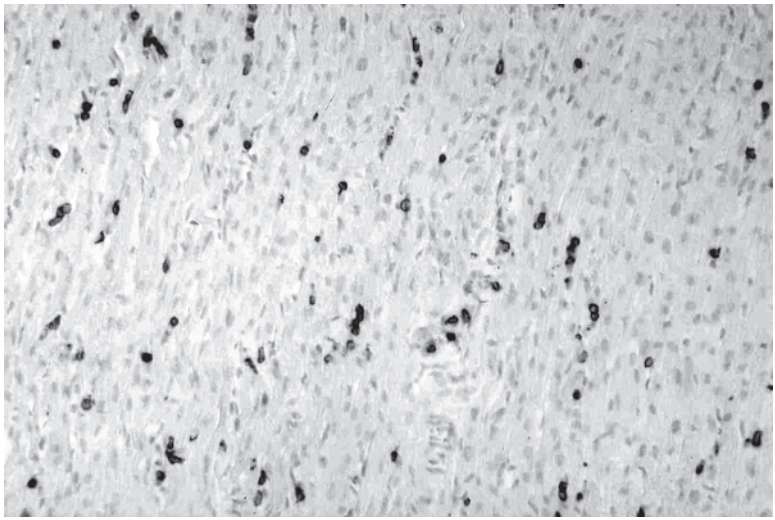

Fig. 7. Increased number of LCA^+-leucocytes, but no myocarditis according to the Dallas criteria. In this case, molecularpathological investigations revealed myocarditis as a result of human herpes simplex virus type 6 (HHSV6). Seven-month-old boy whose death was first regarded as sudden infant death syndrome (original magnification x250).

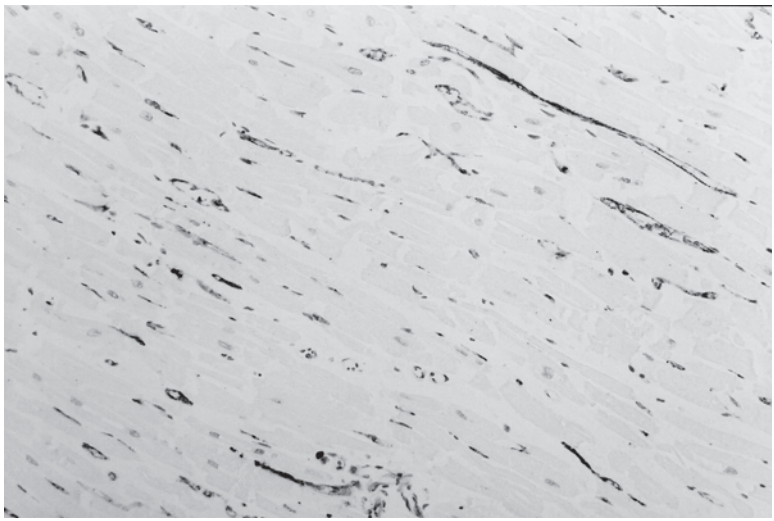

Fig. 8. Myocardium with increased expression of major histocompatibility complex class II molecules on the endothelium of small vessels. Same case as Fig. 5 (original magnification x250).

Table 3
Immunohistochemical Qualification and Quantification of Interstitial LCA$^+$-Leucocytes, CD68$^+$-Macrophages, and CD45R0$^+$-T-Lymphocytes: Suggested Values for Diagnosis of Myocarditis in Babies (Mean Values of 20 High-Power Fields Investigated at 400-Fold Magnification)

Active myocarditis
1. More than 15 LCA$^+$-leukocytes per HPF
2. More than 10 CD45R0$^+$-T-lymphocytes per HPF
Suspicious findings
3. 5 to 9 CD45R0$^+$-T-lymphocytes per HPF
4. More than 10 CD68$^+$-macrophages per HPF

HPF, high-power field.

2.4. Molecularpathological Methods

Polymerase chain reaction (PCR) offers a rapid, sensitive diagnostic method not only for viral infection of the myocardium (*59,60*). PCR used in conjunction with immunohistochemical stains appears to enhance the likelihood of detecting viral genome in the myocardium of persons that have died suddenly and unexpectedly.

In adults, virus detection by reverse transcriptase (rt)-PCR and *in situ* hybridization, as well as serological studies detecting viral antibodies revealed an association between myocarditis and enterovirus infection, especially between the cardiotropic coxsackieviruses group B and myocarditis (*7,61*). Coxsackie B viruses (Fig. 9) are one of the most frequently identified infectious agents responsible for acute myocardial infections and outbreaks of coxsackie B virus infections have been described *(62)*. In countries with temperate climate zones, coxsackie virus infections tend to occur in summer and autumn *(63)*. The outcome of coxsackievirus B3-induced myocarditis is influenced by the cellular immune status *(64)*. A few studies have used molecularpathological methods to detect viral genome in cases of suspected SIDS *(65)*.

Recently, a cDNA clone that encodes the common coxsackie and adenovirus receptor CAR (coxsackie-adenoviral-receptor) was discovered *(66)*. Interestingly, this receptor has been shown to be downregulated after birth

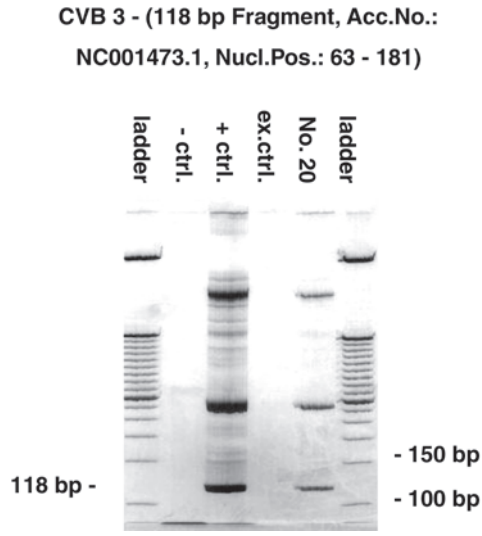

Fig. 9. Coxsackievirus B3 (CVB3)-RNA-detection. This sample was obtained from the cranial part of the left ventricle posterior wall of a 17-month-old boy.

and is not detectable in adolescents and adults, except in cases of chronic inflammatory cardiomyopathies. These observations offer a feasible molecular basis for the explanation of the predominance of coxsackieviruses and adenoviruses in the heart.

With regard to in vitro and animal models (*38,67*) enteroviruses cause a myocytopathic effect *(68)* leading to a direct myocardial injury by enteroviruses *(69)*. The enteroviral protease 2A cleaves and, therefore, functionally impairs dystrophin, a cytosceletal protein of cardiomyocytes. During infection with coxsackievirus B3, the dystrophin–glycoprotein complex becomes disrupted and the sarcolemmal integrity is lost *(70,71)*. So it must be suggested that enteroviral genome within the myocardium, when detected by rt-PCR, is by itself a pathological finding.

Over the past few years, numerous reports based mainly on PCR-derived molecular data have shown an association between parvovirus B19 (PVB19) infection and myocarditis in children and adults *(24,25,72)*. Endothelial cells are the PVB19-specific target cells and not cardiac myocytes as demonstrated by *in situ* hybridization *(25)*.

Cardiotropic viruses cannot be identified only in cases of acute myocarditis, they are also found in myocardial samples of dilated cardiomyopathies in children and adolescents *(73)*.

3. Medicolegal Aspects of Myocarditis-Related Fatalities

Modern immunohistochemical techniques provide a powerful tool to prove lethal myocarditis in cases devoid of traditional histological findings according to the Dallas criteria. This includes cases originally misdiagnosed as SIDS *(13–15,27)*. Furthermore, the detection of viral antigens in the myocardium renders significant information with regard to the underlying etiology of myocarditis. Lympho-monocytic myocarditis in childhood as well as in adults is known to be caused especially by enteroviruses, mainly the cardiotropic coxsackieviruses group B, serotypes B1–B5 *(19,38,74)*. In some cases of sudden, unexpected death that remain unclear even after a full autopsy that includes a thorough toxicological analysis, the aforementioned methods may lead to the final diagnosis of myocarditis. In forensic autopsy cases of younger people without any previous medical history, investigations to reveal virus-induced myocarditis should be initiated at least in cases of sudden death of babies, infants, young athletes, in fatalities following physical exertion as well as in the rare group of cases of sudden death during pregnancy. The classification of myocarditis is traditionally based on either of the two approaches: chronology or etiology. Nowadays, we should regard both chronology and etiology.

References

1. Feldmann AM, McNamara D. Myocarditis. N Engl J Med 2000;343:1388–1398.
2. Pankuweit S, Pratig I, Eckhardt H, Crombach M, Hufnagel G, Maisch B. Prevalence of viral genome in endomyocardial biopsies from patients with inflammatory heart muscle disease. Herz 2000;25:221–226.
3. Droroy TY, HissY. Sudden unexpected death in persons less than 40 years of age. Am J Cardiol 1991;68:1388–1392.
4. Neuspiel DR, Kuller LH. Sudden unexpected natural death in childhood and adolescence. JAMA 1985;254:1321–1325.
5. McCaffrey FM, Braden DS, Strong WB. Sudden cardiac death in young athletes. Am J Dis Child 1991;145:177–183.
6. Huber SA, Gauntt CJ, Sakkinen P. Enteroviruses and myocarditis: viral pathogenesis through replication, cytokine induction, and immunopathogenicity. Adv Vir Res 1999;51:35.
7. Bowles NE. Detection of coxsackie-B-virus-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. Lancet 1986;1:1120–1123.
8. Muir P. Enteroviruses and heart disease. Br J Biomed Sci 1993;50:258–271.
9. Phillips CA, Aronson MD, Tomkow J, Phillips ME. Enteroviruses in Vermont, 1969–1978: an important cause of illness throughout the year. J Infect Dis 1980;141:162–164.

10. Mounts AW, Amr S, Jamshidi R, et al. A cluster of fulminant myocarditis cases in children, Baltimore, Maryland, 1997. Pediatr Cardiol 2001;22:34–39.
11. Kawai C, Matsumori A, Fujiwara H. Myocarditis and dilated cardiomyopathy. Ann Rev Med 1987;38:221–239.
12. Haddad J, Gut J, Wendling M, et al. Enterovirus infections in neonates. A retrospective study of 21 cases. Eur J Med 1993;2:209–214.
13. Dettmeyer R, Baasner A, Winkelmann S, Graebe M, Madea B. Myocarditis and sudden death in infancy—immunohistochemical and molecularpathological investigations. J Perinat Med 2001;29(Suppl 2):25.
14. Dettmeyer R, Baasner A, Schlamann M, Haag C, Madea B. Coxsackie B3 myocarditis in 4 cases of suspected sudden infant death syndrome: diagnosis by immunohistochemical and molecular-pathologic investigations. Pathol Res Pract 2002;198:689–696.
15. Dettmeyer R, Kandolf R, Schmidt P, Schlamann M, Madea B. Lympho-monocytic enteroviral myocarditis: traditional, immunohistological and molecularpathological methods for diagnosis in a case of suspected sudden infant death syndrome (SIDS). Forensic Sci Int 2001;119:141–144.
16. Rambaud C, Cieuta C, Canioni D, et al. Cot death and myocarditis. Cardiol Young 1992;2:266–271.
17. Bajanowski T, Ortmann C, Teige K, et al. Pathological changes of the heart in sudden infant death. Int J Legal Med 2003;117:193–203.
18. Gold E, Carver DH, Heineberg H, Adelson L, Robbins FC. Viral infection. A possible cause of sudden unexpected death in infants. New Engl J Med 1961;264:53–60.
19. Jin O, Sole M, Butany JW, et al. Detection of enterovirus RNA in myocardial biopsies from patients with myocarditis and cardiomyopathy using gene amplification by polymerase chain reaction. Circulation 1990;82:8–16.
20. Lozinski GM, Davis GG, Krous HF, Billman GF, Shimizu H, Burns JC. Adenovirus myocarditis: retrospective diagnosis by gene amplification from formalin-fixed, paraffin-embedded tissues. Hum Pathol 1994;25:831–834.
21. Hebert MM, Yu C, Towbin JA, Rogers BB. Fatal Epstein-Barr virus myocarditis in a child with repetitive myocarditis. Ped Pathol Lab Med 1995;15:805–812.
22. Bajanowski T, Rolf B, Jorch G, Brinkmann B. Detection of RNA viruses in sudden infant death (SID). Int J Legal Med 2003;117:237–240.
23. Maisch B, Schönian U, Crombach M, et al. Cytomegalovirus associated inflammatory heart muscle disease. Scand J Infect 1993;88(Suppl):135–148.
24. Murry CE, Jerome KR, Reichenbach DD. Fatal parvovirus myocarditis in a 5-year-old girl. Hum Pathol 2001;32:342–345.
25. Bültmann BD KK, Sotlar K, Bock TH, Baba HA, Sauter M, Kandolf R. Fatal parvovirus B19-associated myocarditis clinically mimicking ischemic heart disease: an endothelial cell-mediated disease. Hum Pathol 2003;34:92–95.
26. Aretz HT. Myocarditis: the Dallas criteria. Hum Pathol 1987;18:619–624.
27. Dettmeyer R, Schlamann M, Madea B. Immunohistochemical techniques improve the diagnosis of myocarditits in cases of suspected sudden infant death syndrome (SIDS). Forensic Sci Int 1999;105:83–94.
28. Cioc AM, Nuovo GJ. Histologic and in situ viral findings in the myocardium in cases of sudden, unexpected death. Mod Pathol 2002;15:914–922.

29. Drescher J ZP, Verhagen W, Flik J, Milbradt H. Recent influenza virus A infections in forensic cases of sudden unexplained death. Arch Virol 1987;92:63–76.
30. Morens DM. Enteroviral disease in infancy. J Pediatr 1978;92:374–377.
31. Friman G, Fohlman J. The epidemiology of viral heart disease. Scand J Infect Dis 1993;88(Suppl):7–10.
32. Fairley CK, Ryan M, Wall PG, Weinberg J. The organisms reported to cause infective myocarditis and pericarditis in England and Wales. J Infect 1996;32:223–225.
33. Martino TA, Liu P, Sole MJ. Viral infection and the pathogenesis of dilated cardiomyopathy. Circ Res 1994;74:182–188.
34. Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death. Circulation 1999;99:1091–1100.
35. Aretz HT, Billingham ME, Edwards W, et al. Myocarditis: a histopathologic definition and classification. Am J Cardiovasc Pathol 1987;1:5–14.
36. Shanes JG, Ghali J, Billingham ME, et al. Interobserver variability in the pathologic interpretation of endomyocardial biopsy results. Circulation 1987;75:401–405.
37. Strauer B, Kandolf R, Mall G, et al. Myokarditis - Kardiomyopathie. Update 2001. Med Klin 2001;96:608–625.
38. Kandolf R, Klingel K, Zell R, et al. Molecular mechanisms in the pathogenesis of enteroviral heart disease: acute and persistent infections. Clin Immunol Immunopathol 1993;68:153–158.
39. Heusch A, Kühl U, Rammos S, Krogmann ON, Schultheiss HP, Bourgeois M. Complete AV-block in two children with immunohistological proven myocarditis. Eur J Pediatr 1996;155:633–636.
40. Wojnicz R, Nowalany-Kozielska E, Wodniecki J. Immunohistological diagnosis of myocarditis. Eur Heart J 1998;19:1564–1572.
41. Schnitt SJ, Ciano PS, Schoen FJ. Quantification of lymphocytes in endomyocardial biopsies. Hum Pathol 1987;18:796–800.
42. Chow LH, Ye Y, Linder J, McManus BM. Phenotypic analysis of infiltrating cells in human myocarditis. Arch Pathol Lab Med 1989;113:1357–1362.
43. Steenbergen C, Kolbeck PC, Wolfe JA, Anthony RM, Sanfilippo FP, Jennings RB. Detection of lymphocytes in endomyocardium using immunohistochemical techniques. Relevance to evaluation of endomyocardial biopsies in suspected cases of lymphocytic myocarditis. J Appl Cardiol 1986;1:63–73.
44. Southern J, Kaynor B, Howard CA, Bain KM, Palcios IF, Fallon JT. Is immunoperoxidase staining of endomyocardial biopsies for interstitial inflammatory cells helpful in the diagnosis of myocarditis? Eur Heart J 1987;8:195–197.
45. Forcada P, Beigelman J, Milei J. Inapparent myocarditis and sudden death in pediatrics. Diagnosis by immunohistochemical staining. Int J Cardiol 1996;56:93–97.
46. Hufnagel G, Maisch B. Expression of MHC class I and II antigens and the IL-2 receptor in rejection, myocarditis and dilated cardiomyopathy. Eur Heart J 1991;12(Suppl D):137–140.
47. Daar AS, Fuggle SV, Fabre JW, Ting A, Morris PJ. The detailed distribution of MHC class II antigens in normal human organs. Transplantation 1984;38:293–298.
48. Daar AS, Fuggle SV, Fabre JW, Ting A, Morris J. The detailed distribution of HLA-A, B, C antigens in normal human organs. Transplantation 1984;38:287–292.

49. Thorsby E. Structure and function of HLA molecules. Transplant Proceed 1987;19:29–35.
50. Henke A, Nain M, Stelzner A, Gemsa D. Induction of cytokine release from human monocytes by coxsackievirus infection. Eur Heart J 1991;12(Suppl D):134–136.
51. Ino T, Kishiro M, Okubo M, et al. Late, persistent expressions of ICAM-1 and VCAM-1 on myocardial tissue in children with lymphocytic myocarditis. Cardiovasc Res 1997;34:323–328.
52. Noutsias M, Seeberg B, Schultheiss HP, Kühl U. Expression of cell adhesion molecules in dilated cardiomyopathy. Evidence for endothelial activation in inflammatory cardiomyopathy. Circulation 1999;99:2124–2131.
53. Seko Y, Takahashi N, Ishiyama S, et al. Expression of costimulatory molecules B7-1, B7-2, and CD40 in the heart of patients with acute myocarditis and dilated cardiomyopathy. Circulation 1998;97:637–639.
54. Li Y, Bourlet T, Andreoletti L, Mosnier JF, Peng T, Yang Y, et al. Enteroviral capsid protein is present in myocardial tissues from some patients with myocarditis or dilated cardiomyopathy. Circulation 2000;101:231–234.
55. Yousef GE, Mann GF, Brown IN, Mowbray JF. Clinical and research application of an enterovirus group-reactive monoclonal antibody. Intervirology 1987;28:199–205.
56. Edwards WD, Holmes DR, Reeder GS. Diagnosis of active lymphocytic myocarditis by endomyocardial biopsy. Quantitative criteria for light microscopy. Mayo Clin Proc 1982;57:419–425.
57. Linder J, Cassling RS, Rogler WC, et al. Immunohistochemical characterization of lymphocytes in uninflamed ventricular myocardium. Arch Pathol Lab Med 1985;109:917–920.
58. Cassling RS, Linder J, Sears TD, et al. Quantitative evaluation of inflammation in biopsy specimen from idiopathically failing or irritable hearts: experience in 80 pediatric and adult patients. Am Heart J 1985;110:713–720.
59. Martin AB, Webber S, Fricker FJ, et al. Acute myocarditits: rapid diagnosis by PCR in children. Circulation 1994;90:330–339.
60. Severini GM, Mestroni L, Falaschi A, Camerini F, Giacca M. Nested polymerase chain reaction for high-sensitivity detection of enteroviral RNA in biological samples. J Clin Microbiol 1993;31:1345–1349.
61. Bendig JWA, O'Brien PS, Muir P, Porter HJ, Caul EO. Enterovirus sequences resembling coxsackievirus A2 detected in stool and spleen from a girl with fatal myocarditis. J Med Virol 2001;64:482–486.
62. Druyts-Voets E, van Renterghem L, Gerniers S. Coxsackie B virus epidemiology and neonatal infection in Belgium. J Infect 1993;27:311–316.
63. Singer DB. Infections of fetuses and neonates. In: Wigglesworth JS, Singer DB, eds. Textbook of Fetal and Perinatal Pathology. Blackwell Scientific Publications, Boston, 1991, pp. 554,555.
64. Leipner C, Grün K, Borchers M, Stelzner A. The outcome of coxsackievirus B3-(CVB3-) induced myocarditis is influenced by the cellular immune status. Herz 2000;25:245–248.
65. Shimizu H, Rambaud C, Cheron G, et al. Molecular identification of viruses in sudden infant death associated with myocarditis and pericarditis. Ped Infect Dis J 1995;14:584–588.

66. Bergelson JM, Cunningham JA, Droguett G, et al. Isolation of a common receptor for coxsackie B viruses and adenoviruses 2 and 5. Science 1997;275:1320–1323.
67. Schwimmbeck PL, Rohn G, Wrusch A, et al. Enteroviral and immune mediated myocarditis in SCID mice. Herz 2000;25:240–244.
68. Klingel K, Selinka HC, Huber M, Sauer M, Leube M, Kandolf R. Molecular pathology and structural features of enteroviral replication. Toward understanding the pathogenesis of viral heart disease. Heart 2000;25:216–220.
69. McManus BM, Chow LH, Wilson JE, et al. Direct myocardial injury by enterovirus: a central role in the evolution of murine myocarditits. Clin Immunol Immunopathol 1993;68:159–169.
70. Badorff C, Berkely N, Mehrotra S, Talhouk JW, Rhoads RE, Knowlton KU. Enteroviral protease 2A directly cleaves dystrophin and is inhibited by a dystrophin-based substrate analogue. J Biol Chem 2000;275:1191–1197.
71. Badorff C, Lee GH, Knowlton KU. Enteroviral cardiomypathy: bad news for the dystrophin-glycoprotein-complex. Herz 2000;25:227–232.
72. Dettmeyer R, Kandolf R, Baasner A, Banaschak S, Eis-Hübinger AM, Madea B. Fatal parvovirus B19 myocarditis in an 8-year-old boy. J Forensic Sci 2003;48:183–186.
73. Arola A, Jokinen E, Ruuskanen O, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents. A nationwide study in Finland. Am J Epidemiol 1997;146:385–393.
74. Pauschinger M, Meissner G, Preis S, et al. Detection of enteroviral RNA by polymerase chain reaction in patients with myocarditis and dilated cardiomyopathy. JACC 1994;1994:880.

Death Scene Investigation

9

Human Primitive Behavior

Achim Th. Schäfer, MD

Contents

Summary

In dangerous, strenuous, or life-threatening situations, some behavioral patterns may occur that do not belong to the "normal" spectrum of human behavior. Among these are what is referred to here as "sedimentation" (which may result in the finding of a feeble person or a deceased in topographically low-lying sections of buildings), as well as the phenomena of hiding and covering and undressing (a well-known phenomenon related to fatal hypothermia), and other behavioral elements of minor relevance like confusion, fumbling, and screaming. These behavioral peculiarities may lead to dubious findings at a death scene and may be mistaken for signs of a preceding crime by the unwary. Sometimes, circumstantial findings seem to indicate that a fight or a violent or sexual offense took place. However, a more thorough analysis of the scene often shows that the whole situation had been created by the deceased himself or herself prior to death without any third-party involvement. The aforementioned behavioral elements are termed "primitive" here because at least some of them, like covering and hiding, seem to originate

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

from early developmental stages of human instinctive behavior as a reaction pattern in response to danger and stress that also can be observed in animals. These behavioral patterns have their origin in phylogenetically old, autonomous parts of the brain. A good knowledge of the elements and patterns of human primitive behavior and the associated ways of acting is most helpful to all those involved in the death investigation because it often helps in the correct interpretation of curious death scene scenarios that otherwise would remain obscure or even enigmatic. Also, search and rescue teams will benefit from taking these behavioral patterns into consideration because they enable the development of improved search strategies for seeking missing persons.

Key Words: Primitive behavior; human behavior; hiding; covering; undressing; confusion; fumbling; death scene investigation; crime scene; search and rescue.

1. Introduction

Missing persons are sometimes found dead under suspicious or curious circumstances, thus pointing to dubious or even mysterious events taking place prior to death. Such circumstances include finding a deceased individual in a remote or hidden spot, finding a dead body covered by unusual material or partly buried, or finding a deceased individual naked in a cold environment. Any experienced forensic pathologist who is involved in death scene investigation and crime scene analysis has already dealt with such cases. At first glance, the aforementioned scene findings do frequently look as if a homicide took place or at least they seem to indicate the involvement of a third party at the scene of death. Not only the inexperienced or unwary may misinterpret such unusual scene findings, especially in curious death scene scenarios and when the victim is found with additional signs of external violence preceding death. Hastened conclusions may lead the investigative inquiries in a false direction and, in the worst case, to the miscarriage of justice. After a thorough examination of the respective case, it is often discovered that the enigmatic finding situation of the deceased had been created by the affected individual as a result of behavioral patterns that took place in an agonal state.

The underlying motivations for such special behavioral patterns in agony, termed in the following as "human primitive behavior," are often difficult to understand. Human primitive behavior, as mysterious as it may seem, is not generally unpredictable because it seems to follow its own legalities. Immediately prior to death, in agony, when the conscious, rational control of thoughts and ways of acting is fading, impulses for certain activities may sometimes arise. These impulses, according to this author's opinion, originate from early devel-

opmental stages of human instinctive behavior that are normally suppressed in the mentally unaffected but can be resurrected in extreme situations of life.

In this chapter, some primitive behavioral elements that have caught the author's attention over the last couple of years are described and their possible meanings and backgrounds are discussed. Additionally, special attention is paid to the forensic pathological significance of such behavioral patterns.

2. Elements and Patterns of Human Primitive Behavior

2.1. Sedimentation

2.1.1. Case 1

An elderly female in-patient disappeared from an internistic ward the night before she was to be transferred to the closed psychiatric ward because of her nocturnal confusion and restlessness. Despite an extensive search of the entire hospital area, she could not be found for a few days. Five days later, some workers who had heard strange noises, found her in a remote spot of the topographically most low-lying section of the hospital's cellar. She was exsiccated and in bad physical condition, but still alive and survived the strains of her excursion.

Comments

Why was this elderly woman found in the topographically most low-lying area of the cellar and not elsewhere in the hospital? She was restless and confused, and during the night she wandered around. When she accidentally found a stairway, she followed a last strenuous way that led obviously downward. Her weakness did not allow her to climb up the stairway and thus, gradually, she reached the topographically most low-lying part of the building that was accessible.

If there is a chance, the weak, the tired, the injured, the ill, the disorientated, and the ailing who erroneously wander around will follow the easiest way, which is frequently the way downward. As this direction is determined by the forces of gravity rather than by the individual's own intention, this behavior, which is termed here "sedimentation" (analogous to particles sinking down in a liquid) is one of the most elementary of the behavioral patterns discussed in the following.

In confined spaces such as buildings, the phenomenon of sedimentation will lead the way of the persons concerned into the cellar or at least into topographically low-lying areas (Fig. 1A,B). Outdoors, topographically low-lying regions are valleys, trenches, hollows, caves or the bottoms of hills or moun-


A


B

tains. These are the regions where a missing person that is known to be in a state of confusion or disorientation, respectively, is likely to be found (Fig. 2). When lakes, rivers, or canals are located in such lowland, it is a common observation that drunken, intoxicated or otherwise helpless persons drop into such waters.

The fact that the weak and helpless often fall downstairs, thereby sometimes suffering severe injuries, or fall into pits, ditches, or shafts can be regarded to some extent as an exaggerated manifestation of the sedimentation process. One is also tempted to speculate that the certain tendency of young infants (who just have begun to walk) to fall into garden ponds can be, to a certain degree, explained by a similar sedimentation mechanism.

2.2. Hiding

2.2.1. Case 1 (continued)

The elderly woman in this case was not only found in the topographically most low-lying section of the hospital but was also hidden in a metal case (a kind of technical device that belonged to the hospital's air-conditioning system). Had she not produced some strange noises, not voluntarily like yelling for help, but coincidentally by moving herself within the metal case, she would probably have never been found as she was entirely unseeable to anyone passing by.

Comments

Although the process of sedimentation of persons into topographically low-lying areas follows mainly the legalities of physics, the phenomenon of

---

Fig. 1. *(Facing page)* Sedimentation and partly paradoxical undressing: death scene. This 61-year-old homeless man was found dead in the cellar of an abandoned factory building in December 2003. When he was found, the ambient temperature was around 0°C. His jacket, pants, underpants, socks, shoes, and personal belongings were found scattered around on the floor in the near vicinity of the body. Apart from acute purulent bronchitis, autopsy revealed Wischnewsky´s spots in the gastric mucosa, acute hemorrhagic pancreatitis, and edema of the lungs. An intoxication was ruled out by a thorough toxicological analysis. In accordance with the finding situation of the deceased, death was attributed to hypothermia. **(A)** The deceased is lying in a prone position on the floor of the cellar. Note partly undressing as well as clothes, personal belongings, and emptied beer cans in the background. **(B)** Closer look at the deceased's clothes scattered around in the near vicinity of the body. (Courtesy of Dr. Michael Tsokos, Hamburg, Germany.)

Fig. 2. Sedimentation: death scene. This mentally retarded 72-year-old woman who had escaped from a locked psychiatric ward one week earlier was found in December 2002 outdoors in the topographically most low-lying area, a hollow. Outcome of toxicological analysis was negative and external violence could be excluded by autopsy means. Autopsy revealed no acute lethal event and death was stated to be most probably as a result of hypothermia. When this photograph was taken, the body had already been moved from a prone to a supine position as indicated by rigor mortis. (Courtesy of Dr. Michael Tsokos, Hamburg, Germany.)

hiding is a more active, self-induced process that fits the hypothesis of a phylogenetically old, primitive element of behavior. Some humans, when put under extreme stress, seem to have the tendency to hide themselves somewhere in the same manner as we know it from ill or wounded animals. Wounded animals try to hide in the deepest undergrowth, in bushes, thickests, or caverns. Humans may hide outdoors in or under similar structures (Fig. 3) or when inside confined spaces (e.g., buildings), they try to hide in remote niches (i.e., under the bed, in wardrobes, or under other pieces of furniture; Fig. 4).

Hiding gives the critically ill, the injured, and the defenseless, those individuals in need of quiet, at least partial protection against the influence of harm from the outside such as weather or dangerous animals. In such a setting, the individual may rest and possibly recover from his or her strains. The natural benefits of hiding are easily understood, but if a critically ill or confused person hides himself or herself, the probability of a search and rescue team finding this person in time is considerably limited. In the worst case, this

Fig. 3. (Partly) paradoxical undressing and hide-and-die-syndrome: death scene. This 45-year-old man with a previous history of alcohol abuse was found in a small thicket near a clearing in January 2003. When the body was found, the ambient temperature was –9°C. His sweater, day-shirt, and jacket were found on the ground 50 m away, forming a track in the direction of the body. According to the traces in the snow, the man must have crawled on all fours before he reached his final position in the thicket. At external examination, red-purple spots attributable to hypothermia were present on knees and elbows. Apart from a marked edema of the lungs, autopsy findings were unremarkable. Toxicological analysis revealed a blood alcohol concentration of 131 mg/dL and an urine alcohol concentration of 278 mg/dL. According to death scene findings and outcome of autopsy, death was considered to be most probably as a result of hypothermia. (Courtesy of Dr. Michael Tsokos, Hamburg, Germany.)

may result in the ill individual's death. The behavioral element of hiding is therefore not unlikely to cause danger for the person concerned but is, nevertheless, observed from time to time. It has been referred to as the "hide-and-die-syndrome" in forensic medicine textbooks *(1)*.

Persons who hide themselves in extreme situations seek protection in a very elementary way, but from a rational point of view, staying in the open may turn out more advantageous for them to be found and rescued. However, in the severely stressed, the tendency to hide oneself frequently outweighs the benefits of showing oneself in the open. This tendency may be so intense that, if an appropriate place to hide cannot be found, walls, corners, or even trees or similar structures can serve as substitute hiding places. A frightened child

Fig. 4. Hide-and-die-syndrome: death scene. This 56-year-old woman was found in her burned-out apartment hidden under a small table next to her bed. It was reconstructed that the fire had started from ignition of the bed linen by a cigarette. Note heat flexures of the limbs ("pugilistic attitude") and skin splitting on the right lower leg. Death occurred after the fire had started as indicated by soot particles found in trachea, bronchi, esophagus, and stomach and highly elevated carbonmonoxide levels. Blood alcohol concentration was 210 mg/dL. (Courtesy of Dr. Michael Tsokos, Hamburg, Germany.)

who is alone in an empty room will not stay in the middle but will seek a corner in which to cover in a helpless attempt to hide. Sometimes, it seems that this hiding behavior is driven by a tendency to achieve a maximum of skin contact to surrounding surfaces. The more powerful the extent of contact, the greater the protective effect of the hiding place. Although such considerations will never be realized on the level of consciousness, the patterns of human primitive behavior appear to work in such a manner. Therefore, the phenomenon of hiding sometimes results in finding missing persons in very narrow clefts, tubes, or other spaces that seem hardly big enough to hold or cover, respectively, a human body. For this reason, when searching for a missing person, a very careful check of even small holes and similar places is highly recommended.

2.3. Covering

2.3.1. Case 2

A 50-year-old female schizophrenic in-patient ran away from a closed psychiatric ward. A few days later, she was found dead in a remote part of a marshy forest, wrapped into several blankets. However, autopsy revealed fatal hypothermia as the cause of death.

2.3.2. Case 3

Two elderly sisters lived together in the same apartment. One of the women was helpless as a result of an advanced stage of Alzheimer's disease. Her sister, who was still healthy, took care of her. One day, both sisters were found dead in the bedroom. According to death scene investigation and autopsy findings, it was reconstructed that the healthy sister died first from an acute myocardial infarction. She had been found lying on the floor next to her bed. Obviously, some days later, the sister who suffered from Alzheimer's disease had died of exsiccation because she was not able to take care of herself and was not even in a position to leave the room. The door to the room was closed but not locked. The peculiarity of this case was that the sister who suffered from Alzheimer's disease had built a kind of "nest" in one corner of the room. This "nest" was made of bed linen she had pulled from the beds and of other textiles she had managed to pull out of the wardrobe. When she was found, she was covered with clothes, sheets, and similar materials.

Comments

Covering seems to be a behavioral element quite similar to the phenomenon of hiding mentioned previously. It gives the helpless shield and protection, particularly against the cold. The schizophrenic patient in case 2 could have acted quite rational when she covered herself with several blankets.

It is a well-known phenomenon, however, that schizophrenic patients, independent of the ambient temperatures, tend to cover themselves with blankets, sheets, or with several layers of clothing, which was, in earlier times, also considered a diagnostic sign of schizophrenia *(2)*. In this way, such patients seem to try to protect themselves against the dangers of external influences that are so typically imagined in schizophrenia.

The victim in case 3 did not suffer from schizophrenia, nor was she exposed to low ambient temperatures. In this case, it is more difficult to understand why she had covered herself with all the materials. The most likely explanation for her behavior is that she experienced a vague feeling of fright or of being threatened that led her to bundle up the bed linen and clothes in

order to disappear embedded in this comfortable and soft material, like a child who seeks shelter and comfort when hiding in bed under the sheets. However, maybe the "nest" was not intentionally built and only an accidental product of her not organized last ways of acting. In this case, the covering behavior is somehow understandable as a primitive reaction pattern but turned out to be dangerous with respect to survival: if this woman would have shown herself at the window and if she would have yelled for help, her life could have probably been saved. Similar to the phenomenon of hiding mentioned previously, the phylogenetically old, primitive behavior pattern was stronger than any rational decision, at least in this extreme situation.

Covering as a behavioral element is not rare in despairing situations. Any material available may serve as a cover, be it clothes or sheets; papers or cardboards; or anything else inside a confined space; or leaves, grass, boughs, and even earth and stones found outdoors. In the medicolegal literature, this covering behavior has therefore been referred to as "terminal burying behavior" *(3)* and, indeed, sometimes it seems as if the victims have tried to bury themselves prior to death.

Search and rescue teams should be well aware of the possibility that missing persons have covered themselves with some material that was within reach and that such cover may appear like a camouflage that makes it sometimes extremely difficult to detect a body even if one is standing next to it. If no search and rescue dogs are available to back up the search for a missing person, it is at least necessary to turn up any possible cover in order to not overlook the missing person.

2.4. Undressing

Concerning the undressing behavior (so-called "paradoxical undressing"), no illustrative case report example is necessary. This is a well-known behavioral pattern most often seen in cases of fatal hypothermia *(4–9)*, but it has also been described in association with other states of mental confusion, for example, deriving from a relevant internal blood loss resulting from gastrointestinal hemorrhage *(10)*.

Undressing is the most enigmatic element of the behavioral patterns discussed here. It is evident that it cannot be understood as a primitive attempt to seek refuge, shelter, or protection in strenuous situations because undressing is highly dangerous in hypothermia as it increases the loss of warmth and thus shortens the possible survival time. Undressing is a behavior totally contrary to the hiding and covering behavior mentioned previously.

The origin and motives of paradoxical undressing of some individuals under cool or cold environmental temperatures (Fig. 5) are not well under-

Fig. 5. Paradoxical undressing: death scene. This 45-year-old man was found dead one early morning in December 2003 in a sandpit on a playground. The ambient temperatures the night before had ranged between –6°C and –2°C. The deceased was completely undressed with his underpants and pants down his feet. External violence prior to death was ruled out by autopsy. Autopsy revealed unspecific findings pointing out toward hypothermia as cause of death. Blood alcohol concentration was 190 mg/dL. (Courtesy of Dr. Michael Tsokos, Hamburg, Germany.)

stood so far. Most authors believe that in progressive hypothermia, a paradoxical feeling of warmth or even heat, arises, thus causing victims to undress themselves. This hypothesis, however, cannot explain the phenomenon of undressing in people who are suffering from mental confusion not caused by low ambient temperatures. The observation of an elderly, disorientated shoemaker who died of hypothermia one winter night in a dry creek after undressing himself does not support the aforementioned hypothesis of a paradoxical feeling of warmth because this man folded his clothes neatly first and then, finally, put his denture atop of his clothes as if he was in his own bedroom *(11)*. This case may be an exception, but certainly the hypothesis of a paradox feeling of warmth cannot sufficiently explain all cases of hypothermia-induced undressing prior to death. It is difficult to theorize alternative explanations for such a behavior, but this author imagines that one motivation for undressing could occur if the individual's skin itches or hurts so intensely that even the

slightest touch of clothing cannot be tolerated. In other cases, the phenomenon of undressing in a state of confusion or disorientation, respectively, may be a result of aimlessly fumbling around (see later) and of delusion or illusion, respectively. This behavioral element still deserves further elucidation.

Of course, the finding of a dead, naked, or partially undressed "victim," particularly when found outdoors, raises the suspicion of a preceding crime (most frequently that of a sexual assault). In some cases, such an event may actually have caused the dubious scene findings but it is necessary that anyone involved in death scene investigation is well aware of the fact that undressing may be a pure result of the deceased's own terminal activities in agony. Otherwise, this primitive behavioral element could easily be misinterpreted.

2.5. Other Elements of Primitive Behavior

2.5.1. Confusion

Confusion may arise in many situations (i.e., in the critically ill, as a result of intoxication, inebriation, metabolic disorders, psychic or somatic diseases), and also in a number of other underlying pathological conditions. The confused and the disorientated act aimlessly, sometimes without any remarkable effect but sometimes bringing their surroundings into heavy disorder. The mess caused by the confused may resemble the devastating effect of a natural disaster and occasionally their homes look like they had been bombed.

In the worst case, a confused person may build a fire, flood a house, or even induce an explosion by helplessly acting with cooking facilities, electrical equipment, water taps, gas bottles, flammable liquids, and so on. Others wander around on highways or railway lines or manage to enter dangerous places like factories, mills, quarries, and so on. Consequently, the confused may be dangerous to the public, but generally they endanger themselves much more than others.

The confused often may follow their own vague intentions. In such cases, the actions performed by the confused are not entirely absurd but represent activities that are, however, entirely inadequate. The affected individuals may rip their beds in order to build a life-sized dummy from the material or they may use their kitchenware to construct some crazy machinery. This behavior may merge in the hiding or covering behavior discussed before. If such a scene has to be interpreted (e.g., under criminalistic or psychiatric aspects), it is generelly quite obvious that the mess was caused by the victim's own actions, as the scene findings hardly ever resemble those found following a struggle or any other kind of violent offense.

2.5.2. Fumbling

Fumbling is a repeated or permanent slight activity of the fingers and hands like picking, pulling, stretching, turning, wiping, pressing, and similar movements that is frequently seen in senile dementia and in delirium tremens, but also occurs in other underlying pathological or circumstantial disorders because it has also been observed in a victim dying from hypothermia *(12)*. Sometimes these movements resemble activities the patient used to perform during his or her occupational work: the seamstress or tailor produces sewing-like movements, the carpenter seems to hammer, and the cook carries out cutting-like actions.

Even if fumbling is normally harmless, it may nevertheless cause considerable destruction of the person's surroundings. Food products are kneaded to shapeless masses, electrical wires are pulled down, glasses and dishes are turned upside down or broken, bed linen or the affected person's clothes are torn into pieces. Particularly, this last situation may be misinterpreted if such a person is found in torn clothes or partially undressed. Sometimes, the latter cannot be distinguished from the phenomenon of undressing and occasionally, the scenes concerned look as if a third party was involved.

Fumbling actions may also result in self-inflicted wounds if the same part of the body is always pressed, turned, or rubbed. Occasionally, it can turn out to be difficult to differentiate whether such injuries are a result of self-harm (in the sense of autoagressive mutilation), an underlying skin disease, or caused by a third party.

2.5.3. Screaming

Loud screams (shrill, sometimes bestial yelling) were a sign of the approaching death for the physicians of ancient times. Such screams have their origin in phylogenetically old, autonomous parts of the brain and may appear, besides fumbling movements and seizures, when the filtering and suppressing functions of the cerebral cortex are not functioning anymore. This is the case when brain death is approaching: during agony, when sufficient oxygen supply has declined and the neurons of the cerebral cortex have already suffered irreversible damage, deeper (phylogenetically older) parts of the brain that are less vulnerable to oxygen shortage are still active. Today, in times of intensive care and a broad range of drugs administered to patients in their terminal phase of life, such screams are hardly ever heard.

Nevertheless, screaming as a primitive behavioral element deserves to be mentioned here, not only as it has been referred to already in the Bible (*Mark 15:37 and Matthew 27:50: "And Jesus cried with a loud voice, and*

gave up the ghost") but also because such screaming ascribable to human primitive behavior can be easily mistaken for an expression of pain, anger, fear, or similar feelings. Therefore, it is noteworthy that terminal screaming of the dying does not unequivocally indicate a feeling of discomfort or distress of the individual in agony but rather corresponds to a primitive reaction pattern far from the level of consciousness. Originally, such screams may have had a social function as they would warn group or tribal members of life-threatening dangers, but today, they show the proximity of death, nothing more.

3. *Conclusions*

To summarize the behavioral elements presented here under the term "human primitive behavior" represents a somewhat theoretical concept. These behavioral elements hardly ever manifest in a pure or isolated form but rather as a part of complex behavioral patterns of the stressed, injured or terminally ill *in extremis*. This is why they have been named here "elements," being an imaginary basic feature of some irregular and strange behavior. At least some of the behavioral patterns presented here, like covering and hiding, seem to originate from early developmental stages of human instinctive behavior as a reaction pattern in response to danger and stress and can be observed in animals put under similar conditions, too. These behavioral patterns have their origin in phylogenetically old, autonomous parts of the brain. It is quite clear that an individual will benefit from hiding or covering in some situations.

In the vast majority of cases the forensic pathologist or any other investigator involved in death scene analysis and crime scene analysis, respectively, will not find any hints toward these behavioral elements, which is evidently attributable to the fact that death had occurred rapidly or that sudden weakness or loss of consciousness prevented any activity of the deceased prior to death. Human primitive behavior is a rare event. Nevertheless, it is worth mentioning because it occurs now and then and may cause otherwise inexplicable situations and findings at a death scene. Why was this disorientated person found in the topographically most low-lying section of the building and not anywhere else? Why has this man who has died of hypothermia obviously undressed himself prior to death? Why was this confused elderly woman detected in a hollow in the forest and partially covered with leaves? The concept of human primitive behavior sheds light on these and many other problematic finding situations encountered in death scene investigation. Another example of how the concept of human primitive behavior can be applied to elucidate obscure fatalities is that of the German politician Uwe

Barschel, who died in Geneva, Switzerland in 1987. Barschel committed suicide by barbiturate intoxication. He was found dead fully dressed in the bathtub of his hotel room. At autopsy, some bruising zones were detected on his scalp that could not be sufficiently explained by the investigating authorities and hence gave rise to several conspiracy theories *(13)*. These bruising zones are easily understood once the concept of primitive behavior is applied: as a consequence of the intoxication with barbiturates, in a state of mental confusion, he staggered around, once or several times hitting his head against walls or other rigid surfaces that were located in his immediate vicinity in the bathroom, before he, finally, laid himself into the bathtub and died.

Thus, a profound insight into the elements and patterns of primitive human behavior may sometimes turn out helpful in elucidating curious death scene scenarios that otherwise would remain obscure or even enigmatic. Of course, not all those who are put under extreme situations or who are critically ill will eventually die. A large number of them will recover from their strains or diseases, respectively, or might be rescued if help is available in time. This is why a good knowledge of the primitive behavioral elements described here and the associated ways of acting is most useful not only to all those involved in death investigation (in such cases helping to correctly interpret death scenes), but also to members of search and rescue teams who will be able to develop improved search strategies with respect to the phenomena of sedimentation, hiding, covering, and so on. However, not all missing persons will, when put under stress, behave the very same way. The confused or disorientated may walk a long distance from their homes without reaching or falling into topographically low-lying structures. Others will lay down and die without any activities toward hiding, covering, or undressing. Therefore, the concept of human primitive behavior cannot be applied uncritically to any situation but may at least turn out helpful in the interpretion of some findings at a scene of death.

References

1. Saukko P, Knight B. Knight's Forensic Pathology, 3rd ed., 2004 Arnold, London
2. Altschuler E Shakespeare knew the layered clothing sign of schizophrenia (letter). BMJ 1999;319:520,521.
3. Rothschild MA, Schneider V. "Terminal burrowing behavior"—a phenomenon of lethal hypothermia. Int J Legal Med 1995;107:250–256.
4. Gormsen H. Why have some victims of death from cold undressed? Med Sci Law 1972;12:200–202.
5. Wedin B, Vangaard L, Hirvonen J. "Paradoxical undressing" in fatal hypothermia. J Forensic Sci 1979;24:543–553.

6. Sivaloganathan S. Paradoxical undressing due to hypothermia in a child. Med Sci Law 1985;25:176–178.
7. Sivaloganathan S. Paradoxical undressing and hypothermia. Med Sci Law 1986;26:225–229.
8. Kinzinger R, Risse M, Püschel K. "Kälteidiotie"—Paradoxes Entkleiden bei Unterkühlung. Arch Kriminol 1991;187:47–56.
9. Rothschild M. Lethal hypothermia: paradoxical undressing and hide-and-die-syndrome can produce very obscure death scenes. In: Tsokos M, ed. Forensic Pathology Reviews, Vol. 1. Humana Press Inc., Totowa, NJ, 2004, pp. 263–272.
10. Adebahr G, Risse M. Über Verwirrtheitszustände bei Blutungen in den Magen-Darmkanal aus Magenschleimhaut-Erosionen. Beitr Gerichtl Med 1989;47:341–343.
11. Schwarz F. Der außergewöhnliche Todesfall. Enke, Stuttgart, 1970.
12. Meixner K. Ein Fall von Tod durch Erfrieren. Dtsch Z ges Gerichtl Med 1932;18:270–284.
13. Mergen U. Tod in Genf. Kriminalistik Verlag, Heidelberg, 1988.

Forensic Entomology

10

Arthropods and Corpses

Mark Benecke, PhD

Contents

Summary

The determination of the colonization interval of a corpse ("postmortem interval") has been the major topic of forensic entomologists since the 19th century. The method is based on the link of developmental stages of arthropods, especially of blowfly larvae, to their age. The major advantage against the standard methods for the determination of the early postmortem interval (by the classical forensic pathological methods such as body temperature, postmortem lividity and rigidity, and chemical investigations) is that arthropods can represent an accurate measure even in later stages of the postmortem interval when the classical forensic pathological methods fail. Apart from estimating the colonization interval, there are numerous other ways to use

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

arthropods as forensic evidence. Recently, artifacts produced by arthropods as well as the proof of neglect of elderly persons and children have become a special focus of interest. This chapter deals with the broad range of possible applications of entomology, including case examples and practical guidelines that relate to history, classical applications, DNA typing, blood-spatter artifacts, estimation of the postmortem interval, cases of neglect, and entomotoxicology. Special reference is given to different arthropod species as an investigative and criminalistic tool.

Key Words: Arthropod evidence; forensic science; blowflies; beetles; colonization interval; postmortem interval; neglect of the elderly; neglect of children; decomposition; DNA typing; entomotoxicology.

1. Introduction

Hundreds of arthropod species are attracted by corpses, primarily flies (Diptera), beetles (Coleoptera), and their larvae (Fig. 1). The animals feed on the body, and live or breed in and on the corpse, thus depending on their biological preferences, and on the state of body decomposition (Fig. 2).

Because arthropods are by far the largest and most important biological group on earth (they outnumber even plants), they can be found in a wide variety of locations including many crime scenes. This opens a wide range of applications of arthropod evidence to forensic entomologists (i.e., the use of insects recovered from crime scenes and corpses in an investigative or criminalistic context).

By calculating their developmental stage (Fig. 3), arthropods are useful in estimating the time since when a corpse was inhabited by the animals. This estimate is often referred to as the *postmortem interval* (PMI). One has to be well aware that this is, in technical terms, not a determination of the actual PMI in every case because the deceased may have been stored previously in an environment or under conditions that partially restricted access to insects (e.g., very cold, rainy, or tightly sealed environments). The term *colonization interval* is therefore more appropriate for forensic entomology purposes.

Insects are attracted to specific states of decomposition (e.g., bloated decay, fermentation, mummification, or skeletonization). Most species colonize a corpse for only a limited period of time. This change of insects over time is called *faunal succession*.

Together with the knowledge of larval growth rates (always depending on the specific environmental conditions), faunal evidence provides a method for estimating the time elapsed since death, but only if the biological observa-

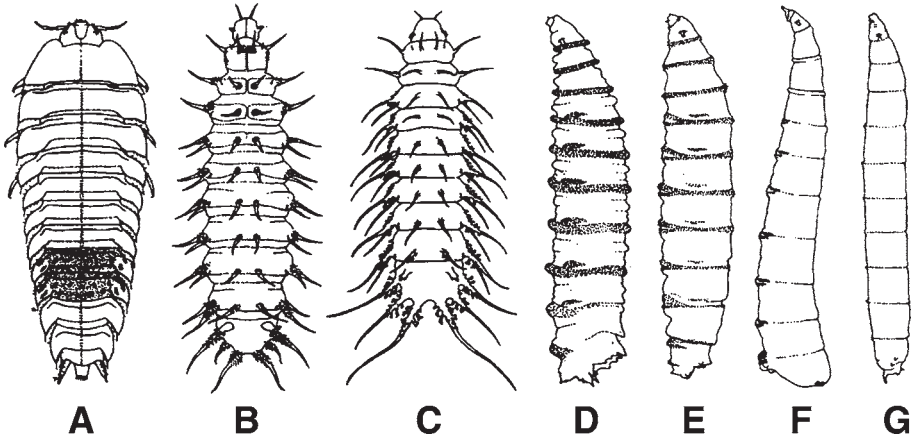

Fig. 1. Larvae of some forensically relevant insects. These insects are attracted by corpses at different yet overlapping times during the first months of decomposition of vertebrate corpses. **(A)** Staphylinid beetle larva (*Silpha* spec., length here: 17 mm). **(B)**–**(G)** fly larvae = maggots. **(B)** Small house fly *Fannia canicularis* (6 mm), **(C)** "bathroom fly" *Fannia scalaris* (5 mm), **(D)** blowfly *Phormia regina* (15 mm), **(E)** green bottle (fly) *Lucilia* spec. (15 mm), **(F)** house fly *Musca* spec. (11 mm), **(G)** cheese skipper *Piophila casei* (8 mm).

tions are set in relation to ecologic, criminalistic, and medicolegal clues *(1–30)*.

There are several other types of information that can be derived from arthropods found at a crime scene. For example, besides the estimation of the colonization time/PMI, the following information can be determined:

- Suspects have been linked to a scene of crime as a result of the fact that they had been bitten by arthropods specific to the vicinity *(119,120)*.
- Insects that live in restricted areas but are found on a corpse in a different area can prove that the body had been moved after death.
- Blowfly larvae can give information on how long children or elderly people were neglected by their relatives or nursing personel.
- Aspects of hygiene (e.g., appearance of larvae and flies in clean, empty rooms, or of maggots in food) can be explained by linking the entomological findings to known death cases or other environmental factors from the surroundings of the death scene *(30,31)*.
- A report describes that in ancient times a murder weapon was identified *(32)*.

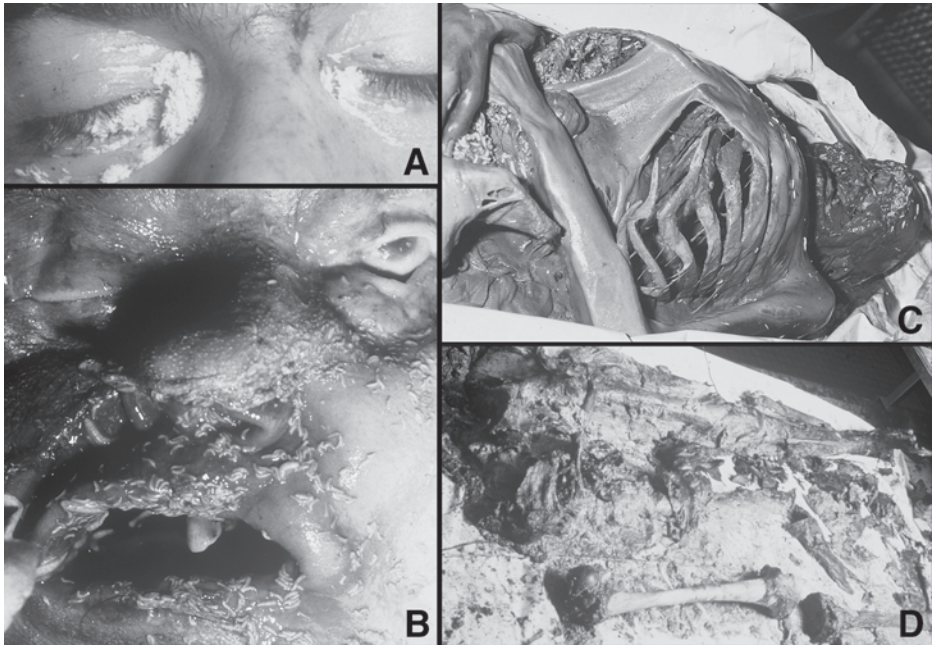

Fig. 2. Different stages of decay are associated with different types of insects and insect activity. Adult pregnant flies prefer to deposit eggs in the eyes, nose, mouth, and ears. **(A)** Patches of eggs (100–200 eggs each) from blowflies (few hours after death), **(B)** first instar larvae hatched and distributed over decomposing tissue (few days after death), **(C)** third instar larvae of flies produced severe tissue losses but left some skin relatively intact (few weeks after death), **(D)** most of the body tissue is vanished as a result of blowfly maggot interference; by now, cheese skipper larvae and adult beetles are present (few month after death). The exact determination of the colonization time ("postmortem interval") is only possible if weather conditions, especially the local environmental temperature, are well-known and documented. The corpses shown in (A)–(D) were found in warm months in Germany (Central Europe).

- Drugs that cannot be detected in severely decomposed tissue of a corpse may still be found in the insects that did feed on the corpse.
- The location of a stab wound can be determined by unusual feeding sites of beetles and maggots *(33)*.
- The question of whether a person was killed and brought outside during day or night time while it was raining or not may be scrutinized *(34–38)*.

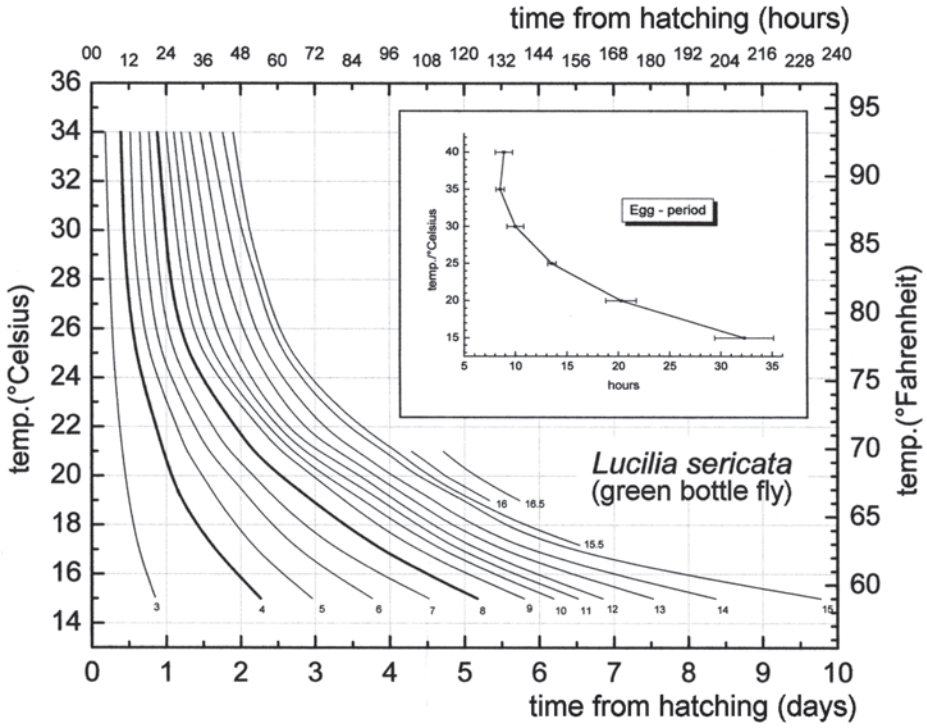

Fig. 3. Isomegale diagram as developed by Reiter and colleagues. Here: developmental times for the green bottle fly *Lucilia sericata,* a common early inhabitant of corpses. Note that the time inside of the egg (*egg period*) needs to be added (insert). (Modified according to ref. *10.*)

2. *History and Early Casework*

The acceleration of decomposition by insect interference has been well documented throughout the past centuries. In many cases, the decompositional stages seen in figurines, paintings, and drawings perfectly match with the influence of insects feeding on corpses (Fig. 4). What seems to be snakes are in many cases larvae of flies and beetles that are located at their preferred feeding sites: face (eyes, nose, ears, and mouth, where they are protected from drying up, rain, and cold) and the gut, after it becomes accessible. It is a phenomenon only of modern times that the actual view of decomposition becomes unusual even to medical doctors.

Correct artistic descriptions of insect activity, especially the early stages of infestation, are present in many sources including the following:

a

hic iacet : Robertus · toule ·
Expecto · resurrectionem · mortuorum ·
b

c

d

e

- Paintings like "Les amants trépassés" from the Musée de l'Œvre Notre-Dame (Strasbourg) from about 1470 (Fig. 4A).
- German woodcuts of "Dances of the Dead" (in German called *Totentänze*) from the late 15th century (Fig. 4C,D) Apart from wars, the exposure to decomposing bodies was partially a result of the plague or a similar disease that killed one-third of all Europeans approximately between the years 1346 and 1351 (but also between 1896 and 1945 starting in Asia and spreading through rats on boards of ships, killing more than 12 million persons worldwide).
- The French poet's Charles Baudelaire's (1827–1876) poem "Une charogne" in the collection of poems *Les fleurs du mal.* It includes an accurate reference to the sound of maggot masses on corpses: "Like water and the wind running/Or corn that a winnower in rhythmic motion/Fans with fiery cunning" *(39)*.
- Sculptures like an ivory skeleton (Fig. 4E), in which the heart is substituted by a blowfly, or the very frequently found *Tödleins* (little skeletons in coffins) from the times of Renaissance and Romanticism.

Artwork such as these accurately depict the insect-mediated pattern of body mass reduction, particularly the skeletonization of the skull and the reduction of internal organs, with large parts of the skin left intact.

The first documented forensic entomology case is reported by the Chinese lawyer and death investigator Sung Tz'u in the 13th century in the medicolegal text book *Hsi Yuan Lu* (one possible translation: "The Washing Away of Wrongs") *(32,40)*. There, he describes the case of a stabbing near a rice field. The day after the murder, the investigator told all workers to put down their working tools (sickles) on the floor. Invisible traces of blood drew blowflies to a single sickle. So confronted, the tool's owner "knocked his head on the floor, and confessed to his crime."

In 1767, the biologist Carl von Linné made the observation that three flies destroy a horse as fast as a lion does, by producing large amounts of

---

Fig. 4. (Facing page) Historical depictions correctly show the destruction pattern caused by arthropod activity. What seems to be snakes are larvae of flies and beetles in most portrayed cases. The insects are located at their preferred feeding sites: face (eyes, nose, ears, mouth where they are protected from rain, cold, and drying up) and gut after it becomes accessible. **(A)** Painting *Les amants trépassés*; ca. 1470, Musée de l'Œvre Notre-Dame, Strasbourg, France (Thank you to Burkhard Madea for bringing this to my attention) **(B)** "Here rests Robert Touse", "I await the resurrection from the dead"; most probably created in the 18th century (*118*), **(C,D)** "Dances of the Dead"; late 15th century, **(E)** ivory skeleton "Skelett in der Tumba"; 16th century, Schnütgen museum, Cologne, Germany; A blowfly substitutes the heart and maggots are visible on the skin.

maggots. During mass exhumations in France and Germany in the 18th and 19th centuries, medicolegal death investigators observed that buried bodies are inhabited by various arthropod species.

The first modern forensic entomology case report that included an estimation of the PMI was published by the French physician Bergeret in 1855 *(41)*. The case dealt with blowfly pupae and larval moths: "Within three years, four different tenants (i.e., families) lived in the flat. … The questions we had to deal with now were: (1) was the newborn delivered at an adequate age of gestation/born at the right time? (2) was it a live birth? (3) how long did the newborn live after confinement? (4) how did the newborn die? and (5) how long was the time interval between birth and death?" The first four questions were answered by means of classical forensic pathology; the fifth question was dealt with by calculating the colonization interval/PMI.

Estimation of the colonization interval of corpses started in the 19th century with the (popular) science book *La faune de cadavres* by Pierre Mégnin, which included already detailed case descriptions *(42,43)*. This entomological method then spread to Canada and the United States and then back to Europe. Starting in the 1920s, species lists and monographs on forensically important insects were finally published, putting the focus on ecology, metabolism, or anatomy. Both pest control and "maggot therapy" *(44–47,59)* received considerable attention during this period and many contributions stem from these fields, creating a major scientific source for interpretation of forensic insect evidence.

A detailed review on the early history of forensic entomology is given in ref. *48*.

3. Wound Artifacts and Unusual Findings

At the end of the 19th century, the bite patterns of cockroaches and ants became of interest. The abrasions of skin caused by these animals were sometimes mistaken for signs of poisoning (e.g., as sulphuric acid that had been running down the chin and neck) or wounds caused by appliance of external violence *(49–52)*.

Some researchers also focused on the influence of aquatic arthropods on corpses. *Gammarus pulex,* a freshwater crustacean, was found to produce large numbers of small needle-like lesions. Caddis-flies (Fig. 5) were also found to be of forensic relevance. They destroy skin layers of body parts that are not covered by clothing.

The casings of caddis-flies can also be used to determine how long a body had been in water (e.g., to answer the question when it was dumped in

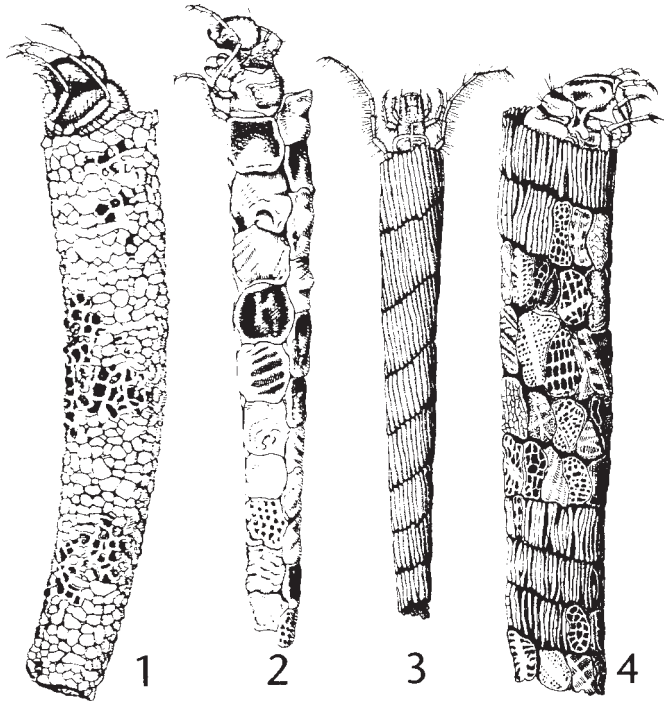

Fig. 5. Underwater (aquatic) arthropods can be used in forensic entomology, too, e.g., to estimate the colonization time of corpses by use of the aquatic arthropod's developmental stages or material used in casings. The animals do not necessarily feed on the corpse but can attach to clothing. Here: Caddis-flies (Tricheroptera) in their casings: **(1)** *Sericostoma* spec. (length of casing ≤15 mm), **(2)** *Lepidostoma hirtum* (≤18 mm), **(3)** *Triaenodes* spec. (≤30 mm), **(4)** *Phryganea* spec. (≤50 mm). Engelhardt in ref. *121*.

the water). In a case from the 1950s a caddis-fly casing (most likely of *Limnophilus flavicornis*) contained fibers of the red socks that were worn by the deceased. However, the fibers were only found at the very top and the very bottom of the casing, which meant that the fly had, for the most part, already built her casing and then finished it at the corpse (fibers on top), and after that attached it to the red sock (fibers on bottom). Because the attachment procedure takes at least a few days, it was estimated that the body had been in the water for at least 1 week *(53,54)*.

Another observation that was first reported in the 1930s were maggots entering the spongiosa of long bones to reach the bone marrow (intact skeleton, PMI 100 days, human remains found outdoors in Bavaria, Germany). It

was suggested that the animals crept through foramina nutritia, tiny gaps in the bones that allow blood vessels and nerves to enter the bones *(55)*. I saw the same phenomenon in an intact skeleton with the body tissues decomposed to a cream-like mass. A large quantity of cheese skipper larvae *(Piophila casei)* had entered the inside of the long bones and were still alive.

4. Exemplary Cases: Neglect of Elderly Persons and Children

Forensic entomology should be embedded in a criminalistic context. As a result of biological variations in growth rates, the influence of the environment can never be fully controlled under field conditions. It is important to give comprehensive answers to those questions that are actually asked by the court, the police, or other investigative authorities involved in a respective case. Therefore, instead of giving an extensive discussion of the determination of the PMI, the cases presented here are intended to show the wide range of possible applications of arthropods as forensic evidence.

Wounds of living persons are potential targets for the same flies that live or feed also on dead bodies during the early PMI *(56)*. This may lead to complications in the estimation of the colonization time. With the field of forensic entomology, and forensic entomologists being more present around the world, even "lower profile cases" (referring to those case in which no external violence has been applied to the victim), like the neglect of older people, come to our attention. Our population becomes older and the increase in the number of elderly people requiring residential care is rising. This leads also to an increased awareness of malpractice and neglect in the professional residential aged care setting *(57)*.

In specific cases, forensic entomology may help one to better understand the circumstances of death and especially those circumstances preceding death. From actual casework we get the impression that nursing injuries of elderly people currently become a severe problem positively correlated with the continuous aging of our society. From a juridical standpoint it is, and will continue to be, very difficult to judge if the nursing personnel in charge is guilty of misconduct. Forensic entomology can give important insights into the dynamics, amount, and final state of bodily care that was given to the respective person in need of care. Forensic entomology may also help to exonerate caregivers (e.g., when maggot infestation of a person's wounds occurred during a normal interval of nonvisits).

It is important that the forensic entomologist should attend the scene because the notice of complex environmental interactions, as well as the col-

Fig. 6. Case of neglect. Elderly woman surrounded by dead stable flies *Muscina stabulans*. Arrow points to intact eyes as an indication for the absence of blowflies that usually colonize corpses. Presence of dead *M. stabulans* strongly hints toward neglect with larvae feeding on excrements of the woman, but not on tissue. No entering/activity of blowflies because windows were closed.

lection of dead animals and pupae, can be problematic for police personnel unfamiliar with the discipline of forensic entomology.

4.1. Clean Apartment With Dead Stable Flies

In October 2002, an elderly woman was found dead in her third-floor apartment in Cologne, Germany. Her skin was mummified, but her eyes, for the most part, were still intact (Fig. 6). The apartment was very clean except for the bathroom, where the bathtub was filled with water and clothing. Apart from larvae, exclusively dead adult flies of the species *Muscina stabulans* were found scattered on the floor and on a window that pointed to the northwest (the apartment had no windows southward). No blowflies in the zoological sense of the word were present in any developmental stage. We decided to base our statement on the fact that all adult flies had already emerged from the pupae. We used the developmental data reported earlier *(12,15)* at a range of reasonably possible room temperatures:

Marchenko (*15*)	19°C	22.8 days
	20°C	21.0 days
	21°C	19.5 days
Nuorteva (*12*)	about 16°C	26–28 days

An approximate minimum interval of around 3 weeks would have been a culpable flaw of the paid professional caregiver who was supposed to look after the woman once every week. The caregiver, however, claimed that she had called the woman about 2 weeks prior, but the elderly woman allegedly rejected any visits. This possibility could not be ruled out because the old woman was known to be healthy, but mentally unstable and displaying "difficult" behavior.

This case shows the importance of a death scene visit by the forensic entomologist: the insects would not have been collected by the police investigators because they did not appear to be feeding on the corpse. They were considered just to "lay around by chance." In marked contrast to the entomological findings, it was assumed that the caregiver had tried her best and no criminal or civil accusation followed.

4.2. Deep Tissue Loss at Wrapped Foot

In September 2002, an elderly woman was found dead in her apartment in an urban town in Germany. Her one foot was wrapped in a plastic bag (Fig. 7). Inside the plastic bag, numerous larvae of *Lucilia sericata* were found. Inside of the flat, the police explicitly stated the absence of adult flies. However, the apartment was in bad shape and even the landlord had noted in January 2002 that renovations were urgently necessary as a result of wet spots in the walls. He also had noted the presence of "small flies." The women did not clean her toilet appropriately, and wet clothing was found in the washbowl. Therefore, a fly population could have been established even without injuries to the woman. To everybody's surprise, the caregiver openly stated that "it is well possible that the foot of the person was wrapped in a plastic bag and that maggots may have been present inside of the plastic bag during the lifetime of the woman." The general practitioner estimated the PMI as more than 2 days. The age of the maggots was estimated from their size (11 mm) as approx 4 days (4 × 24 hours) at a recorded environmental temperature of 20°C.

However, judging by the deep tissue loss of the woman's foot, it was decided that most likely the maggots had been feeding on the living woman for at least 1 week while she was still alive, but then the maggots left the bag to pupate elsewhere. The apartment could not be checked for pupae, however.

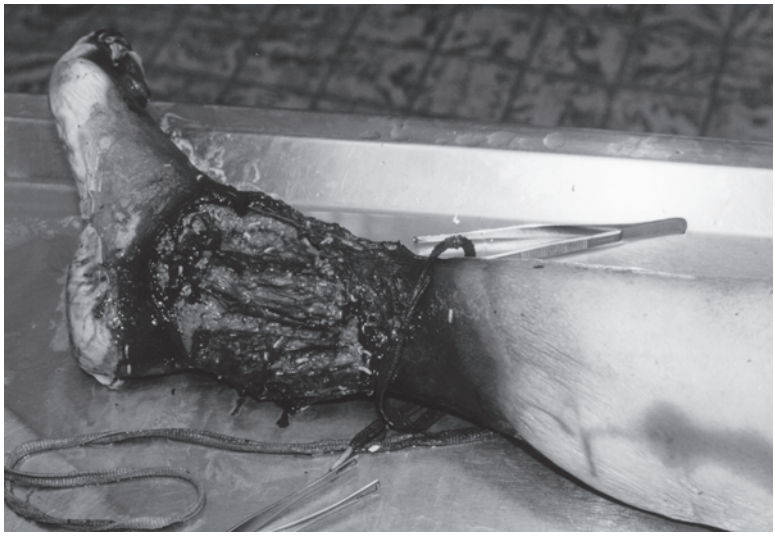

Fig. 7. Deep tissue loss on foot with the remainder of the body intact. Maggots fed on the wound even though the woman was still alive. Lace was used to close a plastic bag around the foot "so that the maggots could not crawl out any more." (Thank you to the Institute of Legal Medicine, Dortmùnd.)

4.3 Dead Mother on Couch

In March 2002, the corpse of an elderly woman was found in her apartment in an urban environment in Germany. The apartment was untidy in non-organic terms, but no rotten organic matter was present. The following insects were found on the corpse: larval *Fannia canicularis* house flies, larval *Muscina stabulans* stable flies, and adult *Dermestes lardarius* larder beetles. These insects are known to build up populations inside of human housings *(37,58)*, but the presence of *Fannia* frequently hints toward the presence of feces and urine (e.g., in cases of neglect).

In this case, further evidence of neglect of the living person was apparent as a result of the fact that the (obviously alive) skin was not fed on by the larvae and that pressure spots (Fig. 8) had formed. The eyes of the corpse were intact. Pupae of an unknown species were mentioned in a police report but they had not been collected. This led us to conclude that the corpse was not inhabited postmortem. If the eggs would have been deposited after the death of the woman, there would have been at least a minimal presence of eggs or larvae in the region of the eyes, ears, or nose because these are, together with wounds, preferred spots for colonization.

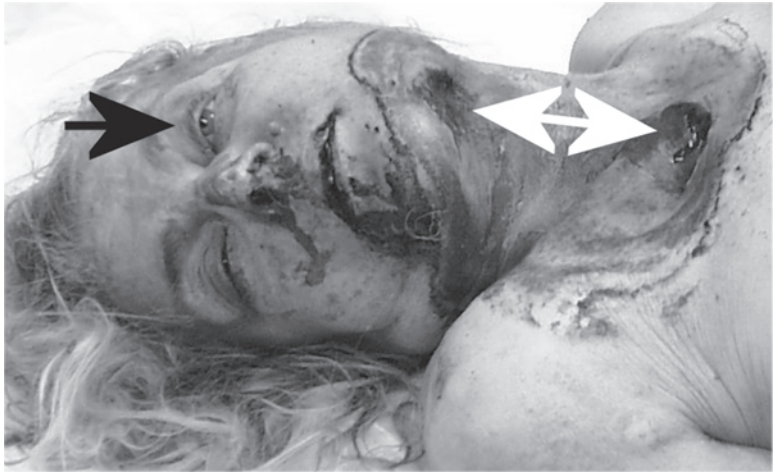

Fig. 8. Eyes intact, matching pressure points on the neck. The presence of larval *Fannia canicularis* house flies, larval *Muscina stabulans* stable flies, and adult *Dermestes lardarius* larder beetles strongly hinted toward neglect of this woman (i.e., colonization of the body while she was still alive).

The woman's son was prosecuted for neglect of his mother. He claimed that he fed his mother the evening before she died and that she was well at that time. Referring to the entomological findings and the pressure spots, his statement was not believed by the court.

We could not answer whether or not the woman had suffered from pain by larvae living on her body. From physicians performing maggot therapy *(44–47,59–61)* it is known that blowfly maggots inside of wounds may cause no pain at all, but may also cause severe pain.

4.4. Time of Neglect vs Time of Death

Close cooperation between forensic scientists, medicolegal investigators, and police forces have made it possible to estimate not only the PMI but also the amount of time a child was left neglected. In one particular case, on the skin surface under the diaper of a dead child (anogenital region), third instar larvae of the false stable fly *Muscina stabulans* and the lesser house fly *Fannia canicularis* L. were found. *F. canicularis* adults are attracted to both feces and urine.

From the face, larvae of the bluebottle fly *Calliphora vomitoria* were collected. *C. vomitoria* maggots are typical early inhabitants of corpses. From the developmental times of the flies it was estimated that the anogenital region

of the child had not been cleaned for about 14 days (range: 7–21 days) and that death had occurred only 6–8 days prior to the finding of the body. This led to a conviction not only of the mother but also of the welfare workers involved. The court decided that the time span between the onset of neglect and death of the child was long enough to seek medical advice and help, thus the child´s life could have been saved *(62–64)*.

4.5. Maggots in Only One Eye Socket of a Dead Person

A 41-year-old physician was found dead on his bed. The body was partially mummified and parts of the hip region were skeletonized as a result of maggot activity. In the face, blowfly maggots (*Lucilia [Phaenicia] sericata*) were found exclusively in one eye socket (Fig. 9). This is a very unusual occurrence because on that side a bedlight (40 W light bulb) had been switched on during the 7-week duration of the PMI. All other lights in the apartment were switched off, and no direct sunlight could enter the room where the body was found (only a TV set had been running all the time, about 2 m away from the head, at the foot of the bed). Obviously, the maggots, which usually flee light, had used the one eye that was further away from the light at the bed as the primary feeding source. Because continuing mummification led to a substantial restriction of the feeding material, the maggots finally switched to the eye on which the light was shining *(65)*.

4.6. Credit Card Fraud and Forensic Entomology

In November 2000, a decomposed woman's corpse was found in an apartment in a town in Central Germany. Because the doors were regularly closed, police assumed that the dead person was the tenant. As a result of the severity of decay, the PMI could not be determined by means of classical forensic pathology. On the other hand, determination of the PMI was important in this case because a credit card of the woman had been used, possibly after her death. At the death scene, numerous larvae of the "fly of the dead," *Cynomya mortuorum,* were found.

C. mortuorum larvae are known to normally feed on decomposing animal tissue. In this case, *C. mortuorum* could outcompete other fly species because of the closed rooms/restricted access. According to Nuorteva and Stærkeby *(2,7),* who found that at 15–16.6ºC the developmental time from egg to adult for *C. mortuorum* takes at least 26.2 days (maximum 31 days), we gave a similar estimation of colonization time. It was therefore possible that the bank card was used after the death of the woman *(62)*.

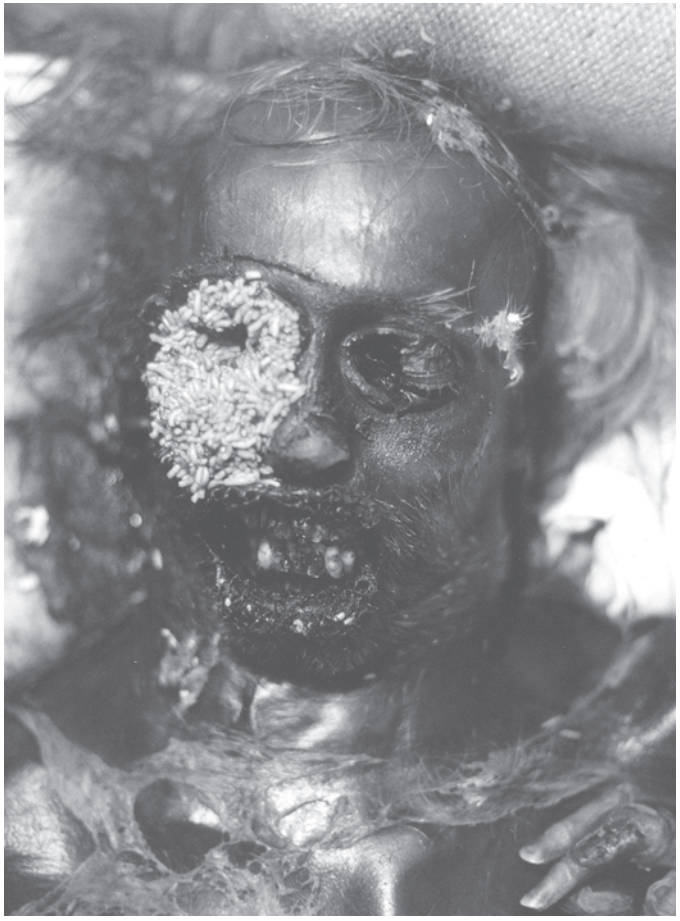

Fig. 9. Partly mummified body. In the face, blowfly maggots of the green bottle fly *Lucilia sericata* were found exclusively in one eye socket. See text for further details on this case.

4.7. Absence of Pupae as an Indication That a Corpse Was Moved

The corpse of a man was found in the trunk of his car. The body was partially decomposed. Because blood was found at the scene where the man was suspected to be killed, and as a result of witnesses' observations, it was assumed that (a) the man had been killed several days before in his car, then had been stored somewhere else and then was moved back or (b) he had been stored all the time in the trunk of the car.

About 1 year later, we were asked for an entomological expert opinion. The car was still in police custody and therefore could be examined. We found that no pupae had entered the gaps between the trunk and the back seats. This was unusual because maggots prefer to pupate in hidden places. Furthermore, the temperature had fluctuated heavily at one point so that maggots were expected to hide from the cold and/or to enter diapause. Apart from species determination of maggots and pupae that had been collected by the police the year before, we delivered the opinion that most likely the person was colonized by maggots at one point and then stored somewhere until many larvae went into a postfeeding or diapause state. Afterward, the corpse was moved back into the trunk of the car where only a few maggots were left on the corpse. Of those few, none entered the gaps. This clue became of great interest for the police and the district attorney's (prosecution's) office. Since this incident, the district attorney makes out search warrants for suspects' houses in respective cases to search them for matching pupae.

5. Collection of Arthropod Evidence

Under real casework conditions it might be necessary to adapt the collection procedure of arthropod evidence to the given situation or to local procedural regulations (e.g., chain of custody regulations). However, for training of federal agents of the Federal Bureau of Investigation (United States of America) and Bundeskriminalamt (Germany) we developed the following guidelines *(66,67)*.

5.1. Ten Golden (and Easy) Rules for Collection of Arthropod Evidence

1. Take very good close-up photographs of all locations from where animals are collected. The state of insect-aided decomposition can severely change within days, even under cool conditions, and even when the body is stored in a cooling apparatus (Fig. 10). Also, bites of mites should be documented on living persons (e.g., possible offenders; Fig. 11).
2. Photograph without a flash. Maggots will "flash out," which means they become "just white nothings," especially on digital photographs.
3. A metric *and* an inch scale should always be used on every single picture (Fig. 12).
4. Collect one spoon full of insects from at least three different sites of the corpse and the crime scene in three different, clearly labeled jars.
5. Put half of the insects in 98% ethanol. Cheap ethanol (i.e., methylated spirit for camping purposes) can be used without any problems. Neither isopropyl alcohol

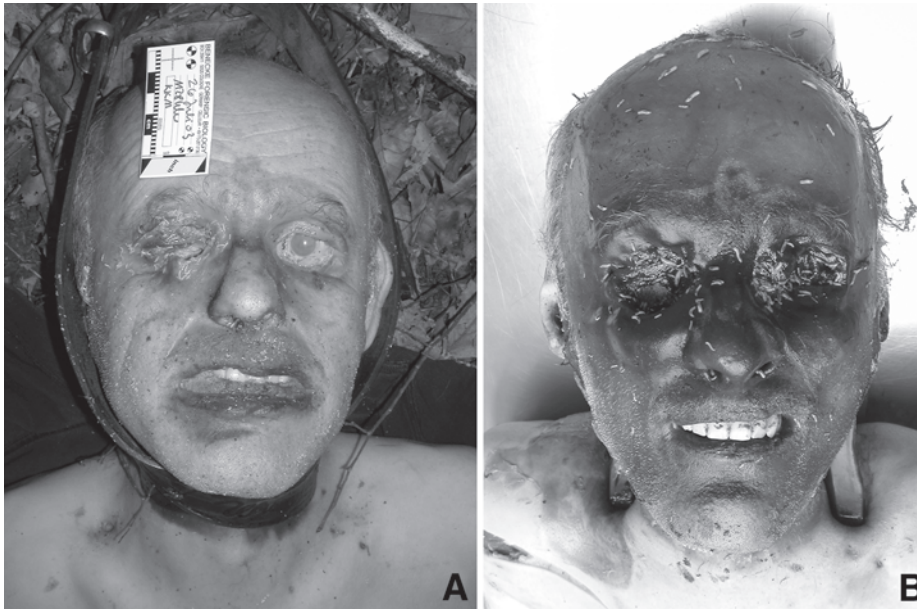

Fig. 10. Effects of storage on corpses. **(A)** Body found at a crime scene in the very hot summer of 2003 in Western Germany: maggot length did not exceed 5 mm, eyes intact. **(B)** Three days later, at autopsy: the skin is dried up, both eyes are destroyed by the maggots; marked contrast to appearance of the corpse when it was found at the scene of crime.

("hand cleaning alcohol") nor formalin should be used! Killed insects can be stored frozen with or without ethanol.

6. Attempts should be made to kill the animals with hot water ("tea water") before placing them in ethanol.
7. If possible, put half of the insects alive in a refrigerator (not a freezer). Put fabric on top so the insects can breathe. Maturing might become an issue, so forward the animals to a biologist within 1 or 2 days. Keep white larvae separate from brownish larvae and separate larvae from adults if possible.
8. Label excessively: location, exact time, date, initials.
9. If questions arise during collection, a forensic entomologist should be called.
10. Determination (i.e., identification of the arthropod species) *must* be performed by an experienced entomologist using keys that can be applied to the local fauna (e.g., *68–76)*. However, for many regions of the world, appropriate keys are not yet available. Some forensic entomologists determine third instar larvae of known maggot species by the characteristics of the maggot's mouth parts (Fig. 13 *[5,36,74,77,78])*.

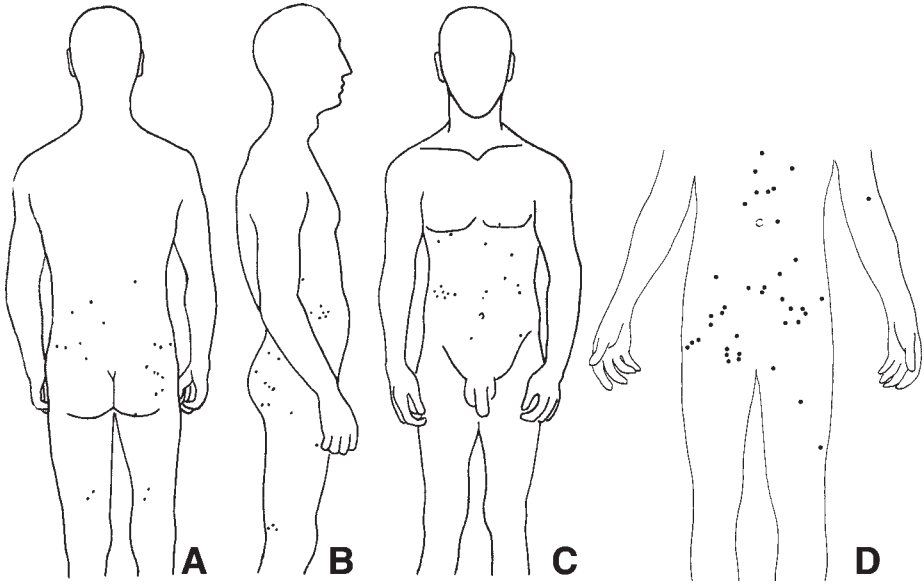

Fig. 11. Photographic documentation of the bite pattern of mites that led to a life sentence for homicide in this case. **(A)–(C)** The pattern of *Eutrombicula belkini* mite bites on the offender was similar to the pattern seen on the body of a police investigator who attended the crime scene. Development of reddening (swelling and shrinking) allowed to match time and location of the offender at the crime scene. **(D)** Self-test of this author in summer 2004 with *Neotrombicula autumnalis* leads to a similar pattern of bites. (For details see refs. *119,120.)*

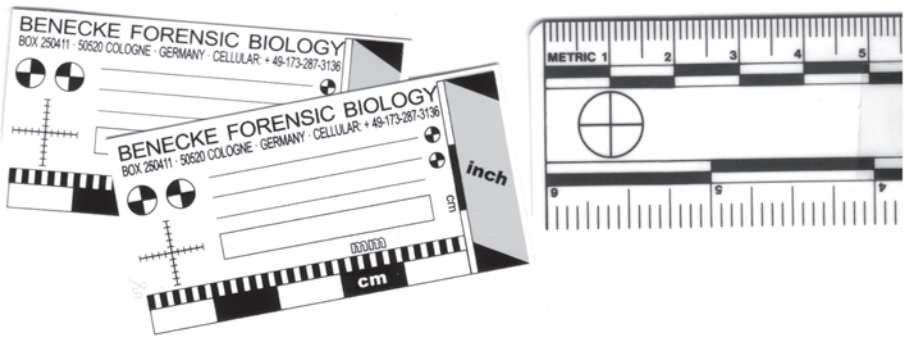

Fig. 12. Use of scales is essential to determine the length of larvae on photographs. International scales should be used as a result of different units of measurement in different countries. (From ref. *66.*)

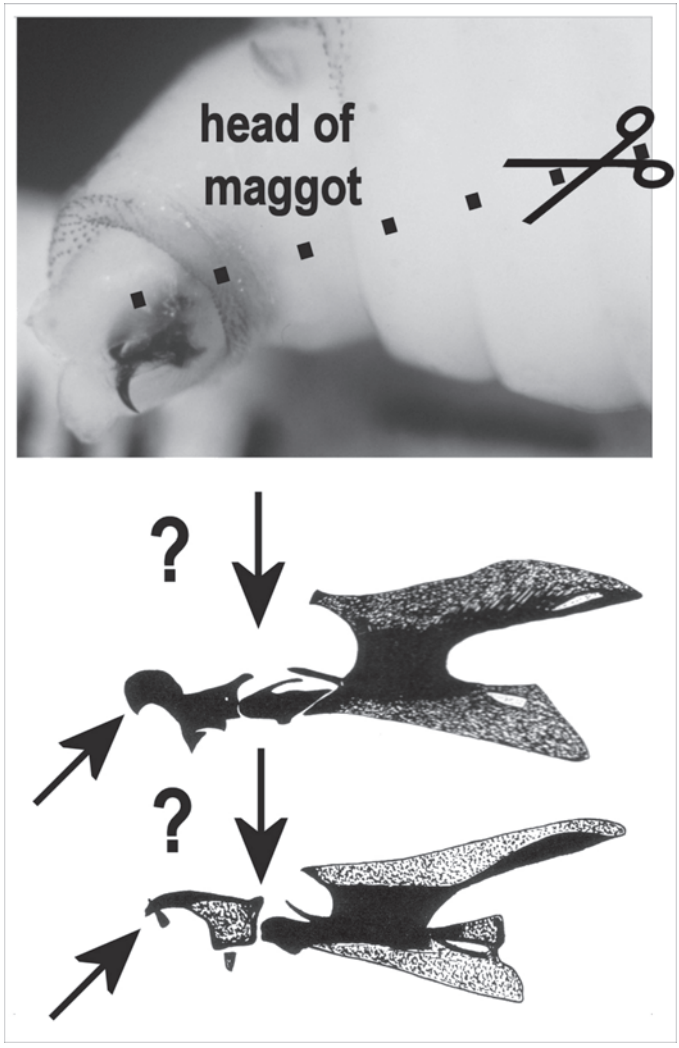

Fig. 13. Out of maggots that are stored in 98% ethanol (no isopropanol, never formalin), mouth hooks (cephalo-pharyngeal skeleton) can be extracted even after years. This may allow determination of species by comparing morphological features like the presence of an anterior apical sklerite (see question marks in drawing), and the shape and coloration of the structures. (From ref. *66*.)

6. DNA

6.1. DNA Typing

Identification of arthropod species found at a crime scene or on a corpse is essential but can be difficult on the morphological level. At the same time, the number of experts for morphological identification of arthropods is most dramatically decreasing since the 1990s.

Since 1985, DNA typing of biological material has become one of the most powerful tools for identification purposes in the field of forensic medicine and in criminal investigations *(79)*. The advantages of using DNA are as follows: (a) it provides a huge amount of diagnostic information compared to some older techniques (such as blood-group typing), (b) it is present in all biological tissues (except of red blood cells), and (c) it is much more resistant to environmental degradation than most other biological molecules (e.g., proteins).

Another benefit of DNA typing is that many loci for polymerase chain reaction (PCR) analysis are less than about 350 bp in length, allowing the use of sample DNA that is strongly degraded and broken into short pieces.

It would be helpful if DNA laboratories of medicolegal institutes were able to support forensic entomologists with DNA typing ("genetic fingerprints") of arthropod specimens. Because these laboratories are used to working with human DNA, such a service can frequently not be provided. Currently, one of the main goals in typing forensic DNA of arthropods is to find suitable PCR primers or sequencing sites for identification of arthropods on the species (not on the individual) level. Possible targets are all types of repetitive DNA like random amplified polymorphic DNA (RAPDs), short tandem repeats (STRs), and all types of minisatellite DNA, as well as nonrepetitive but unique sites on mitochondrial DNA (mtDNA *[80–94]*).

Invertebrates have a noncoding mtDNA region that contains a high proportion of adenine and thymine bases and might be useful for DNA typing in forensic entomology questions. There is a great deal of basic biological information available concerning fly mtDNA. This makes it relatively easy to design PCR primers and to interpret the results of any study on a new fly species. For insects, the base sequence of protein-coding genes like cytochrome oxidase subunits I and II (COI+II) may also help in determining species.

Closely related species can often be separated using a relatively short region (around 300 bp) that can even be obtained from degraded DNA. However, because of intraspecific variation in mtDNA haplotypes, two samples from the same species may not match exactly. Only experience with the taxo-

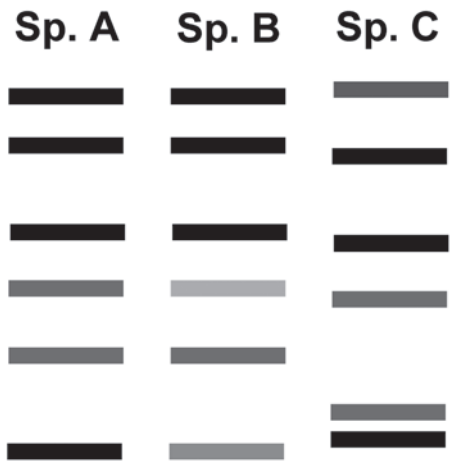

Fig. 14. To determine arthropod species, instead of morphological methods, the banding patterns as produced by separation of (randomly) amplified DNA stretches or cleavage with one or multiple restriction enzymes can be used. Both methods produce a DNA type or "genetic fingerprint" that looks like in this schematic presentation. Comparing species A, B, and C can still be difficult because point mutation may already have severely altered the pattern. Phylogenetic trees derived from restriction experiments/restriction site maps can be helpful if the actual local ecological parameters are known. In the future, direct sequencing may provide a better source for species identification. Still, only experience with the taxonomic group in question will allow an investigator to know if the differences observed between two samples fall within the range of normal variation for that zoological species, genus, or order.

nomic group in question will allow an investigator to know if the differences observed between two samples fall within the range of normal variation for that species *(93–96)*. In RAPDs, a single point mutation can eliminate a restriction site, so a reliable PCR restriction fragment length polymorphism analysis (performed after PCR) test would have to utilize restriction sites that are fixed or nearly fixed for the respective species (Fig. 14 *[92,97–99]).*

For an overview of DNA typing in forensic entomology see ref. *80*.

6.2. Non-Insect DNA

To date, there are only a few published reports on the use of DNA techniques by forensic entomologists. Because it is also possible to identify the gut contents (including human sperm and blood) of carrion-feeding arthropods and, thereby, relate an insect to a living person or a deceased, even when

contact between the two has not been observed, further developments in this field can be expected soon. Insect specimens can thus be a source of non-insect DNA (e.g., that of the organism on which they have fed). Recently, human mtDNA was successfully determined from the gut contents of insects *(100,101)*. Additionally, the gut contents of blowfly maggots were DNA typed as well as successfully tested for prostate-specific antigen that is present in sperm *(102)*. Such analyses may prove to be crucial evidence in the creation of victim/suspect associations. Investigators who find maggots but no corpse now have the potential to identify the insect's "last meal." There are also occasions, particularly if the scene has been disturbed, where both maggots and a corpse are present but not in physical contact. DNA analysis of maggot gut contents provides an independent means for relating larvae to a potential victim. This possibility also may prove useful in cases of multiple homicides or mass burials.

6.3. Collection for DNA Typing

For DNA typing purposes, freezing at –20°C or deeper temperatures as well as preserving in 98% ethanol is strongly recommended. These methods of storage allow one to undertake molecular genetic studies when necessary or to make this material available to others who are typing the DNA for identification purposes even after decades have passed. The old-fashioned method of drying the specimens on a needle may preserve the DNA for years, but storage as suggested above has been shown to be much more efficient *in praxi*.

6.4. Case Example: Maggots From Body Bag

As with all other criminalistic and forensic methods of investigation, DNA typing should not be understood as the ultimate method. For this reason, the German High Court even ruled out the use of DNA evidence as the *only* basis for conviction of a suspect. The following case illustrates that DNA typing has to embedded into the course of biological investigations and interpreted in the light of the actual findings at the scene.

In October 1997, a body that was in a state of severe decay was scrutinized for insect colonization to determine the colonization interval/PMI. Hundreds of maggots of an average size of 9 mm were found on the corpse that was stored inside a closed body bag. Additionally, numerous maggots were found on the outside of this body bag. The question was whether the maggots on the outside had squeezed themselves through tiny holes of the body bag to find a place for pupation, or if a second oviposition had taken place after the body was stored in the bag. Additionally, pupae were found on the floor beneath

the corpse. Because pupae represented the oldest developmental stage of arthropod infestation in this case, the next question was whether these pupae had fallen down from the corpse or whether they had fallen down from other corpses that had been stored in the same cooling room earlier.

Different fly species develop within different times. Therefore, estimation of colonization time is only possible if the insect species is known. In such cases, the insects can be used to estimate the time elapsed since death. The species of maggots, especially that of younger ones, is difficult to identify. For this reason, a quick inexpensive and reliable DNA test by use of RAPDs was applied in the aforementioned case. With it, at least the distinction of different maggot species was possible. The pupae found on the floor beneath the corpse were not related to the maggots found inside the body bag. Their developmental stage was of no relevance in this case. The age of the maggots was calculated and used for estimating the colonization time *(97)*.

7. *Forensic Entomotoxicology*

Insects that feed on tissue that contains substances relevant under toxicological aspects will, in many cases, ingest and store these toxicological-relevant substances in their own tissue. Extraction of the substance out of the insects was successfully used in cases in which the corpse was too decomposed to perform toxicological analysis on tissue samples:

- *Cochliomyia macellaria* blowflies were found on the corpse of a person who had bought phenobarbital the day before he was missing. They contained 100 μg phenobarbital per gram of larva.
- Arsenic, organophosphates, mercury, morphine (>10 μg/g in an empty pupa), cocaine, amitryptiline, 3,4-methylenedioxymethamphetamine, and nortryptiline were found in maggots and empty puparia up to 5 months after persons had died.
- In a suicide case, triazolam, oxazepam, phenobarbital, alimemazin, and clomipramin were detected 67 days postmortem in blowfly larvae recovered from the corpse but not in kidney and liver tissue of the decomposed body (Table 1 *[103–113]*).

It is difficult to calculate the amount of substances that were present in the dying person from the concentrations that are found in insect tissues. However, for qualitative purposes, the method does lead to useful results when embedded in the actual criminalistic context.

Table 1
Substance Concentrations in Tissue and Maggots That Were Found on a Decomposing Corpse (Concentrations in ng/g)

	Triazolam (benzodiazepine)	Oxazepam (benzodiazepine)	Phenobarbital (barbiturate)	Alimemazine (neuroleptic)	Clorіpramin (tricyclic antidepressant)
Heart	398	1317	1391	318	2479
Liver	490	403	3630	368	433
Lung	173	1641	1233	344	455
Kidney	no result	286	1439	66	327
Maggot	204	153	761	22	28

Modified according to ref. *108*.

8. Further Artifacts Caused by Arthropods

8.1. Lesions

In contrast to blowflies, maggots, adult ants, cockroaches, and beetles can and will destroy layers of fresh or dried up (mummified) skin.

Dermestid beetles mostly feed on severely dried up corpses, whereas "bacon beetles" and "corpse beetles" (e.g., Silphid, Histerid or Clerid beetles like *Nicrophorus* spp., *Hister* spp., and *Necrobia* spp.) will cause lesions that may resemble close range or long range gun shot wounds (Figs. 15 and 16).

8.2. Blood Spatter

Adult blowflies can transfer actual blood (e.g., from a pool of blood) so that a fake blood-spatter pattern emerges (Fig. 17 *[114–117]*). The typical characteristics of fake blood spatter patterns caused by adult blowflies can be summarized shortly as follows:

1. Stains that have a tail-to-body (L[tl]/L[b]) ratio greater than 1.
2. Stains with a tadpole/sperm type structure.
3. Stains with a sperm cell-type structure that do not end in a small dot.
4. Any stains without a distinguishable tail and body.
5. Any stains with a wavy and irregular linear structure.
6. Any stains that do not participate in directional consistency with other stains that suggest a point of convergence at a point of origin.

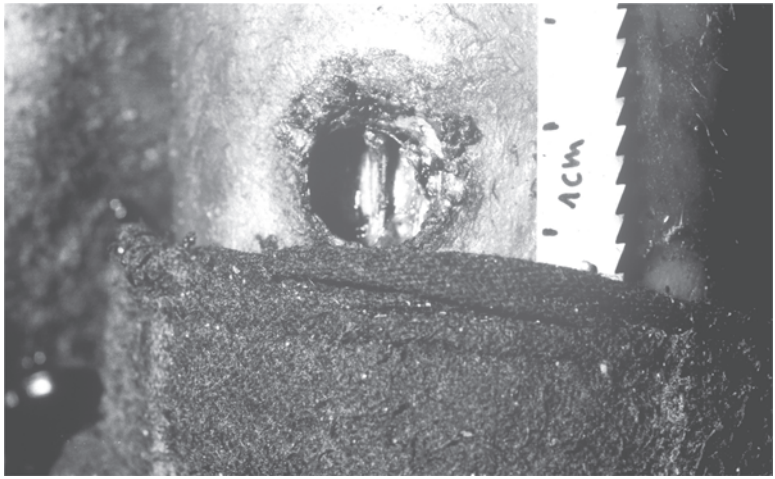

Fig. 15. Artifacts produced by beetles. Adult Histerid beetles produced a lesion that could be mistaken for a close range gunshot hole (partially mummified body found in summer in woodland in Cologne, Germany [Central Europe]).

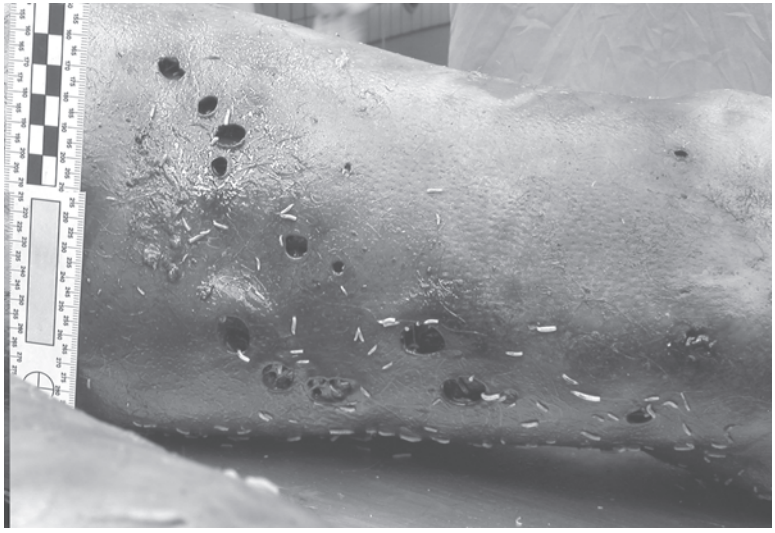

Fig. 16. Artifacts produced by beetles. Adult Silphid beetles built breeding holes or removed tissue for breeding holes from a corpse that was put into a cooling apparatus during a very hot summer in Cologne, Germany (Central Europe). Maggots are present but did not cause the lesions. The author observed beetles feeding.

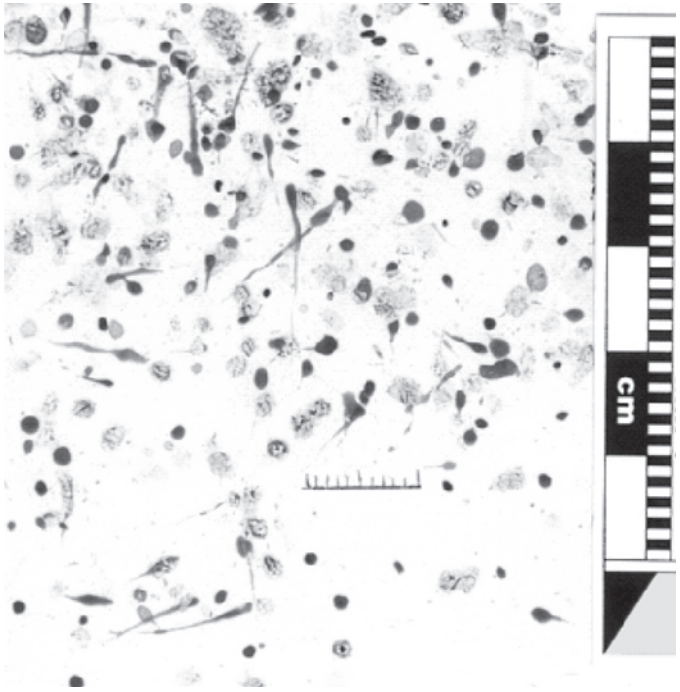

Fig. 17. Bloodstains as here produced by adult blowflies may have similarities with medium- or high-velocity blood spatter. Comparing the features of the fly spots (produced both by defecation and regurgitation) allows a distinction from true blood spatter caused by external violence. (From ref. *114*.)

Larger fly artifacts, within a group, will point in all directions. In contrast, trickling down of human blood or blood spread by violence will produce stains, within a group, that indicates a common general convergence point.

References

1. Reiter C. Zum Wachstumsverhalten der Maden der blauen Schmeißfliege *Calliphora vicina*. Z Rechtsmed 1984;91:295–308.
2. Nuorteva P. A three-year survey of the duration of development of *Cynomyia mortuorum* (L.) (Dipt., Calliphoridae) in the conditions of a subarctic fell. Ann Entomol Fenn 1972;38:65–74.
3. Byrd JH, Castner JL. Entomological Evidence: Utility of Arthropods in Legal Investigations. CRC Press, Boca Raton, 2000.
4. Nuorteva P, Isokoski M, Laiho K. Studies on the possibilities of using blowflies (Dipt.) as medicolegal indicators in Finland. 1. Report of four indoor cases from the city of Helsinki. Ann Entomol Fenn 1967;33:217–225.

5. Smith KGV. A Manual of Forensic Entomology. The Trustees of the British Museum (Natural History), London, 1986. Erratum in Smith KGV Forensic Sci Int 2001;120:160.
6. VanLaerhoven SL, Anderson GS. Insect succession on buried carrion in two biogeoclimatic zones of British Columbia. J Forensic Sci 1999;44:32–43.
7. Stærkeby M. Dead larvae of *Cynomya mortuorum* (L.) as indicators of post mortem interval—a case history from Norway. Forensic Sci Int 2001;120:77,78.
8. Goff ML. A Fly for the Prosecution, Harvard University Press, London, Cambridge, 2000.
9. Benecke M, Seifert B. Forensische Entomologie am Beispiel eines Tötungsdeliktes. Eine kombinierte Spuren- und Liegezeitanalyse [Forensic entomology in a high profile murder case: a combined stain and post mortem interval analysis]. Arch Kriminol 1999;204:52–60.
10. Grassberger M, Reiter C. Effect of temperature on *Lucilia sericata* (Diptera: Calliphoridae) development with special reference to the isomegalen- and isomorphen diagram. Forensic Sci Int 2001;120:32–36.
11. Kamal A. Comparative study of thirteen species of sacrophagous Calliphoridae and Sarcophagidae (Diptera). 1. Bionomics. Ann Entomol Soc Am 1958;51:261–227.
12. Nuorteva P. Age determination of a blood stain in a decaying shirt by entomological means. Forensic Sci 1974;3:89–94.
13. Evans AC. Studies on the influence of the environment on the sheep blow-fly *Lucilia sericata* (Mg.) II. The influence of humidity and temperature on praepupae and pupae. Parasitology 1935;27:291–298.
14. Nishida K. Experimental studies on the estimation of postmortem intervals by means of fly larvae infesting human cadavers. Jp J Legal Med 1984;38:24–41.
15. Marchenko MI. Medicolegal relevance of cadaver entomofauna for the determination of the time of death. Forensic Sci Int 2001;120:89–109.
16. Leclercq M, Quinet L. Quelques cas d'application de l'entomologie a la détermination de l'époque de mort [Several cases concerning the application of entomology on determination of post mortem interval]. Ann Med lég 1949;29:324–326.
17. Schoenly K. A statistical analysis of successional patterns in carrion-arthropod assemblages: implications for forensic entomology and determination of the postmortem interval. J Forensic Sci 1992;37:1489–1513.
18. Leclercq M, Tinant-Dubois J. Entomologie et médicine légale. Observations inedites [Entomology and legal medicine. Unedited observations]. Bull méd lég tox urg méd 1973;16:251–267.
19. Catts EP, Goff ML. Forensic entomology in criminal investigations. Ann Rev Entomol 1992;37:257–272.
20. Lord WD, Goff ML, Adkins TR, Haskell NH. The black soldier fly *Hermetia illuscens* (Diptera: Stratiomyidae) as a potential measure of human post mortem interval: observations and case histories. J Forensic Sci 1994;39:215–222.
21. Whiting PW. Observations on blowflies; duration of the prepupal stage and colour determination. Biol Bull Mar Biol Lab (Woods Hole) 1914;26:184–194.
22. Davison TF. Changes in temperature tolerance during the life cycle of *Calliphora erythrocephala*. J Ins Phys 1969;15:977–988.

23. Smirnov E, Zhelochovtsev AN. Change of characteristics in Calliphora erythrocephala Mg. under the influence of shortened feeding periods of the larval stages. Wilh Roux' Arch Entwicklungsmechanik 1926;108:579–595.
24. Rosales AL, Krafsur ES, Kim Y. Cryobiology of the face fly and house fly. J Med Entomol 1994;51:671–680.
25. Johnston W, Villeneuve G. On the medico-legal application of entomology. Montr Med J 1897;26:81–90.
26. Mellanby K. The influence of atmospheric humidity on the thermal death point of a number of insects. J Exp Biol 1939;9:222–231.
27. Schroeder H, Klotzbach H, Püschel K. Insect colonization of human corpses in warm and cold season. Legal Med (Tokyo) 2003;5(Suppl 1):S372–S374.
28. Hédouin V, Martin-Bouyer L, Bourel B, Revuelta E, Gosset D. Influence de la température sur la ponte des diptères: application à l´entomologie médico-légale. J Méd Lég Droit Méd 1996;39:153–157.
29. Erzinçlioglu YZ. Maggots, Murder and Men. Harley Books, Colchester, 2000.
30. Benecke M. Six forensic entomology cases: description and commentary. J Forensic Sci 1998;43:797–805,1303.
31. Benecke M. (2002) A police quarrel over "maggots" in Soljanka stew. Zoology 2002;105(Suppl 5):96.
32. Sung Tz'u. The washing away of wrongs. Translation of Hsi yuan chi lu, translated by Brian E. McKnight. Ann Arbor: Center for Chinese Studies, University of Michigan, 1981; 2nd book, 5th chapter, pp. 69–70.
33. Merkel H. Die Bedeutung der Art der Tötung für die Leichenzerstörung durch Madenfrass [The influence of the circumstances of death on the destruction of corpses by maggots]. Dtsch Z ges Gerichtl Med 1925;5:34–44.
34. Benecke M, ed. Forensic Entomology Special Issue. Forensic Sci Int 2001;120:1–160.
35. Nuorteva P. Sacrophagous insects as forensic indicators. In: Tedeschi CG, Eckert WE, Tedeschi LG, eds. Forensic Medicine Vol. II. Saunders, Philadelphia, 1977, pp. 1072–1095.
36. Benecke M. Zur insektenkundlichen Begutachtung in Faulleichenfällen [Expert insect identification in cases of decomposed bodies]. Arch Kriminol 1996;198:99–109.
37. Schroeder H, Klotzbach H, Oesterhelweg L, Püschel K. Larder beetles (Coleoptera, Dermestidae) as an accelerating factor for decomposition of a human corpse. Forensic Sci Int 2002;127:231–236.
38. Lord WD. Case histories of the use of insects in investigations. In: Catts PE, Haskell NH, eds. Entomology & Death. A Procedural Guide. Joyce's Print Shop, Clemson, 1990, pp. 9–37.
39. Baudelaire C. Une Charogne. In Mathews M, Mathews J, eds. The Flowers of Evil. New Directions Publishing, New York, 1955, pp. 264–265.
40. Sung Tz'u. The "Hsi Yuan Lu" or "Instructions to Coroners" (version from 1843, compiled by T'ung Lien.). Transl. by Giles HA. Proc Royal Soc Med 1924;17:59–107.
41. Bergeret M. Infanticide. Momification naturelle du cadavre. Découverte du cadavre d'un enfant nouveau-né dans une cheminée où il s'était momifié. Détermination de

l´epoque de la naissance par la présence de nymphes et de larves d´insectes dans le cadavre, et par l´étude de leurs métamorphoses [Homicide of a newborn found in a chimney, and its natural mummification. Determination of post mortem interval by the use of insect larvae and their metamorphosis]. Ann Hyg Méd lég 1855;4:442–452.
42. Mégnin P. La faune de cadavres. Application de l'entomologie a la médicine légale [The fauna of corpses. Use of entomology in legal medicine]. Encyclopedie scientifique des Aides-Mémoire, Masson, Paris, Gauthier-Villars, 1894.
43. Mégnin P. La faune des tombeaux [The fauna of graves]. Prés. par Brown-Sequard M. C-R Heb Seances Acad Sci 1887;105:948–951.
44. Baer WS. The treatment of chronic osteomyelitis with the maggot (larva of the blowfly). J Bone Joint Surg 1931;13:438–475.
45. Robinson W. Surgical maggots in the treatment of infected wounds; culture of sterile maggots. J Lab Clinical Med 1933;18:406–412.
46. Hase A. Fliegenmadenzuchten und Fliegenhaltung für chirurgische Zwecke [Maggot breeding and maturing for their use in surgery]. Naturwissenschaften 1934;31: 523–525.
47. Imms AD. Dipterous larvae and wound treatment. Nature 1939;144:516,517.
48. Benecke M. A brief history of forensic etomology. Forensic Sci Int 2001;120:2–14.
49. Klingelhöffer. Zweifelhafte Leichenbefunde durch Benagung von Insekten [Misinterpretation on the cause of death as a result of insects feeding upon corpses]. Vjschr Gerichtl Med 1898;25:58–63.
50. von Horoszkiewicz S. Casuistischer Beitrag zur Lehre von der Benagung der Leichen durch Insecten [A case report concerning the feeding of insects upon human corpses]. Vjschr Gerichtl Med 1902;23:235–239.
51. Maschka. Angeblicher Tod eines Kindes infolge von Verletzungen. - Natürliche Todesart. - Entstehung der Verletzung nach dem Tod durch Ameisenbisse [Alleged death of a child due to injuries. - Natural cause of death. - Injury patterns caused by ant bites]. Vjschr Gerichtl Med (Neue Folge) 1881;34:193–197.
52. Roth LM, Willis ER. The medical and veterinary importance of cockroaches. Smithon Misc Coll 1957;134:30–34.
53. Holzer FJ. Zerstörung an Wasserleichen durch Larven der Köcherfliege [Destruction of corpses submerged in water by Trichoptera (caddis-fly) larvae]. Z ges ger Med 1939;31:223–228.
54. Caspers H. Ein Köcherfliegen-Gehäuse im Dienste der Kriminalistik [A caddis-fly casing in the service of criminalistics]. Arch Hydrobiol 1952;46:125–127.
55. Walcher K. Das Eindringen von Maden in die Spongiosa der großen Röhrenknochen [Maggots entering the spongiosa of long bones]. Dtsch Z ges Gerichtl Med 1933;20:469–471.
56. Davis WT. *Lucilia* flies anticipating death. Bull Brooklyn Entomol Soc 1928;23:118.
57. DPA (German Press Agency) Studie an 17000 Leichen: Jeder Siebte vor Tod falsch gepflegt [Study on 17,000 corpses: every seventh elderly person not cared for correctly], German Press Agency, 2003.
58. Benecke M. Insects and Corpses. In: Baccino E, ed. 16th Meeting of the International Association of Forensic Sciences, Montpellier, France, Sept. 2–7, 2002, Monduzzi Editore, Bologna, 2002, pp. 135–140.
59. Fleischmann W, Grassberger M, Sherman R. Maggot Therapy. A Handbook of Maggot-Assisted Wound Healing. Thieme, New York, 2004.

60. Bonn D. Maggot therapy: an alternative for wound infection. Lancet 2000;356:1174.
61. Sherman RA, Hall MJR, Thomas S. Medicinal maggots: an ancient remedy for some contemporary afflictions. Ann Reviews Entomol 2000;45:55–81.
62. Benecke M. Forensic entomology: lethal child neglect, and credit card fraud. Zoology 2001;104(Suppl IV):53.
63. Benecke M, Lessig R. Child neglect and forensic entomology. Forensic Sci Int 2001;120:155–159.
64. Chapman RK. An interesting occurrence of *Musca domestica* L. larvae in infant bedding. Canad Entomol 1944;76:230–232.
65. Benecke M. Rein einseitiges Auftreten von Schmeißfliegenmaden im Gesicht einer Faulleiche [Purely unilateral occurrence of blowfly maggots in the face of a decomposing body]. Arch Kriminol 2001;208:182–185.
66. Benecke M. Insects on Corpses. In: Marks M, ed. UT ARF FBI Manual: Ver 1.0 (March 2003). University of Tennessee, Anthropological Research Facility, Knoxville TN, 2003.
67. Benecke M. Insekten auf Leichen [Insects on Corpses]. Kriminalistik 2000;54:680–682.
68. van Emden FI. Diptera Cyclorrhapta Calyptrata, Section (a), Tachinidae and Calliphoridae. In: Royal Entomological Society, ed. Handbooks for the Identification of British Insects, Vol. 10, (4a). Royal Society of London, London, 1956.
69. Freude H, Harde KW, Lohse GA. (1964–1983) Die Käfer Mitteleuropas [The beetles of Central Europe]. Goecke & Evers, Krefeld (cont. with Koch K (1985) Die Käfer Mitteleuropas, Ökologie. Goecke & Evers, Krefeld).
70. Dorsey CK. A comparative study of the larvae of six species of *Silpha* (Coleoptera, Silphidae). Ann Ent Soc Amer 1940;33:120–139.
71. Knipling EF. A comparative study of the first instar larvae of the genus Sarcophaga (Calliphoriadae, Diptera), with notes on its biology. J Parasitol 1936;22:417–454.
72. Malloch JR. A preliminary classification of Diptera, exclusive of puparia, based upon larval and pupal characters, with keys to imagines in certain families, part 1. Bull Illinois State Lab Natural Hist 1917;12:161–409, plates 28–57.
73. Greenberg B, Singh D. Species identification of calliphorid (Diptera) eggs. J Med Entomol 1995;32:21–26.
74. Erzinçlioğlu YZ. Immature stages of British Calliphora and Cynomya, with a reevaluation of the taxonomic characters of larval Calliphoridae (Diptera). J Natural History 1985;19:69–96.
75. Erzinclioğlu YZ. Blowflies. Richmond Publishing Co., Slough, 1996.
76. Liu D, Greenberg B. Immature stages of some flies of forensic importance. Ann Entomol Soc Am 1989;82:80–93.
77. Nuorteva P, Schumann H, Isokoski M, Laiho K. Studies on the possibilities of using blowflies (Dipt., Calliphoridae) as medicolegal indicators in Finland. 2. Four cases in which species identification was performed from larvae. Ann Entmol Fenn 1974;40:70–74.
78. Reiter C, Wollenek G. Zur Artbestimmung der Maden forensisch bedeutsamer Schmeißfliegen. Z Rechtsmed 1983;90:309–316.
79. Jeffreys AJ, Wilson V, Thein SL. Individual specific "fingerprints" of human DNA. Nature 1985;316:76–79.

80. Benecke M, Wells J. Molecular techniques in forensically important insects. In: Byrd JH, Castner JL, eds. Entomological Evidence: Utility of Arthropods in Legal Investigations. CRC Press, Boca Raton, 2000, pp. 341–352.
81. Stevens J, Wail R. Species, sub-species and hybrid populations of the blowflies *Lucilia cuprina* and *Lucilia sericata* (Diptera:Calliphoridae). Proc Royal Soc London, Series B. Biol Sci 1996;263:1335–1341.
82. Sperling FAH, Anderson GS, Hickey DA. A DNA-based approach to the identification of insect species used for postmortem interval estimation. J Forensic Sci 1994;39:418–427.
83. Sonvico A, Manso F, Quesada-Allue LA. Discrimination between the immature stages of *Ceratitis capitata* and *Anstrepha fraterculus* (Diptera:Tephritidae) populations by random amplified polymorphic DNA polymerase chain reaction. J Econ Entomol 1996;89:1208–1212.
84. Brown RJ, Malcolm CA, Mason PL, Nichols RA. Genetic differentiation between and within strains of the saw-toothed beetle, *Oryzaephilus surinamensis* (Coleoptera: Silvanidae) at RAPD loci. Insect Mol Biol 1997;6:285–289.
85. Malgorn Y, Coquoz R. DNA typing for identification of some species of Calliphoridae. Forensic Sci Int 1999;102:111–119.
86. Wells JD, Introna F, DiVella G, Campobasso CP, Hayes J, Sperling FA. Human and insect mitochondrial DNA analysis from maggots. J Forensic Sci 2001;46:657,658.
87. Narang SK, Degrugillier ME. Genetic fingerprinting of the screwworm (Diptera: Calliphoridae) infestation in North Africa by mitochondrial DNA markers. Florida Entomol 1995;78:294–304.
88. Roehrdanz RL, Johnson DA. Mitochondrial DNA restriction site map of *Cochliomyia macellaria* (Diptera: Calliphoridae). J Med Entomol 1996;33:863–865.
89. Wells JD, Sperling FAH. Molecular phylogeny of *Chrysomya albiceps* and *C. rufifacies*. Med Entomol 1999;36:222–226.
90. Zhang DX, Hewitt GM. Insect mitochondrial control region: a review of its structure, evolution and usefulness in evolutionary studies. Biochem Sys Ecol 1997;25: 99–120.
91. Wells J, Sperling FAH. DNA-based identification of forensically important Chrysominae (Diptera:Calliphoridae). Forensic Sci Int 2001;120:110–115.
92. Zehner R, Zimmerman S, Mebs D. RFLP and sequence analysis of the cytochrome b gene of selected animals and man: methodology and forensic application. Int J Legal Med 1998;111:323–327.
93. Harvey ML, Mansell MW, Villet MH, Dadour IR. Molecular identification of some forensically important blowflies of southern Africa and Australia. Med Vet Entomol 2003;17:363–369.
94. Hillis DM, Moritz C, Mable BK, eds. Molecular Systematics. Sinauer, Sunderland, 1996.
95. Simon C, Frati R, Beckenbach A, Crespi B, Liu H, Flook R. Evolution, weighting and phylogenetic utility of mitochondrial gene sequences and a compilation of conserved polymerase chain reaction primers. Ann Entomol Soc Am 1994;87:651–701.

96. Caterino MS, Cho S, Sperling FAH. The current state of insect molecular systematics: a thriving tower of Babel. Ann Rev Entomol 2000;45:1–54.
97. Benecke M. Random amplified polymorphic DNA (RAPD) typing of necrophageous insects (Diptera, Coleoptera) in criminal forensic studies: validation and use in praxi. Forensic Sci Int 1998;98:157–168.
98. Schroeder H, Klotzbach H, Elias S, Augustin C, Püschel K. Use of PCR-RFLP for differentiation of calliphorid larvae (Diptera, Calliphoridae) on human corpses. Forensic Sci Int 2003;132:76–81.
99. Ratcliffe ST, Webb DW, Weinzierl RA, Robertson HM. PCR-RFLP identification of Diptera (Calliphoridae, Muscidae and Sarcophagidae)—a generally applicable method. J Forensic Sci 2003;48:783–785.
100. Repogle J, Lord WD, Budowle B, Meinking TL, Taplin D. Identification of host DNA by Amplified Fragment Length Polymorphism: preliminary analysis of human crab louse (Anoplura: Pediculidae) excreta. J Med Entomol 1994;31:686–690.
101. Lord WD, DiZinno JA, Wilson MR, Budowle B, Taplin D, Meinking TL. Isolation, amplification, and sequencing of human mitochondrial DNA obtained from human crab louse, *Pthirus pubis* (L.) blood meals. J Forensic Sci 1998;43:97–100.
102. Clery JM. Stability of prostate specific antigen (PSA), and subsequent Y-STR typing of *Lucilia sericata* (Meigen) (Diptera:Calliphoridae) maggots reared from a simulated post-mortem sexual assault. Forensic Sci Int 2001;120:72–76.
103. Beyer JC, Enos YF, Stajic M. Drug identification through analysis of maggots. J Forensic Sci 1980;25:411,412.
104. Goff ML, Lord WD. Entomotoxicology. A new area for forensic investigation. Am J Forensic Med Pathol 1994;15:51–57.
105. Sadler DW, Fuke C, Court F, Pounder DJ. Drug accumulation and elimination in *Calliphora vicina.* Forensic Sci Int 1995;71:191–197.
106. Sadler DW, Chuter G, Seneveratne C, Pounder DJ. Barbiturates and analgesics in *Calliphora vicina* larvae. J Forensic Sci 1997;42:1214,1215.
107. Miller ML, Lord WD, Goff ML, Donnelly B, McDonough ET, Alexis JC. Isolation of amitryptiline and nortryptiline from fly puparia (Phoridae) and beetle exuviae (Dermestidae) associated with mummified human remains. J Forensic Sci 1994;39:1305–1313.
108. Kintz P, Godelar B, Tracqui A, Mangin P, Lugnier AA, Chaumont AJ. Fly larvae: a new toxicological method of investigation in forensic science. J Forensic Sci 1990;35:204–207.
109. Goff ML, Miller ML, Paulson JD, Lord WD, Richards E, Omori AI. Effects of 3,4-methylenedioymethamphetamine in decomposing tissues on the development of *Parasarcophaga ruficornis* (Diptera:Sarcophagidae) and detection of the drug in postmortem blood, liver tissue, larvae, and puparia. J Forensic Sci 1997;42:276–280.
110. Sadler DW, Seneviratne C, Pounder DJ. Effects of 3,4-methelenedioxymethamphetamine in decomposing tissues on the development of Parasarcophaga ruficornis (Diptera: Sarcophagidae) and detection of the drug in postmortem blood, liver tissue, larvae and pupae. J Forensic Sci 1997;42:1212,1213.

111. Introna F, Campobasso CP, Goff ML. Entomotoxicology. Forensic Sci Int 2001;120:42–47.
112. Bourel B, Tournel G, Hédouin V, Deveaux M, Goff ML, Gosset D. Morphine extraction in necrophageous insect remains for determining ante-mortem opiate intoxication. Forensic Sci Int 2001;120:127–131.
113. Carvalho LML, Linhares AX, Trigo JR. Determination of drug levels and the effect of diazepam on the growth of necrophageous flies of forensic importance in south-eastern Brazil. Forensic Sci Int 2001;120:140–144.
114. Benecke M, Barksdale L. Distinction of bloodstain patterns from fly artifacts. Forensic Sci Int 2003;137:152–159.
115. Bevel T, Gardner RM. Fly spots. In: Bevel T, Gardner RM, eds. Blood Stain Pattern Analysis. CRC Press, New York, 1997.
116. James SH, Sutton TP. Medium- and high-velocity impact blood spatter. In: James SH, Eckert WG, eds. Interpretation of Bloodstain Evidence at Crime Scenes. CRC Press, Boca Raton, 1998.
117. Brown RE, Hawkes RI, Parker MA, Byrd JH. Entomological alteration of bloodstain evidence. In: Byrd JH, Castner JL, eds. Entomological Evidence: Utility of Arthropods in Legal Investigations. CRC Press, Boca Raton, 2000.
118. Langlois EH. Essai historique, philosophique et pittoresque sur les danses des morts [Historic, philosophic, and picturesque essay on the dances of the dead]. Lebrument, Rouen, 1852.
119. Prichard JG, Kossoris PD, Leibovitch RA, Robertson LD, Lovell FW. Implications of trombiculid mite bites: report of case and submission of evidence in a murder trail. J Forensic Sci 1986;31:301–306.
120. Webb JP, Loomies RB, Madon MB, Bennett SG, Green GE. The chigger species *Eutrombicula belkini* GOULD (Acari: Trombiculidae) as a forensic tool in homicide investigation in Ventura County, California. Bull Soc Vect Entomol 1983;8:141–146.
121. Honomichl K, Jacobs W, Renner M. Biologie und Ökologie der Insekten, 3rd ed. G. Fischer, Stuttgart, 1998, p. 638.

Toxicology

11

Practical Toxicology for the Forensic Pathologist

James R. Gill, MD

Contents

Summary

The forensic pathologist utilizes toxicological results on a daily basis. There are many findings at autopsy that may be suggestive of drug abuse or poisoning, however, there are few anatomic findings that are diagnostic of poisoning. The cause and manner of death that would be suspected at the autopsy table may be completely changed by the toxicology data. A person may have marked coronary disease at autopsy. If, however, a markedly elevated concentration of barbiturates also is detected in the blood, the heart disease becomes moot. The relationship between the forensic toxicologist and forensic pathologist is symbiotic. Pathologists need the toxicology results for the death investigation, whereas forensic toxicologists need the pathologist's help

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

to focus their toxicological investigation. Just as a forensic pathologist should not do an autopsy in a circumstance vacuum, the forensic toxicologist should not be expected to blindly analyze body fluids and tissues. The toxicologist will routinely screen for certain substances depending on the area of practice and the type of death. One should not assume that because "toxicology" was done and it is "negative" that all substances have been looked for and excluded. A forensic pathologist does not need to know the precise details of how those black boxes in the toxicology laboratory analyze samples (analytical toxicology). But the forensic pathologist must understand the limitations of toxicology and how to interpret those results (interpretive toxicology). It is the forensic pathologist's role to incorporate those results into the entire case study. This review will not focus on analytical toxicology but rather on what those results mean, what a forensic pathologist should do with those results, and what a forensic pathologist is asked about those results.

Key Words: Forensic toxicology; forensic pathology; drugs of abuse; ethanol; autopsy; postmortem.

1. Introduction

Toxicology is the study of poisons. Forensic toxicology is the application of toxicology in the legal field. As a result of possible legal implications, rigorous confirmation of all forensic toxicological results is required. This confirmation may be accomplished by the use of a different methodology on the same specimen or the use of a different specimen. In the forensic setting, an unconfirmed result is equivalent to no result. Partial or unconfirmed results should not be reported. The forensic toxicologist is the expert in charge of the laboratory testing of the samples *(1–3)*. The forensic pathologist is the expert in interpreting the results in the setting on an entire case. The toxicologist gives the forensic pathologist information but not conclusions. The forensic pathologist must maintain perspective and not render a diagnosis on isolated findings *(4)*. The interpretation of the effects of drugs on the body occurs in two forums for the forensic pathologist. The first is to interpret its role in the cause of death. The second occurs in the courtroom regarding the effects drugs could have on an individual.

All drugs have side effects and there is a wide range of drug concentrations (including therapeutic concentrations) that result in death. The toxicologist can screen for particular intoxicants but it is the forensic pathologist's role to help direct certain testing depending on the circumstances. Toxicological analysis detects substances that are in the specimen at the time of testing.

Sometimes, these substances may not have been in the body at the time of death. Sometimes, substances that were in the body at the time of death are no longer detectable. Therefore, even though the toxicology result is technically correct, there are various pitfalls that one must consider before offering an opinion on the results.

2. *Pitfalls*

One must consider postmortem artifacts that may result in the production of substances that were not in the body at the time of death *(5)*. Additionally, toxicology testing may be unable to detect certain chemicals that were present at the time of death. Artifacts may produce qualitative as well as quantitative toxicological differences. Potential culprits include: postmortem redistribution, storage and transportation (inadequate refrigeration or lack of preservatives such as sodium fluoride), decomposition of the decedent, embalming, and contamination at the autopsy table.

Certain substances may undergo postmortem redistribution in which, for example, a higher concentration of a drug may be detected in cardiac blood than in femoral blood *(6,7)*. This is common with drugs that have a high volume of distribution or that get concentrated in certain organs. Digoxin, for example, is concentrated in the myocardium and it may leech into the cardiac blood after death resulting in a higher concentration. Contamination of cavity blood by gastric contents may result in spuriously high concentrations of substances that were ingested *(8)*. Therefore, peripheral blood specimens are preferred.

Postmortem ethanol production may occur in vivo as a result of putrefaction or in vitro as a result of poor storage or preservation of the specimen. Cocaine will continue to metabolize after death. Sodium fluoride will slow this postmortem metabolism.

Once the postmortem artifacts are considered, in order to diagnose an acute intoxication at the time of death, one should detect the active drug in the blood, brain (cerebrospinal fluid), liver, kidney, or muscle *(9,10)*. The concentrations of drugs differ in various tissues of the body because of the diverse compositions of the tissues and because drugs may be metabolized differently in different tissues. Detection of a drug or metabolite in bile, hair, or urine is indicative of prior use but is not always equivalent to an acute intoxication.

Once a drug has been detected, one must then interpret the concentration. There are various toxicological compendiums that provide common blood concentrations seen experimentally as well as from published reviews on

numerous intoxication deaths *(11–13)*. The potential problem with the referenced studies is that they are a very heterogeneous population. Each death is unique and there are many factors that may alter the effect a certain drug has on the body. For example, in a study of 40 intoxication deaths as a result of drug *X*, the postmortem concentration ranged from 1.2 to 3.2 mg/dL. Do we know how many of those were infants or had heart disease or were decomposed or were peripheral blood samples or had other drugs in their system? Every factor cannot be controlled in every study. These ranges, however, may provide a sense of typical concentrations but they should not be taken as dogma. If one were to see a concentration of drug *X* that is 10 times the typical concentration, one should certainly investigate it further. Is there a history of depression? How many pills were found at the scene? Has the toxicology laboratory analyzed the gastric contents?

Interpreting concentrations of drugs in decomposed bodies also is perilous. How does one interpret a 0.2 mg/mL benzoylecgonine concentration in a liver that has been putrefying for 3 months in partially skeletonized remains? How about 3 years in mummified remains? The comparison databases are simply not available.

The concept of a "fatal concentration" of a drug is an oversimplified fallacy. Is there a concentration of drug *X* that will kill all people? Are there concentrations that will kill some or one person but not others? Are there some drugs that regardless of the dose will not cause death? The answers to these questions are "yes." Thus, it is arbitrary and meaningless to select a number as "the fatal concentration." People who die from an acute cocaine intoxication may have near trace concentrations detected in their blood, whereas people who die from a gunshot wound of the head may have markedly elevated cocaine concentrations that are well above so-called "fatal" concentrations. One may find "fatal" concentrations of various drugs in people who commit suicide by descent from a height. Obviously, they were alive with that "fatal concentration" when they stepped off the edge.

It is a mistake to rely solely on most hospital toxicology tests for drugs of abuse other than blood ethanol. Hospitals often test for metabolites in urine. So, even though a patient had a "positive cocaine" in the urine, it does not necessarily mean that the person was acutely intoxicated. What the hospital laboratory commonly detects is benzoylecgonine. This means that the person may have used cocaine days before the test and may not be acutely intoxicated at the time of the test. Additionally, because this result is a single test on a single specimen, it does not meet forensic confirmation standards.

The conclusion that death was caused by an acute intoxication requires that three conditions be met: the forensic toxicology concentrations must be

within the range typically encountered in such fatalities, the history and circumstances must be consistent with a fatal intoxication, and the postmortem examination must fail to disclose a disease or physical injury that has an extent or severity inconsistent with continued life. In deaths caused by an intoxication with more than one drug in concentrations greater than trace amounts, it is customary to include all of the identified drugs in the cause of death. If a person dies from a traumatic injury while intoxicated, the proximate cause of death should be, in the vast majority of cases, the injury. The intoxication may help explain why a person crashed a car, but it did not play a pathophysiologic role in the death. The decedent died from the lacerated aorta not from the 180 mg/dL blood alcohol concentration. The toxicological results are included on the death certificate in two circumstances. The first is when the intoxication pathophysiologically causes or contributes to the death (e.g., acute opiate intoxication). The second is when the death does not make sense without the intoxication (e.g., an otherwise neurologically intact adult does not choke to death on a bolus of food).

How a certain drug or a certain concentration of a drug will effect a given person is often difficult to know. The dose-related effects of ethanol are well characterized and generally accepted. Chronic alcoholics, however, who are more tolerant to the effects of ethanol, may be able to mask the intoxication better than a novice with a similar blood alcohol concentration. What about other drugs? How does a person with a 0.2 mg/L blood cocaine act? This person is acutely intoxicated but one could only speculate regarding how that specific person is feeling or acting from that concentration. How does a person with a 0.2 mg/L blood cocaine and 0.2 mg/L morphine act? How does a person with a phencyclidine (PCP) concentration of 50 ng/mL act? This concentration of PCP is consistent with an acute intoxication; it also is consistent with use days before the person died. Without further information, one could only guess if this person were having any effects from the PCP.

One may testify to average and expected effects of a drug but, with few exceptions, one cannot always predict the actual effects in a specific person with a specific concentration or dose *(5)*. Ethanol concentrations are one of the exceptions; a person with a blood ethanol concentration of 80 mg/dL or above, for example, is impaired for purposes of driving a motor vehicle. The other fact to remember is that toxicological concentrations typically follow a nonlinear distribution of absorption and elimination. Concentrations increase during absorption and decrease during the elimination phase. One data point will not by itself reveal if the person was on the rising side of the curve or the descending side. The foregoing is important to consider when there is a survival interval between an injury and death.

Medical treatment, particularly a vigorous fluid resuscitation, may affect the concentrations of certain drugs. A man who was stabbed had an admission whole blood ethanol concentration of 190 mg/dL. He was fluid resuscitated for 3 hours in the hospital before death. His blood ethanol concentration at autopsy was 90 mg/dL. This blood ethanol concentration is lower than the 140 mg/dL expected from metabolism alone if the decedent was in the elimination phase.

3. Specimen Samples

The amount and types of specimens collected may depend on a physician's practice, storage facility, and so forth. Common specimens include blood (peripheral preferred), urine, bile, brain, liver, vitreous, gastric contents, and subdural hemorrhage (if present). All specimens are not tested in every case but having them available is an invaluable potential resource.

3.1. Blood

The addition of sodium flouride (NaF) to autopsy blood has several benefits: it prevents bacterial fermentation, stops the spontaneous hydrolysis of cocaine to benzoylecgonine, and blocks clotting. As a result of postmortem redistribution and potential gastric contamination of cardiac blood, peripheral blood samples are preferred *(6,14,15)*. If only a small amount of a peripheral sample is collected, a second separate sample may be obtained from the heart. The toxicology lab may use the heart blood for the initial qualitative tests and the peripheral blood for quantitation. If a decedent survived in the hospital for several hours or days and there is a potential toxicological issue, one may obtain the hospital admission blood samples. On trauma cases, it is routine for hospital personnel to collect a type and cross blood sample. This is usually done soon after arrival at the hospital and so it is temporally the best specimen for the toxicological status at the time of incident. Because the type and cross blood is usually held for 7 to 14 days, it is more likely to be available for chemical studies than the other initial blood specimens, which may be discarded after 1 or 2 days. One usually contacts the hospital blood bank to retrieve this specimen.

3.2. Subdural Hemorrhage

Subdural hemorrhage is a worthwhile specimen to collect and analyze, especially in delayed deaths, because it may best represent the state of intoxication at the time of the injury *(16)*. The volume (or weight) of the subdural blood should be recorded and a sample submitted for toxicology testing. Care

should be taken in the collection to leave some clot on the dura (if adherent) for possible microscopic examination.

3.3. Vitreous Fluid

Vitreous fluid should be routinely collected at autopsy. The benefits include electrolyte (especially glucose) and ethanol quantification *(15,17–20)*. Because the vitreous is in a relatively sequestered location, it may help distinguish whether ethanol detected in the blood is from premortem consumption or postmortem production (*see* below). Vitreous glucose should be routinely performed on individuals in whom ketones (acetone) are detected on the gas chromatography volatile screen or on a positive urine dipstick (glucose). Previously diagnosed and undiagnosed diabetics who die from diabetic ketoacidosis will be identified. Because glucose concentrations decrease in the vitreous after death, a vitreous glucose concentration of over 200 mg/dL is, with few exceptions, diagnostic of diabetes *(20)*. Vitreous is the choice postmortem specimen to test for digoxin because it is relatively uninfluenced by postmortem redistribution. Detection of digitalis-like compounds also may represent inadvertent ingestion of alternative remedies *(21)*.

The study and use of the vitreous to quantitate electrolytes, ethanol, and glucose made a great contribution to the practice of forensic pathology *(19,20)*. Vitreous electrolyte concentrations change with increasing postmortem intervals. After death, the vitreous glucose and sodium will decrease and the potassium will increase as a function of the postmortem interval. Therefore, one may diagnose hyperglycemia but one cannot diagnose hypoglycemia from the vitreous analysis. Some have attempted to use potassium as a marker to estimate the time of death *(22)*. Unfortunately, as a result of the unknown starting concentration of potassium, artifacts induced by sample collection, and variability of breakdown of retinal cells, this analysis, in practice, is of little value in the majority of deaths. Vitreous creatinine and urea nitrogen are stable after death and may diagnose renal failure. Certain patterns (particularly helpful in infants) may demonstrate dehydration (high sodium and urea nitrogen).

3.4. Urine

As a result of the ease of analysis and renal clearance of many drugs, urine is an excellent screening specimen. The detection of a substance in the urine, however, is not always evidence of an acute intoxication. Drugs and metabolites may be detected in the urine during as well as following an acute intoxication. Blood (or other tissues such as brain) are the best specimens to diagnose an acute intoxication.

3.5. Bile

Approximately 500 to 600 mL of bile is secreted per day and the bile pool circulates 5 to 10 times per day (i.e., 2.5 hours recirculation). Detection of substances in bile may be owing to acute or chronic use. Opiates will undergo enterohepatic circulation (*see* Section 4.3).

3.6. Liver

Liver testing may be helpful in certain intoxications such as with propoxyphene and tricyclic antidepressants. Propoxyphene (Darvon®) is a mild narcotic, similar to methadone but with a smaller margin of safety. Propoxyphene is metabolized to norpropoxyphene, which has a much longer half-life. The ratios of propoxyphene and norpropoxyphene in blood and liver may help differentiate an acute vs chronic ingestion *(23)*. The liver concentrations of amitriptyline and nortriptyline (combined concentrations of greater than 50 mg/kg) may help differentiate an acute intoxication from therapeutic use *(11)*.

3.7. Gastric Contents

Gastric contents should be collected routinely at autopsy and stored for potential toxicological testing if the need arises. In deaths with a high index of suspicion of an ingestion, one also may collect proximal small bowel contents. The analysis of the gastric contents is important with ingestion deaths, particularly regarding the manner of death. When gastric results are reported, care must be taken to distinguish the gastric drug concentration from the amount of drug (milligram) in the total amount of submitted gastric contents (gram). The concentration may be impressively high but is meaningless from the pathologist's point of view. The important datum is the total amount of drug in the submitted specimen.

A typical toxicology report may have gastric contents with: acetaminophen concentration of 11,712 mg/kg (1241 mg in 103 g). Because the 1241 mg is the total amount of acetaminophen, then the person recently ingested at least four 325 mg tablets of acetaminophen. The concentration (11,712 mg/kg) will vary depending on how much "food" is also in the stomach. If the gastric contents are homogeneous and 103 g is a sample of 800 g of gastric content, then the amount of drug must be multiplied by eight. In the acetaminophen case, this would correspond to nearly 10,000 mg of acetaminophen. This is equivalent to more than thirty 325 mg tablets and is evidence of an intentional overdose.

3.8. Nasal Swabs

As a result of the high sensitivity of testing, cocaine may be detected from bloody nasal mucosal cells in someone who injected cocaine and did not snort it. Therefore, routine nasal swab testing is not helpful or cost effective.

3.9. Hair

Hair is not routinely collected. Because forensic pathologists, for the most part, are interested in acute intoxications, the fact that a person used cocaine 2 months previously is of little interest in most deaths. In deaths in which there is a question of "first-time use" (typically by parents who believe that someone slipped a drug to their teenager), it may be illuminating to test the hair to see if there has been prior use, which may be supportive of chronic voluntary abuse *(24,25)*.

3.10. Insects

Drugs of abuse may be detected in various insects and larvae that ingest the decomposing body *(26–29)*.

3.11. Intestine Contents

Drug packers ("mules") smuggle packets of drugs in the gastrointestinal tract. If these packets burst or cause an obstruction, the person may die. An autopsy of a body packer should be done under the watchful eye of multiple law enforcement or evidence unit personnel to protect against pilfering or accusations of pilfering. The number, size, and weight of the packets should be recorded. A small sample of one packet should be sent for toxicological testing. The cause of death is typically from an intoxication as a result of a disrupted packet; however, obstruction and sepsis also may cause death *(30)*.

4. Common Intoxicants

4.1. Ethanol

Peak blood ethanol concentrations following ingestion typically occur within 30 to 120 minutes. The majority of ethanol, however, is absorbed in the proximal small bowel, therefore, food in the stomach may delay absorption for up to 6 hours. At autopsy, one may detect a distinct odor as a result of alcohol ingestion. Because ethanol is odorless, what one actually smells are the various metabolites and congeners associated with ethanol ingestion.

Chronic alcohol abuse may cause death with or without a concurrent acute ethanol intoxication. There are a variety of anatomic changes of the liver, heart, brain, and pancreas that occur with chronic alcohol abuse. These include hepatic steatosis/cirrhosis, alcoholic cardiomyopathy, and acute and chronic pancreatitis. The effects on the central nervous system are broad and include seizures (commonly during withdrawal), Wernicke's encephalopathy, cerebellar atrophy (anterior vermis), and the Marchiafava Bignami syndrome. Delirium tremens is aggressively prophylaxed or treated with high-dose benzodiazepines. Its 10 to 20% mortality has decreased in recent years *(31–33)*. The diagnosis of associated metabolic derangements, including hypomagnesemia and alcoholic ketoacidosis may be aided with the analysis of vitreous electrolytes and β-hydroxybutyric acid *(34)*.

Most deaths resulting from purely acute alcohol intoxication occur with a blood alcohol content (BAC) of more than 400 mg/dL. One, however, may see lower concentrations if hypoxic brain injury with survival and metabolism occurred before death. People may survive with a BAC of more than 400 mg/dL. One case report included an adolescent who survived a BAC of 750 mg/dL *(35)*.

Because ethanol distributes in total body water, its concentration in various body fluids will depend on the water content of that fluid. The forensic/legal standard is measured on whole blood. Hospitals often measure ethanol in plasma, which gives a higher value than in whole blood because of the greater water content. A plasma concentration of 100 mg/dL is equivalent to 80 mg/dL in whole blood. Because whole blood is the typical legal standard, a 100 mg/dL in plasma would be just at the 80 mg/dL whole blood legal limit (Table 1).

Vitreous and urine autopsy specimens also may be analyzed for ethanol. Because vitreous has a greater water content than blood and it takes longer for ethanol to distribute to the vitreous, the blood–vitreous ratio can be used to determine if the blood ethanol concentration was rising at the time of death. At equilibrium, the BAC is roughly three-quarters of the vitreous alcohol content (VAC): BAC = 0.75 VAC or VAC = 1.3 BAC. Only in the absorptive phase (before alcohol has reached its peak) and early postabsorptive phase before equilibration, will the VAC be lower than the BAC. If the blood–vitreous ratio is greater than 0.95 (essentially if BAC is greater than VAC) then death occurred before equilibrium was achieved.

Caution must be used when interpreting urine ethanol concentrations because the bladder is a reservoir that may not have been completely empty when the person started ingesting ethanol or may not be emptied for some time after the ingestion has stopped *(36)*. It is possible to detect ethanol in

Table 1
Ethanol Ratios and Conversions

Ethanol whole blood ratio in various body fluids
1:1.0 whole blood (standard specimen for forensic cases)
1:1.2 plasma (specimen commonly tested in hospitals)
1:1.3 vitreous fluid (at equilibrium)
1:1.4 urine (ureteral)
One equivalent = 1 oz whiskey (50% ethanol) = 4 oz wine (12%) = 12 oz beer (3–5%)
50% ethanol = 100 proof ethanol
70 kg man, one equivalent will raise blood ethanol by 0.02%
35 kg man, one equivalent will raise blood ethanol by 0.04%
Average metabolic degradation = 0.015% per hour, decrease in blood ethanol.
Helpful conversions
0.1% = 1 mg/mL = 100 mg/dL
1200 ng/mL = 1.2 mcg/mL = 1200 mcg/L = 1.2 mg/L

urine while having a 0 BAC (e.g., if the person had not urinated for some time after ingestion stopped). It also is possible to have a urine ethanol concentration that is lower than the BAC (e.g., if the bladder was nearly full when the ingestion started). The 1:1.4 ratio is technically only for ureteral urine, which, in practice, is not recovered at autopsy. It may be recovered in the living if the specimen is collected shortly after voiding. The extrapolation of blood ethanol from urine ethanol concentrations is not sufficiently accurate in autopsy samples for forensic purposes. The qualitative detection of ethanol in the bladder or vitreous, however, may be very helpful in interpreting BAC in putrefied bodies.

Putrefaction is a microorganism-driven process. Some bacteria may ferment alcohols. This postmortem production of ethanol may cause problems in the interpretation of ethanol detected in the blood of putrefied bodies *(37,38)*. Is the ethanol from premortem ingestion or postmortem production? Typically, BAC are reliable for the first 24 hours. One study, that is known as the "smell bad" study (as a result of a mnemonic that was used to grade the extent of putrefaction) has examined this issue *(37)*. They found an increase in detection and concentrations of ethanol that paralleled the extent of putrefaction. Overall, 23 of 130 putrefied decedents had endogenous ethanol detected. The vast majority (19 of 23) had concentrations of less than 0.07 mg/dL. Four

decedents, however, had endogenous ethanol concentrations of 0.11, 0.12, 0.13, and 0.22 mg/dL.

One may differentiate endogenous (postmortem) ethanol from exogenous (premortem) ethanol ingestion by testing the urine and/or vitreous for ethanol. Because the urinary bladder and vitreous body are relatively sequestered areas, they may have delayed, little, or no bacterial intrusion and so there is little or no production of ethanol. Therefore, if ethanol is detected in the blood but not in the urine or vitreous, this would be evidence that the blood ethanol is endogenous. If ethanol is detected in all three samples, premortem ingestion has most likely occurred. Unfortunately, in many markedly decomposed bodies, there may be no vitreous or urine remaining at autopsy. In these cases, unless the circumstances are compelling, the interpretation of the blood ethanol should be conservative. Without vitreous or urine, one does not know if part or all of the ethanol is endogenous. There is one remaining caveat with ethanol detected in urine in diabetics. Because diabetics may have glucosuria as well as bacterial colonization of the urinary bladder, one may produce endogenous ethanol in the bladder as well *(37)*.

4.2. Cocaine

Cocaine (*coke, blow, crack, rock*) may be snorted, smoked, or injected *(39,40)*. Cocaine raises blood epinephrine and norepinephrine, which results in hypertension, an increased myocardial oxygen demand, and decreased myocardial oxygen supply (through vasoconstriction, atherosclerosis, or enhanced platelet aggregation/thrombus formation) *(41)*. Virtually any concentration of cocaine may cause death in a variety of ways. Therefore, the term "cocaine overdose" is misleading and implies that one died from taking too much. In fact, one may die from taking the same amount that he or she has previously taken on numerous occasions. The various immediate causes or mechanisms include myocardial infarcts secondary to vasospasm or atherosclerosis, intracerebral hemorrhages, aortic dissections, cardiac arrhythmias secondary to cocaine-induced cardiac hypertrophy, hyperthermia, agitated delirium, and ruptured cerebral artery aneurysms *(42–45)*. Chronic use can result in cardiac hypertrophy, which may cause sudden death. Heart size is an independent risk for sudden death, even when no cocaine is in the blood *(46)*. Heart weights are higher in cocaine-related deaths than in controls when cocaine is an incidental finding *(47)*. Microscopically, one may see contraction bands (as a result of reperfusion), fibrosis, and/or a myocarditis. The risk of an acute myocardial infarct is increased 24-fold during the first hour after cocaine use in people who are at low risk *(41)* and is unrelated to the amount, route, or frequency

used. Approximately 50% of cocaine-related myocardial infarcts will have no atherosclerosis on coronary angiogram *(41)*.

Cocaine is usually sold in powder (cocaine HCL) or freebase forms. Crack (cocaine alkaloid) is cocaine that was treated with sodium bicarbonate. Chemical manipulation of cocaine can alter the melting point and allow cocaine to be smoked. Crack cocaine caused a marketing revolution for two major reasons. First, the route of administration produced a much faster onset and peak of action, which potentiated its ability to cause addiction (Table 2). The second factor was that crack could now be sold as single dose units. Small single-dose vials of crack are sold for US$3 or $4. Previously, it was not cost effective for a dealer to sell a single dose of powder cocaine because of product loss in plastic wrap, and so on. Powdered cocaine would be sold in larger quantities, which increased its price and limited its availability.

4.2.1. Metabolism

The chemical name for cocaine is benzoylmethylecgonine and it has various metabolites including benzoylecgonine (BE), cocaethylene, and ecgonine methyl ester. Cocaine is inactivated by hydrolysis of one of the ester linkages. Even in water, cocaine will readily hydrolyze to BE. In blood or plasma, cocaine is hydrolyzed to ecgonine methyl ester by cholinesterase. In vitro, blood to which no inhibitor has been added will lose 100% of the cocaine in 21 days. But with the addition of 0.5% NaF, 70% of the cocaine will remain intact by 21 days *(11)*. Cocaethylene/ethylbenzoyleconine are metabolites of cocaine that occur when cocaine is metabolized in the presence of ethanol.

4.2.2. Detection

Typical blood cocaine concentrations are 0.2 to 0.7 mg/L. Cocaine has a half-life of approx 1 hour (30–90 minutes). BE has a half-life of 6 hours. Therefore, even though one dose of cocaine may be detected in blood (or urine) for several hours (8–12 hours) after exposure, BE may be detected for up to 24 hours in blood and several days in urine. Brain concentrations of cocaine accurately reflect the toxicological state at the time of death. Cocaine rapidly crosses the blood–brain barrier, however, BE does not. BE that is detected in the brain was produced in the brain. Therefore, concentrations of BE in the brain are lower than in the blood for up to 2 hours after use. The ratio of cocaine to BE may give an indication of patterns of use. A high blood concentration of cocaine with a low blood BE concentration is indicative of very recent use. A high brain BE concentration with a low brain cocaine concentration is not indicative of recent use. The detection of more BE in the brain than in the blood is as a result of extensive prior use *(14)*.

Table 2
Drugs of Abuse: The Chronicity and Extent of Use Affects the Detection Durations

Drug route	Onset of action	Duration	Half-life	Detection in blood	Detection in urine
Cocaine			30–90 minutes	4–6 hours	8–12 hours
Smoking	3–5 seconds	5–15 minutes			
Intravenous	10–60 seconds	15–60 minutes			
Nasal snorting	1–5 minutes	60–120 minutes			
Benzoylecgonine			6 hours	24 hours	3 days
Heroin			10 min	30 min	3–4 days[a]
Intravenous	10–20 seconds	4–5 hours			
Subcutaneous/intramuscularly	5–8 minutes	4–5 hours			
Smoking	5–15 seconds	3–5 hours			
Morphine (intravenously)	10–20 seconds	4–5 hours	1–3 hours	<2 days	3–4 days
Cannabinoids					
Smoking	10–30 minutes	1–4 hours	1–13 days	>3 days	3–90 days
MDMA (oral)	30–60 minutes	3–4 hours	8–9 hours	24 hours	1–2 days
GHB (oral)	15–30 minutes	3 hours	1/2–1 hr	<12 hours[b]	12–24 hours
Phencyclidine					
Smoking	1–5 minutes	4–6 hours	12 hours	1–3 days	5–20 days
Methamphetamine			11–12 hours	1–3 days	3–5 days
Smoking	5–10 seconds	4–8 hours			
Intravenous	5–10 seconds	4–8 hours			
Nasal snorting	3–5 minutes	4–16 hours			
Oral	30 minutes	4–24 hours			

[a]Morphine metabolites.
[b]N.B., postmortem endogenous production occurs.

4.3. Opiates

Opiates are any preparation or derivative of opium. Opium is a mixture of many compounds including morphine (10–15%), codeine (1–3%), papaverine (1–3%), and thebaine (1–2%). Opiodes are synthetic drugs with morphine-like pharmacologic actions.

Heroin (*H, horse, smack*) is the most popular illicit opiate. It may be injected, smoked ("chasing the dragon"), or snorted *(48,49)*. As a result of increases in purity, snorting of heroin is now an effective route of administration. Deaths resulting from acute heroin intoxication follow two patterns, which may be related to the mechanism of death. The first is a relatively slow death with respiratory depression and coma. The second is a sudden fatal collapse immediately following injection. These deaths may be the result of adulterants (e.g., quinine, lidocaine) rather than a dose-related effect.

The street purity of heroin has increased over the years. It is typically a tan granular substance but may be white depending on how it is processed. In 1990, 25% purity was common; however, this increased to 60 to 75% purity in 2001. Black tar heroin is most commonly seen on the west coast of the United States.

4.3.1. Metabolism

The chemical name for heroin is diacetylmorphine and it is quickly (half-life is 10 min) metabolized to 6-monoacetylmorphine. This compound is then metabolized (half-life is 20 min) to morphine, which has a longer half-life (half-life is 2 hours). As a result of these short half-lives, diacetylmorphine is rarely detected and morphine is unlikely to be detected in blood after 12 hours. Morphine is *not* metabolized to codeine. Trace amounts of codeine (or acetylcodeine) found with high morphine concentrations in the body most likely represent heroin abuse with codeine impurities from opium manufacturing. Similarly in these deaths, one may find papaverine (also used medically as a muscle relaxant), another component of opium. Testing of illicit heroin samples, commonly obtained in deaths of drug packers, reveals a variety of impurities and contaminants even before the drug is further cut on the street *(30)*.

Codeine is a naturally occurring alkaloid found in opium. It is predominately metabolized to codeine-6-glucoronide and norcodeine. A small amount of codeine (<1%) is metabolized to morphine. Oxycodone is a semisynthetic derivative of codeine. It is available as a long-acting, delayed-release, oral pharmaceutical used in the treatment of pain (e.g., Oxycontin®, Perdu Pharma, Stamford, CT). It has become a popular drug of abuse, because if the tablet is crushed, one can usurp the intended slow-release formulation. It has been called

"the poor man's heroin" and its popularity began in rural, underserved heroin regions.

4.3.2. Detection

Radioimmunoassay (RIA) detection of opiates is nonspecific. The antibodies detect morphine and other opiates and opiate metabolites. The resultant concentrations reflect several different compounds (not all are active) including codeine but not methadone or fentanyl. Ingestion of poppy seeds or cough syrups with codeine will give positive opiate results in urine. Poppy seeds contain both morphine and codeine but not 6-monoacetylmorphine, which is a unique metabolite of heroin and, if detected, allows differentiation of poppy seed ingestion and heroin abuse.

4.4. Methadone

Methadone is a long-acting synthetic narcotic with a half-life of 15 hours. It is used for heroin detoxification and chronic pain syndromes. Typically, when methadone is used to treat opiate addiction, a person starts with a dose of 20 mg per day and it is increased until the patient "feels well." Patients may be maintained on more than 100 mg per day. This degree of tolerance is further emphasized by the fact that a nonuser may die from a dose of 40 mg. Tolerance and polysubstance use creates problems with the interpretation of methadone concentrations in people receiving methadone maintenance *(50,51)*.

Before certifying a death as a result of an acute methadone intoxication, one must know if the person was in a methadone program *(52)*. A fatal concentration of methadone in one person may be another person's baseline *(53,54)*. One should not certify any death as a result of an intoxication based solely on the blood concentration, but this is particularly relevant when interpreting a methadone concentration in a patient on methadone maintenance. One should be very hesitant to certify such a death as as a result of a methadone intoxication. Some users may take amitriptyline with the methadone because it potentiates the methadone effects. Buprenorphine, a semisynthetic opiate derived from thebaine, is also an effective treatment of chronic opiate abuse *(55)*. It may replace methadone as the standard treatment for opiate addiction as a result of a longer half-life and the ability of primary care physicians to prescribe it.

4.5. Other Opiodes

Other opiodes include meperidine, which is a synthetic narcotic analgesic. The metabolite, normerperidine, has half the analgesia of meperidine and

may cause seizures. Normeperidine has a longer half-life than meperidine and accumulates with chronic use. MPPP is a potent meperidine analogue that is made in clandestine labs. Methyl-phenyl-tetrahydropyridine is a neurotoxic byproduct of the careless synthesis of MPPP (an illicit narcotic compound) that causes symptoms of Parkinsonism *(56)*. Substance abuse in the medical field (e.g., anesthesia residents) commonly involves meperidine or fentanyl abuse as a result of accessibility *(57)*.

Fentanyl is a synthetic opiode with a structure similar to meperidine. It is not detected by routine opiate screens. A death with circumstances consistent with opiate abuse and no opiates detected deserves a call to the toxicologist to discuss further testing for fentanyl *(58)*. Fentanyl may be injected but also is supplied medically as a transdermal patch. Fentanyl concentrations may be quite high in hospitalized patients.

4.6. Cannabinoids

Tetrahydrocannabinol is the most active of the various constituents of marijuana (*pot, grass, weed, smoke, reefer, herb*). It has a high volume of distribution, and cannabinoids may be detected for days after a single use. In chronic users, cannabinoids may be detected in the blood for up to 2 weeks after abstinence. Detection of cannabinoids is consistent with recent use but the extent of the current intoxication is difficult to know. The clinical history and circumstances combined with the toxicology results offer the best ability to offer an opinion about the degree of intoxication. Death from an intoxication by cannabinoids has not been reported.

4.7. Amphetamines

Methamphetamine (*ice, meth, crank, crystal*), and its metabolite amphetamine (*bennies, dexies, black beauties, speed*) are synthetic stimulants that increase norepinephrine in the neuronal synapse and enter the presynapse to inhibit monoamine oxidase, which prevents further storage of catecholamines. Methamphetamine may be smoked, injected, inhaled, or ingested. “Ice” is the smokable form of methamphetamine HCL. They can result in hypertensive and other cardiovascular problems *(59–63)*. Other untoward effects include psychosis, rhabdomyolysis, and hyperthermia. Methamphetamine is synthesized from naturally occurring ephedrine. Ephedrine is available over-the-counter and can cause false-positive results for methamphetamine on screening tests. The body cannot convert ephedrine to amphetamine. Methamphetamine has a half-life of 12 hours and is metabolized to amphetamine, which is then converted to norephedrine.

4.7.1. Detection

Urine is one of the best specimens for amphetamine screening *(64–68)*. If urine is not available, blood may be examined. If methamphetamine is detected, amphetamine also should be detected (if not, then be suspicious for a false-positive result). There is extensive postmortem redistribution and other confounding factors including tolerance that make the interpretation of their concentrations difficult *(7,63,69)*.

4.8. Hallucinogens/Disassociative Anesthetics

Common hallucinogens include lysergic acid diethylamide (LSD), phencyclidine (PCP), mescaline, ketamine, substituted amphetamines, and other phenylalkylamines including tryptamine compounds. The vast majority of deaths that occur during LSD, PCP, and mescaline intoxications are a result of trauma rather than to a primary intoxication mechanism.

LSD (*acid*) is a potent hallucinogen with a low-acute toxicity. LSD may be detected in the urine but it usually is not part of routine drug screen panels *(70–72)*.

PCP (*angel dust, hog*) is a veterinary tranquilizer that also is a drug of abuse. It is related structurally to ketamine and blocks dopamine uptake. It may be smoked, snorted, ingested, or injected. It causes disorientation, hallucination, and loss of coordination. Cigarettes may be dipped in PCP and smoked (so-called "sherms"). PCP is lipid soluble so it has one of the highest volumes of distribution of any illicit drug. It may be detected in the blood and urine for days and even weeks after taking the dose because of its large volume of distribution. Blood and urine measurements only reveal that the decedent did at one time take PCP but the concentration is otherwise difficult to interpret. Measurable concentrations may persist for months *(73)*.

Psilocybin and mescaline are naturally occurring hallucinogens that are ingested. Psilocybin (*mushrooms, shrooms*) is a tryptamine hallucinogen found in certain mushrooms. Mescaline (*buttons, peyote*) is made from the peyote cactus and has been used by Native Americans for centuries. There have been no reported deaths solely as a result of a mescaline or psilocybin intoxication.

4.9. Club Drugs (Substituted Amphetamines, Ketamine, and γ-Hydroxy Butyrate)

Certain drugs have a popularity in certain settings. Common "club drugs" include ecstasy, ketamine, and γ-hydroxy butyrate (GHB). There are numerous chemical variations of these drugs and a new one always seems just around the corner. Various websites and government agencies are a source for infor-

mation on the latest, in vogue, creation (e.g., *Microgram* from the US Drug Enforcement Agency or the National Institute on Drug Abuse).

Substituted amphetamines (e.g., *ecstasy, X, XTC, Adam*) are a group of drugs with the backbone of methamphetamine with various chemical alterations *(74–78)*. MDMA (*Ecstasy, XTC, Adam*) is 3,4-methylenedioxymethamphetamine and is metabolized to 3,4-methylenedioxyamphetamine (MDA), which also is a byproduct during manufacturing. MDEA (*Eve*) is 3,4-methylenedioxyethamphetamine *(74,79–81)*. There are numerous other derivatives including paramethoxyamphetamine (PMA), trimethoxyamphetamine (TMA), DOM (4-methyl-2,5-dimethoxyamphetamine), DOB (4-bromo-2,5-dimethoxyamphetamine), and Nexus *(82)*. These drugs have amphetamine and hallucinogenic effects and are taken for their combination of increased energy and empathy (*83,84*). Complications include hyperthermia *(85–87)*, rhabdomyolysis, arrhythmias, disseminated intravascular coagulation, dehydration, and death *(88–100)*. MDMA has a half-life of 8 to 9 hours with peak at 1.5 to 2 hours. After MDMA ingestion, MDA peaks at 5 to 7 hours and has a half-life of 25 hours *(101)*.

Ketamine (*Special K, K*, *vitamin K*) is an analgesic/anesthetic used in pediatric surgery and emergency medicine. Because it is one of the rare anesthesia agents that does not cause hypotension, it is very useful in these specialty areas. It has a structure similar to PCP and causes a dissociative state. It may be injected, snorted, or ingested *(102–108)*.

GHB (*Liquid X, Grevious Bodily Harm*) is used recreationally *(25,109–112)*. Postmortem concentrations of GHB are difficult to interpret as a result of its short half-life and because it naturally occurs in the body *(110,113–119)*. Therefore, the detection of GHB at autopsy may not be as a result of exogenous ingestion. In order to better differentiate exogenous from endogenous GHB, there have been several suggestions and studies.

GHB, if not ingested, should not be detected in the blood or urine of living persons or in postmortem urine *(120)*. In blood samples from the living, GHB may be produced in vitro if the specimen container contains citrate-buffer *(121)*. GHB has been detected (3.2–168 mg/L) in autopsy blood from non-GHB-related deaths. Postmortem analysis for GHB should be performed on urine (*121,122*) and NaF-preserved blood samples *(113)*.

4.10. Sexual Assault-Facilitating ("Date Rape") Drugs

Flunitrazepam (*Roofies*, Rohypnol®, Hoffman LaRoche, Switzerland) is a fast-acting benzodiazepine that is illegal in the United States. The manufacturer has altered the pill filler to cause a blue particulate change as the pill dissolves in a liquid *(123–126)*.

Chloral hydrate (*Mickey Finn*) is detected in the blood as trichloroethanol *(127)*. GHB is described above *(128)*.

4.11. Inhalants

Inhalants include aerosol propellants, fuels, chlorinated solvents, and adhesive solvents. So-called "whip-its" in which nitrous oxide is inhaled, received this name from the initial use of inhaling nitrous from whip-cream canisters. Small canisters of nitrous oxide, which are sold for homemade whip-cream use, also are abused.

Other examples include toluene (in paints and thinners); chlorinated hydrocarbons such as typewriter correction fluid (trichloroethylene) and ethyl chloride *(129–131)*; amyl nitrate (*poppers, locker room*); and difluroethane, a computer dust cleaner. Postmortem testing for these substances is very difficult as a result of their volatility. Some, such as nitrous oxide, nitrogen, and propane, typically cause death by exclusion of oxygen *(132–135)*. Tracheal aspirates and lung specimens submitted in red-top tubes are often suggested for collection, however, the laboratory result is often disappointing. Usually, the circumstances and findings at the scene will be more illuminating than the toxicology results.

5. Conclusion

The forensic pathologist must interpret the toxicological findings in the setting of an entire death investigation. The pitfalls of toxicology testing always need to be considered. The forensic pathologist should remember that the forensic toxicologist is a colleague that must be given appropriate case information. Providing quality information to the toxicologist will result in better and timely toxicological analysis on a particular death.

References

1. Jentzen J. Forensic toxicology. An overview and algorithmic approach. Am J Clin Pathol 1989;92(Suppl 1):S48–S55.
2. Freireich AW. Alexander O. Gettler 1883–1968. J Forensic Sci 1969;14:vii–xi.
3. Wu AH, Hill DW, Crouch D, Hodnett CN, McCurdy HH. Minimal standards for the performance and interpretation of toxicology tests in legal proceedings. J Forensic Sci 1999;44:516–522.
4. Cordner SM. Deciding the cause of death after necropsy. Lancet 1993;341:1458–1460.
5. Wetli CV. Investigation of drug-related deaths. An overview. Am J Forensic Med Pathol 1984;5:111–120.

6. Hilberg T, Rogde S, Morland J. Postmortem drug redistribution—human cases related to results in experimental animals. J Forensic Sci 1999;44:3–9.
7. Moriya F, Hashimoto Y. Redistribution of basic drugs into cardiac blood from surrounding tissues during early-stages postmortem. J Forensic Sci 1999;44:10–16.
8. Pounder DJ, Smith DR. Postmortem diffusion of alcohol from the stomach. Am J Forensic Med Pathol 1995;16:89–96.
9. Langford AM, Taylor KK, Pounder DJ. Drug concentration in selected skeletal muscles. J Forensic Sci 1998;43:22–27.
10. Williams KR, Pounder DJ. Site-to-site variability of drug concentrations in skeletal muscle. Am J Forensic Med Pathol 1997;18:246–250.
11. Baselt R. Disposition of Toxic Drugs and Chemicals in Man, 6th ed. Chemical Toxicology Institute, Foster City, CA, 2002.
12. Stead AH, Moffat AC. A collection of therapeutic, toxic and fatal blood drug concentrations in man. Hum Toxicol 1983;2:437–464.
13. Winek CL, Wahba WW, Winek CL Jr., Balzer TW. Drug and chemical blood-level data 2001. Forensic Sci Int 2001;122:107–123.
14. Hearn WL, Keran EE, Wei HA, Hime G. Site-dependent postmortem changes in blood cocaine concentrations. J Forensic Sci 1991;36:673–684.
15. Hardin GG. Postmortem blood and vitreous humor ethanol concentrations in a victim of a fatal motor vehicle crash. J Forensic Sci 2002;47:402,403.
16. Hirsch C, Adelson L. Ethanol in sequestered hematomas. Am J Clin Pathol 1973;59:429–433.
17. Wetherton AR, Corey TS, Buchino JJ, Burrows AM. Fatal intravenous injection of potassium in hospitalized patients. Am J Forensic Med Pathol 2003;24:128–131.
18. Khuu HM, Robinson CA, Brissie RM, Konrad RJ. Postmortem diagnosis of unsuspected diabetes mellitus established by determination of decedent's hemoglobin A1c level. J Forensic Sci 1999;44:643–646.
19. Coe JI. Postmortem chemistries on vitreous humor. Am J Clin Pathol 1969;51:741–750.
20. Coe JI. Postmortem chemistry of blood, CSF, and vitreous. Tedeshi's Forensic Medicine 1977;45:1033–1060.
21. Brubacher JR, Hoffman RS, Bania T, et al. Deaths associated with a purported aphrodisiac—NYC February 1993–May 1995. MMWR Morb Mortal Wkly Rep 1995;44:853–855.
22. Munoz JI, Suarez-Penaranda JM, Otero XL, et al. A new perspective in the estimation of postmortem interval (PMI) based on vitreous. J Forensic Sci 2001;46:209–214.
23. Baselt RC, Wright JA. Propoxyphene and norpropoxyphene tissue concentrations in fatalities associated with propoxyphene hydrochloride and propoxyphene napsylate. Arch Toxicol 1975;34:145–152.
24. Gaillard Y, Pepin G. Evidence of polydrug use using hair analysis: a fatal case involving heroin, cocaine, cannabis, chloroform, thiopental and ketamine. J Forensic Sci 1998;43:435–438.

25. Kintz P, Cirimele V, Jamey C, Ludes B. Testing for GHB in hair by GC/MS/MS after a single exposure. Application to document sexual assault. J Forensic Sci 2003;48:195–200.
26. Sadler DW, Richardson J, Haigh S, Bruce G, Pounder DJ. Amitriptyline accumulation and elimination in Calliphora vicina larvae. Am J Forensic Med Pathol 1997;18:397–403.
27. Hedouin V, Bourel B, Martin-Bouyer L, et al. Determination of drug levels in larvae of Lucilia sericata (Diptera: Calliphoridae) reared on rabbit carcasses containing morphine. J Forensic Sci 1999;44:351–353.
28. Bourel B, Fleurisse L, Hedouin V, et al. Immunohistochemical contribution to the study of morphine metabolism in Calliphoridae larvae and implications in forensic entomotoxicology. J Forensic Sci 2001;46:596–599.
29. Bourel B, Tournel G, Hedouin V, Goff ML, Gosset D. Determination of drug levels in two species of necrophagous Coleoptera reared on substrates containing morphine. J Forensic Sci 2001;46:600–603.
30. Gill JR, Graham SM. Ten years of "body packers" in New York City: 50 deaths. J Forensic Sci 2002;47:843–846.
31. Cushman P, Jr. Delirium tremens. Update on an old disorder. Postgrad Med 1987;82:117–122.
32. Erwin WE, Williams DB, Speir WA. Delirium tremens. South Med J 1998;91:425–432.
33. Griffin RE, Gross GA, Teitelbaum HS. Delirium tremens: a review. J Am Osteopath Assoc 1993;93:924, 929–932, 935.
34. Iten PX, Meier M. Beta-hydroxybutyric acid—an indicator for an alcoholic ketoacidosis as cause of death in deceased alcohol abusers. J Forensic Sci 2000;45:624–632.
35. Morgan DL, Durso MH, Rich BK, Kurt TL. Severe ethanol intoxication in an adolescent. Am J Emerg Med 1995;13:416–418.
36. Heise H. Concentrations of alcohol in samples of blood and urine taken at the same time. J Forensic Sci 1967;12:454–462.
37. Zumwalt R, Bost R, Sunshine I. Evaluation of ethanol concentrations in decomposed bodies. J Forensic Sci 1982;27:549–554.
38. Gilliland MG, Bost RO. Alcohol in decomposed bodies: postmortem synthesis and distribution. J Forensic Sci 1993;38:1266–1274.
39. Escobedo LG, Ruttenber AJ, Agocs MM, Anda RF, Wetli CV. Emerging patterns of cocaine use and the epidemic of cocaine overdose deaths in Dade County, Florida. Arch Pathol Lab Med 1991;115:900–905.
40. Mittleman RE, Wetli CV. Death caused by recreational cocaine use. An update. JAMA 1984;252:1889–1893.
41. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. N Engl J Med 2001;345:351–358.
42. Wetli CV. Fatal cocaine intoxication. A review. Am J Forensic Med Pathol 1987;8:1,2.
43. Mittleman RE, Wetli CV. Cocaine and sudden "natural" death. J Forensic Sci 1987;32:11–19.

44. Virmani R, Robinowitz M, Smialek JE, Smyth DF. Cardiovascular effects of cocaine: an autopsy study of 40 patients. Am Heart J 1988;115:1068–1076.
45. Karch SB, Billingham ME. The pathology and etiology of cocaine-induced heart disease. Arch Pathol Lab Med 1988;112:225–230.
46. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. Ann Intern Med 1969;71:89–105.
47. Karch SB, Stephens B, Ho CH. Relating cocaine blood concentrations to toxicity—an autopsy study of 99 cases. J Forensic Sci 1998;43:41–45.
48. Hirsch CS, Adelson L. Acute fatal intranasal narcotism. Report of two fatalities following narcotic "snorting." Hum Pathol 1972;3:71–73.
49. Darke S, Ross J. Fatal heroin overdoses resulting from non-injecting routes of administration, NSW, Australia, 1992–1996. Addiction 2000;95:569–573.
50. Karch SB, Stephens BG. Toxicology and pathology of deaths related to methadone: retrospective review. West J Med 2000;172:11–14.
51. Mikolaenko I, Robinson CA, Jr., Davis GG. A review of methadone deaths in Jefferson County, Alabama. Am J Forensic Med Pathol 2002;23:299–304.
52. Green H, James RA, Gilbert JD, Harpas P, Byard RW. Methadone maintenance programs—a two-edged sword? Am J Forensic Med Pathol 2000;21:359–361.
53. Bastos ML, Galante L. Toxicological findings in victims of traumatic deaths. J Forensic Sci 1976;21:176–186.
54. Gagajewski A, Apple FS. Methadone-related deaths in Hennepin County, Minnesota: 1992–2002. J Forensic Sci 2003;48:668–671.
55. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med 2000;343:1290–1297.
56. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science 1983;219:979,980.
57. Ward CF, Ward GC, Saidman LJ. Drug abuse in anesthesia training programs. A survey: 1970 through 1980. JAMA 1983;250:922–925.
58. Fernando D. Fentanyl-laced heroin. JAMA 1991;265:2962.
59. Swalwell CI, Davis GG. Methamphetamine as a risk factor for acute aortic dissection. J Forensic Sci 1999;44:23–26.
60. Shaw KP. Human methamphetamine-related fatalities in Taiwan during 1991–1996. J Forensic Sci 1999;44:27–31.
61. Massello W, 3rd, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin). J Forensic Sci 1999;44:220,221.
62. Lora-Tamayo C, Tena T, Rodriguez A. Amphetamine derivative related deaths. Forensic Sci Int 1997;85:149–157.
63. Logan BK, Fligner CL, Haddix T. Cause and manner of death in fatalities involving methamphetamine. J Forensic Sci 1998;43:28–34.
64. Poklis A, Fitzgerald RL, Hall KV, Saady JJ. EMIT-d.a.u. monoclonal amphetamine/methamphetamine assay. II. Detection of methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA). Forensic Sci Int 1993;59:63–70.

65. Lurie IS, Bethea MJ, McKibben TD, et al. Use of dynamically coated capillaries for the routine analysis of methamphetamine, amphetamine, MDA, MDMA, MDEA, and cocaine using capillary electrophoresis. J Forensic Sci 2001;46:1025–1032.
66. Koester CJ, Andresen BD, Grant PM. Optimum methamphetamine profiling with sample preparation by solid-phase microextraction. J Forensic Sci 2002;47:1002–1007.
67. Jurado C, Gimenez MP, Soriano T, Menendez M, Repetto M. Rapid analysis of amphetamine, methamphetamine, MDA, and MDMA in urine using solid-phase microextraction, direct on-fiber derivatization, and analysis by GC-MS. J Anal Toxicol 2000;24:11–16.
68. Felscher D, Schulz K. Screening of amphetamine/methamphetamine and their derivatives in urine using FPIA and Triage 8 and the Scope and limits of a subsequent identification by means of the REMEDi HS system. J Forensic Sci 2000;45:1327–1331.
69. Karch SB, Stephens BG, Ho CH. Methamphetamine-related deaths in San Francisco: demographic, pathologic, and toxicologic profiles. J Forensic Sci 1999;44:359–368.
70. White SA, Kidd AS, Webb KS. The determination of lysergide (LSD) in urine by high-performance liquid chromatography-isotope dilution mass spectrometry (IDMS). J Forensic Sci 1999;44:375–379.
71. de Kanel J, Vickery WE, Waldner B, Monahan RM, Diamond FX. Automated extraction of lysergic acid diethylamide (LSD) and N-demethyl-LSD from blood, serum, plasma, and urine samples using the Zymark RapidTrace with LC/MS/MS confirmation. J Forensic Sci 1998;43:622–625.
72. Bergemann D, Geier A, von Meyer L. Determination of lysergic acid diethylamide in body fluids by high-performance liquid chromatography and fluorescence detection—a more sensitive method suitable for routine use. J Forensic Sci 1999;44:372–374.
73. Aniline O, Pitts F. Phencyclidine (PCP): a review and perspective. CRC Crit Rev Toxicol 1982;10:145–177.
74. Dowling G, McDonough E, Bost R. Eve and ecstasy: a report of five deaths associated with the use of MDEA and MDMA. JAMA 1987;257:1615–1617.
75. Gill JR, Hayes JA, deSouza IS, Marker E, Stajic M. Ecstasy (MDMA) deaths in New York City: a case series and review of the literature. J Forensic Sci 2002;47:121–126.
76. Brown C, Osterloh J. Multiple severe complications from recreational ingestion of MDMA ("Ecstasy"). JAMA 1987;258:780,781.
77. Burgess C, O'Donohoe A, Gill M. Agony and ecstasy: a review of MDMA effects and toxicity. Eur Psychiatry 2000;15:287–294.
78. Henry JA, Jeffreys KJ, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). Lancet 1992;340:384–387.
79. Weinmann W, Bohnert M. Lethal monointoxication by overdosage of MDEA. Forensic Sci Int 1998;91:91–101.
80. Tsatsakis AM, Michalodimitrakis MN, Patsalis AN. MDEA related death in Crete: a case report and literature review. Vet Hum Toxicol 1997;39:241–244.

81. Fineschi V, Centini F, Mazzeo E, Turillazzi E. Adam (MDMA) and Eve (MDEA) misuse: an immunohistochemical study on three fatal cases. Forensic Sci Int 1999;104:65–74.
82. Karch S. The Pathology of Drug Abuse, 3rd ed. CRC Press, Boca Raton, 2002.
83. Schwartz R, Miller N. MDMA (ecstasy) and the rave: a review. Pediatrics 1997;100:705–708.
84. Cami J, Farre M, Mas M, et al. Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. J Clin Psychopharmacol 2000;20:455–466.
85. Chadwick IS, Curry PD, Linsley A, Freemont AJ, Doran B. Ecstasy, 3-4 methylenedioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia. J R Soc Med 1991;84:371.
86. Dar KJ, McBrien ME. MDMA induced hyperthermia: report of a fatality and review of current therapy. Intensive Care Med 1996;22:995,996.
87. Screaton GR, Singer M, Cairns HS, Thrasher A, Sarner M, Cohen SL. Hyperpyrexia and rhabdomyolysis after MDMA ("ecstasy") abuse. Lancet 1992;339:677,678.
88. Hughes JC, McCabe M, Evans RJ. Intracranial haemorrhage associated with ingestion of "ecstasy." Arch Emerg Med 1993;10:372–374.
89. Fineschi V, Masti A. Fatal poisoning by MDMA ("ecstasy") and MDEA: a case report. Int J Legal Med 1996;108:272–275.
90. Duflou J, Mark A. Aortic dissection after ingestion of "ecstasy" (MDMA). Am J Forensic Med Pathol 2000;21:261–263.
91. Lo D, Goh E, Yao Y, Wee K. The first fatal overdose with MDMA in Singapore. Bulletin of the International Association of Forensic Toxicologists XXXI, 2001, pp. 13,14.
92. Coore JR. A fatal trip with ecstasy: a case of 3,4- methylenedioxymethamphetamine/ 3,4- methylenedioxyamphetamine toxicity. J R Soc Med 1996;89:51,52.
93. Forrest AR, Galloway JH, Marsh ID, Strachan GA, Clark JC. A fatal overdose with 3,4-methylenedioxyamphetamine derivatives. Forensic Sci Int 1994;64:57–59.
94. Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. Arch Intern Med 1999;159:2221–2224.
95. Matthai SM, Davidson DC, Sills JA, Alexandrou D. Cerebral oedema after ingestion of MDMA ("ecstasy") and unrestricted intake of water. BMJ 1996;312:1359.
96. Milroy CM, Clark JC, Forrest AR. Pathology of deaths associated with "ecstasy" and "eve" misuse. J Clin Pathol 1996;49:149–153.
97. Mueller PD, Korey WS. Death by "ecstasy": the serotonin syndrome? Ann Emerg Med 1998;32:377–380.
98. O'Connor A, Cluroe A, Couch R, Galler L, Lawrence J, Synek B. Death from hyponatraemia-induced cerebral oedema associated with MDMA ("Ecstasy") use. N Z Med J 1999;112:255,256.
99. Walubo A, Seger D. Fatal multi-organ failure after suicidal overdose with MDMA, "ecstasy": case report and review of the literature. Hum Exp Toxicol 1999;18:119–125.
100. Suarez RV, Riemersma R. "Ecstasy" and sudden cardiac death. Am J Forensic Med Pathol 1988;9:339–341.

101. de la Torre R, Farre M, Roset PN, et al. Pharmacology of MDMA in humans. Ann N Y Acad Sci 2000;914:225–237.
102. Felser J, Orban D. Dystonic reaction after ketamine abuse. Ann Emerg Med 1982;11:673–675.
103. White P, Way W, Trevor A. Ketamine—its pharmacology and therapeutic uses. Anesthesiol 1982;56:119–136.
104. Reich D, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 1989;36:186–197.
105. Moore K, Kilbane E, Jones R, Kunsman G, Levine B, Smith M. Tissue distribution of ketamine in a mixed drug fatality. J Forensic Sci 1997;2:1183–1185.
106. Licata M, Pierini G, Popoli G. A fatal ketamine poisoning. J Forensic Sci 1994;39:1314–1320.
107. Jansen K. Non-medical use of ketamine. BMJ 1993;306:601,602.
108. Gill JR, Stajic M. Ketamine in non-hospital and hospital deaths in New York City. J Forensic Sci 2000;45:655–668.
109. Anonymous. Gamma hydroxy butyrate use—New York and Texas, 1995–1996. MMWR Morb Mortal Wkly Rep 1997;46:281,282.
110. Kalasinsky KS, Dixon MM, Schmunk GA, Kish SJ. Blood, brain, and hair GHB concentrations following fatal ingestion. J Forensic Sci 2001;46:728–730.
111. Hornfeldt C, Lothridge K, Upshaw Downs JC. Forensic science update: gamma-hydroxybutyrate (GHB). Forensic Science Communications 2002;4:1–10.
112. Chin M, Kreutzer R. Acute poisoning from GHB in California. West Med J 1992;156:380–384.
113. Karch SB, Stephens BG, Nazareno GV. GHB. Club drug or confusing artifact? Am J Forensic Med Pathol 2001;22:266–269.
114. LeBeau MA, Montgomery MA, Jufer RA, Miller ML. Elevated GHB in citrate-buffered blood. J Anal Toxicol 2000;24:383,384.
115. Stephens BG, Coleman DE, Baselt RC. In vitro stability of endogenous gamma-hydroxybutyrate in postmortem blood. J Forensic Sci 1999;44:231.
116. Mesmer M, Satzger R. Determination of gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL) by HPLC/UV-VIS spectrophotometry and HPLC/thermospray massspectometry. J Forensic Sci 1998;43:489–492.
117. Elliot S. The presence of gamma-hydroxybutyric acid (GHB) in postmortem biological fluids. J Anal Toxicol 2001;25:152.
118. Ciolino LA, Mesmer MZ, Satzger RD, Machal AC, McCauley HA, Mohrhaus AS. The chemical interconversion of GHB and GBL: forensic issues and implications. J Forensic Sci 2001;46:1315–1323.
119. Andera KM, Evans HK, Wojcik CM. Microchemical identification of gamma-hydroxybutyrate (GHB). J Forensic Sci 2000;45:665–668.
120. Fieler EL, Coleman DE, Baselt RC. Gamma-hydroxybutyrate concentrations in pre- and postmortem blood and urine. Clin Chem 1998;44:692.
121. LeBeau MA, Montgomery MA, Jufer RA, Miller ML. Elevated GHB in citrate-buffered blood. J Anal Toxicol 2000;24:383,384.
122. Timby N, Eriksson A, Bostrom K. Gamma-hydroxybutyrate associated deaths. Am J Med 2000;108:518,519.

123. McKibben T. Simple and rapid color screening tests for flunitrazepam (Rohypnol). J Forensic Sci 1999;44:396–400.
124. Negrusz A, Moore CM, Stockham TL, et al. Elimination of 7-aminoflunitrazepam and flunitrazepam in urine after a single dose of Rohypnol. J Forensic Sci 2000;45:1031–1040.
125. Negrusz A, Moore CM, Hinkel KB, et al. Deposition of 7-aminoflunitrazepam and flunitrazepam in hair after a single dose of Rohypnol. J Forensic Sci 2001;46:1143–1151.
126. Matschke J, Tsokos M, Sperhake J. Further comment on abnormally pigmented organs presenting at autopsy. Arch Pathol Lab Med 2002;126:400.
127. Gaulier JM, Merle G, Lacassie E, et al. Fatal intoxications with chloral hydrate. J Forensic Sci 2001;46:1507–1509.
128. Stillwell ME. Drug-facilitated sexual assault involving gamma-hydroxybutyric acid. J Forensic Sci 2002;47:1133,1134.
129. Broussard LA, Broussard AK, Pittman TS, Lirette DK. Death due to inhalation of ethyl chloride. J Forensic Sci 2000;45:223–225.
130. Isenschmid DS, Cassin BJ, Hepler BR, Kanluen S. Tetrachloroethylene intoxication in an autoerotic fatality. J Forensic Sci 1998;43:231–234.
131. Fagin J, Bradley J, Williams D. Carbon monoxide poisoning secondary to inhaling methylene chloride. Br Med J 1980;281:1461.
132. Winek CL, Wahba WW, Rozin L. Accidental death by nitrous oxide inhalation. Forensic Sci Int 1995;73:139–141.
133. McLennan JJ, Sekula-Perlman A, Lippstone MB, Callery RT. Propane-associated autoerotic fatalities. Am J Forensic Med Pathol 1998;19:381–386.
134. Rohrig TP. Sudden death due to butane inhalation. Am J Forensic Med Pathol 1997;18:299–302.
135. Gill JR, Ely SF, Hua Z. Environmental gas displacement: three accidental deaths in the workplace. Am J Forensic Med Pathol 2002;23:26–30.

Performance-Enhancing Drugs

12

Long-Term Effects of Anabolic-Androgenic-Steroid Abuse

Morphological Findings Associated With Fatal Outcome

Roland Hausmann, MD

Contents

Summary

The use of performance-enhancing drugs is an important and increasing phenomenon no longer limited only to elite athletes. Nowadays, people employ a broad variety of drugs in order to improve their athletic performance. Recent studies suggest that 3 to 12% of male adolescents and about 1 to 2% female adolescents use anabolic-androgenic-steroids (AAS) at some time during their

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

lives. Serious alterations of different organ systems have been attributed to long-term use of these drugs. Adverse effects of AAS include myocardial hypertrophy and fibrosis, vascular disease and hepatic pathology such as hepatoma, peliosis hepatis, and cholestasis. Steroid-related abnormalities in lipid profiles with elevated low-density lipoprotein (LDL) cholesterol and depressed high-density lipoprotein (HDL) cholesterol, as well as hematological disorders, may increase the risk of cardiac infarction and stroke. Recently, a number of case reports of acute cardiac death associated with steroid abuse has appeared in the literature. The overwhelming majority of fatalities reported in the literature is associated with acute myocardial infarction (MI) with or without thrombotic occlusion of the coronary arteries. Steroid-associated cardiovascular lesions could be demonstrated in animal studies but there seem to exist no steroid-specific pathological findings in humans. Consequently, other possible reasons, apart from AAS use, responsible for structural organ changes have to be clarified by extensive morphological examination and toxicological analysis, including the circumstances of death as well as the individual's previous medical history.

Key Words: Anabolic steroids; performance-enhancing drugs; adverse effects; fatalities; autopsy findings; histopathology.

1. Introduction

Anabolic-androgenic-steroid (AAS) abuse seems to be widespread among professional athletes and amateur sportsmen (*1–3*), but the real incidence is difficult to estimate. The investigations of the National Household Survey on Drug Abuse in 1990 indicated that more than 1 million Americans are current or former AAS users *(4,5)*. As reported by Dawson *(6)*, the use of performance-enhancing drugs is no longer limited to the elite athlete: in 1993, the Canadian Center for Drug-free Sport estimated that 83,000 children between the ages of 11 and 18 had used anabolic steroids in the previous 12 months and there is evidence that anabolic steroids are now the third most commonly offered drug to children in the United Kingdom. In Germany, the estimated number of juvenile users is about 100,000 *(7)*. Recent studies have shown that 3 to 12% of male adolescents and about 1 to 2% female adolescents admit to taking an ASS at some time during their life *(8)*.

There are several reports in the literature regarding the adverse effects of anabolic steroids on various organ systems including cardiovascular and hepatic pathologies, as well as abnormalities in lipid profiles, which may increase the risk of cardiovascular disease. Alterations of the endocrine function have been

shown to be associated with testicular atrophy, oligospermia, and decreased testosterone levels. Furthermore, psychiatric disturbances such as dependence and withdrawal syndromes have been reported to be frequent and often severe in anabolic steroid abusers *(9)*.

Because unexpected death as a result of cardiomyopathy, myocardial infarction (MI), and stroke can occur as a result of different effects of the substances used *(10–19)*, the growing incidence of steroid abuse is of considerable interest to the forensic pathologist.

After a brief review of the different adverse effects of AAS, characteristic morphological alterations associated with performance-enhancing drug abuse as well as fatalities reported in the literature are presented.

2. Vascular Events

Androgens have been discussed to predispose to thrombosis by effecting the structure and function of vascular tissues. Structurally, androgens decrease elastin and increase collagen and other fibrous proteins in arterial vascular tissue and skin *(20–23)*. Functionally, androgens have been linked with an enhancement of vascular reactivity and with a decrease in aortic smooth muscle prostaglandin 12 *(24)*. Consistent with these findings has been the identification of specific androgen receptors in the vascular tissues of several animal species *(25)*. Further evidence implicates that androgens may affect platelet function and there are data to support steroid-induced alterations in all stages of the coagulation cascade *(9)*.

Recently, Tischer et al. *(26)* reported the case of a 32-year-old male body builder who died of cardiac arrest (CA) attributable to long-term abuse of anabolic steroids. Coronary angiography and autopsy findings showed ectasia of the coronary arteries with hypertrophic intima and media. Such structural changes of the coronary arteries together with the alterations of the lipid profiles predispose users of anabolic steroids to the development of thrombosis.

3. Myocardial Alterations

3.1. Ventricular Hypertrophy and Fibrosis

Structural effects of AAS could be demonstrated both in studies on primary myocardial cell cultures *(27)* and in animal experiments (*28–30*). Additionally, quantitative electron microscopy showed an enlargement of the

sarcoplasmatic space and an imbalance of the mitochondrial–myofibrillar ratio. When the administration of anabolic steroids and training are combined, pathological alterations such as destruction of mitochondria and aberrant myofibrils, focal dehiscent intercalated discs, necrotic cells, mitochondrial disruption, and a decrease in myocyte capillary supply can be observed *(31,32)*. There is also evidence of an increased collagen production in experimental animals after steroid exposure *(30)*.

Structural alterations to the heart have also been observed in humans. Luke et al. *(12)* reported the case of a previously healthy 21-year-old steroid-abusing weight lifter who died of CA. In addition to renal hypertrophy and hepatosplenomegaly, biventricular hypertrophy could be detected. The myocardium showed extensive fibrosis, small foci of necrosis, and myocytes with contraction band necrosis. Additionally, cases with widespread patchy fibrosis *(13,15)*, cardiomyopathy *(33)*, and ventricular hypertrophy *(34,35)* have appeared in the literature. Myocardial fibrosis is thought to be caused by a lack of blood supply in the hypertrophic myocardium *(36)*. Melchert *(37)* suggested four hypothetical models of AAS-induced adverse cardiovascular effects: (a) an atherogenic model involving the effects of AAS on lipoprotein concentrations, (b) a thrombosis model involving the effects of AAS on clotting factors and platelets, (c) a vasospasm model involving the effects of AAS on the vascular nitric oxide system, and (d) a direct myocardial injury model involving the effects of AAS on individual myocardial cells.

The existence of a concentric left ventricular (LV) hypertrophy in strength-trained athletes is still a topic of debate but is rejected according to a recent clinical study *(38)*. In some highly trained athletes, the thickness of the LV wall may increase as a consequence of exercise training. In these athletes, the differential diagnosis between physiological and pathological hypertrophy may be difficult or impossible. On the basis of echocardiography data, the upper limit to which the thickness of the LV wall may be increased by training appears to be 16 mm. Therefore, athletes with a wall thickness of more than 16 mm are likely to have primary forms of pathological hypertrophy, such as hypertrophic cardiomyopathy, possibly associated with a long-term AAS abuse *(39,40)*.

3.2. Myocardial Infarction

Several case reports dealing with sudden cardiac death as a result of acute MI following steroid abuse have been published. The first documented MI in an athlete using anabolic steroids was that of a 22-year-old world-class weight lifter with no past or family history of cardiac diseases who claimed to have

used the drugs for only 6 weeks *(10)*. Angiography was normal, total cholesterol and LDL cholesterol were markedly elevated and HDL cholesterol depressed conversely. The proposed etiology in this case was coronary artery spasm combined with increased platelet aggregation, both secondary to anabolic steroid abuse.

A further case of fatal acute MI associated with depressed HDL and elevated LDL cholesterol was reported in a 29-year-old male body builder with secondary analphalipoproteinemia *(41)*.

A 23-year-old body builder presented with severe tight retrosternal chest pain. He had been using anabolic steroids for the past 5 years, at least 5 weeks previously. He was a nonsmoker with no family history of heart disease. His electrocardiogram showed evidence of an acute lateral infarction, and despite treatment with streptokinase he subsequently developed signs of a full thickness infarct with a rise in cardiac enzyme activities *(11)*.

Ferenchick *(42)* described the case of a 22-year-old athlete who died of MI. Postmortem examination revealed occlusion of the left main and left-anterior descending coronary arteries by acute thrombosis.

A 37-year-old weight lifter suffered an MI after 7 years of steroid abuse. Cardiac catheterization 3 days after treatment with intravenous tissue plasminogen activator showed a normal LV function and unremarkable coronary arteries *(14)*.

Huie *(17)* described the case of a 25-year-old male amateur weight trainer with no prior medical history who suffered from an acute MI. The patient denied using illicit drugs except for anabolic steroids. To improve his strength, he took his first weekly 100-mg dose of nandrolone decanoate intramuscularly 16 weeks prior to his admission to hospital and continued this for 6 weeks. He stopped using it for the following 4 weeks, but then resumed the injections at the higher dose of 200 mg for another 6 weeks. His last injection took place 2 days prior to his admission to hospital. In this case, a coronary thrombosis was lysed with urokinase and a follow-up angiogram revealed only slight residual wall irregularities. The patient did well with cardiac rehabilitation and was discharged home 13 days after the MI took place. Although the specific cause of coronary thrombosis in this patient remains unknown, hematologic effects of this class of drugs and the subsequent impact on ischemic heart disease have to be considered.

4. Cerebrovascular Insults

Since 1988, five cases of athletes suffering major arterial events following AAS abuse have been reported in the literature. A 34-year-old male using

various anabolic steroids for 4 years developed an acute right hemiparesis and experienced a speech disorder as well as a simple partial seizure activity *(43)*. A state of hypercoagulability secondary to anabolic steroids was postulated to have caused the middle cerebral artery event as documented by angiography.

Further middle cerebral artery events were reported in a 32-year-old body builder who had used a variety of anabolic steroids for 16 years *(44)*.

Laroche *(45)* presented the case of a 28-year-old athlete who had consumed mega-doses of steroids and anabolics prepared for animals such as horses and cows that had been sold on the black market. He administered himself monthly intramuscular injections of stanozolol oxandrolone, nandrolone decanoate, trembolone acetate, chorionic gonadotropins, and methyltestosterone. After taking these drugs for 3 years, the man experienced a cerebrovascular insult caused by thrombembolism of a carotid artery that partially embolized to the brain. The patient was treated with acetylsalicylic acid for 6 days and became totally asymptomatic. Three years later, he was admitted to hospital again with a severe ischemic episode in a lower limb caused by distal arterial thromboembolism.

5. Steroid-Related Hepatic Diseases

In addition to steroid-related disorders of the cardiovascular system, liver diseases such as hepatic tumors, peliosis hepatis, and cholestasis have been observed in steroid-abusing athletes.

5.1. Liver Tumors

The development of a hepatoma during androgen therapy was first recorded in 1965 by Recant and Lancy *(46)* and followed by other reports of liver tumors in patients receiving therapeutic doses of anabolic steroids for many years *(47,48)*. Three cases of liver tumors presenting in athletes with a previous history of anabolic steroid abuse have been published in the literature so far. A 26-year-old Caucasian body builder developed a primary hepatic malignancy after taking methandrostenolone, oxandrolone, stanozolol, nandrolone decanoate, and methenolon for 4 years in various doses *(49)*. A 37-year-old man who took methandrostenolone and oxymetholone sequentially over almost 5 years developed a liver carcinoma *(50)*. A 27-year-old Indian body builder who had taken anabolic steroids (not further specified) for 3 years died as a result of a ruptured hepatic tumor *(51)*. The fatal clinical outcome in each case occurred within weeks to months after establishing the diagnosis and despite the withdrawal of anabolic steroids.

5.2. Peliosis Hepatis

Peliosis hepatis is a rare entity characterized histologically by the presence of scattered, small, blood-filled cystic spaces throughout the liver parenchyma. Some of the cysts may be lined by sinusoidal cells whereas others are not *(52)*. These blood-filled spaces are often located adjacent to zones of hepatocellular necrosis.

Peliosis hepatis was first described in patients with tuberculosis *(53)*, but over the years reports have been published linking peliosis to many other underlying pathological conditions. The connection between anabolic steroids and peliosis was first noted in 1952 *(54)*. Since then, it has been reconfirmed in series of patients with hematological disorders that were treated with 17 a-alky-substituted steroids *(55)*. The pathogenesis of peliosis hepatis still remains unclear. Congenital *(53)* and underlying infectious mechanisms *(56)* also have been discussed. Paradinas et al. postulated that hyperplasia of the hepatocytes, perhaps related to the anabolic effect of methyltestosterone, could partly be responsible for the formation of cysts through mechanical obstruction of hepatic veins and for the formation of nodules and tumors *(57)*.

5.3. Cholestasis

Several deaths from cholestatic jaundice have been attributed to steroids, but they occurred in elderly, debilitated patients, and the evidence of causality is far from convincing *(58)*. Based on animal studies, the mechanism for bile accumulation appears to involve a disruption of the microfilaments within the hepatocytes that reduces the ability of the cells to transport bile *(59)*. Histologically, steroid-associated cholestasis is characterized by the occurrence of bile accumulates in the canaliculi but without evidence of inflammation or necrosis *(60)*.

6. Case Reports: Literature Review

Only a paucity of published autopsy cases of fatal steroid abuse including detailed description of postmortem findings is available so far.

In 1990, Luke et al. presented the case of a previously healthy 21-year-old weight lifter who collapsed during a bench press workout *(12)*. He had taken AAS (testosterone and nandrolone) parenterally over a period of several months. Autopsy findings included marked LV and right ventricular hypertrophy of the heart with extensive regional myocardial fibrosis. The coronary arteries exhibited no evidence of atherosclerosis. The cardiac valves were

unremarkable. Microscopic examination of the heart revealed regional fibrosis with principal involvement of the subepicardial and central LV and interventricular septal areas but without evidence of inflammation. Additionally, there were several tiny foci of acute myocardial fiber necrosis accompanied by sparse neutrophilic and round cell infiltrates. Occasionally, myocardial fibers exhibited contraction band formation. Furthermore, there was marked bilateral renal hypertrophy and hepatosplenomegaly. Gross inspection and microscopic examination of the other organs revealed no significant pathological abnormalities aside from pulmonary edema. Two possible etiologies of the cardiac findings were discussed by the authors: (a) occult episode of viral or toxic myocarditis, and (b) rapid growth of the myocardium induced by the steroids thus leading to a deficiency in myocardial blood supply.

Madea and Grellner *(35)* reported two cases of body builders who used oral anabolic steroids (Dianabol®, Oral-Turinabol®) for more than 10 years. One of them, a 28-year-old adipose male (weight 136 kg, height 178 cm) developed severe cardiovascular side effects such as atherosclerosis, recurrent MI, and stroke as well as enlargement of all internal organs (organ weights: heart 800 g, liver 5719 g, both kidneys 910 g). Histological examination revealed disseminated interstitial as well as perivascular fibrosis and focal scars in the myocardium as well as signs of chronic congestion of the lungs, liver, and spleen. Furthermore, the authors observed sclerosis of the coronary arteries without significant occlusions. An acute cardiac failure as a result of massive biventricular hypertrophy ("cor bovinum") was discussed as the actual cause of death. The other case dealt with a 40-year-old male who committed suicide by a gun shot to the head. The main pathological findings were ventricular hypertrophy (heart weight 470 g), acute myocardial necrosis adjacent to a myocardial scar, mild sclerosis of the coronary arteries, mild atherosclerosis, encephalomalcia in cerebellum and brain stem without any cerebrosclerosis, and an old infarction in the right kidney.

Recently, this author portrayed the case of a 23-year-old male body builder who had used anabolic steroids in combination with other performance enhancing drugs over a period of about 9 months and died of acute CA without previous symptoms *(59)*. After he had visited a dance hall, he went to bed. Six hours later he was found unconscious. Resuscitation attempts performed by an emergency physician were not successful. Table 1 lists the drugs that were were found in the apartment. In brief, gross autopsy findings were as follows: body weight 94 kg, height size 192 cm, male of athletic build, hypertrophy of the heart (weight 500 g), dilatation of the right ventricle, focal induration of the endocardium, soft and fragile liver parenchyma, cerebral edema, acute congestion of liver, spleen, and kidneys. Histologically, the myocar-

Table 1
Substances Found in the Apartment of 23-Year-Old Body Builder Who Died of Acute Cardiac Arrest

Drug	Substance	Main effects
Testex Leo 250 prolongatum i.m.	Testosterone cyclo-pentilpropionate	Androgenic and anabolic effects
Primobolan Depot 100 mg i.m.	Methenolone enantate	Androgenic and anabolic effects
Proviron 25 mg tablets	Mesterolone	Anabolic effect without inhibiting gonado-tropine secretion
Thybon 100 μg tablets	Liothyronin hydrochloride	Thyroid hormone T3
Aldactone 100 mg tablets	Spironolactone	Aldosterone antagonist used for reducing the subcutaneous water content and in order to prevent potassium defi-ciency
Clomifen 25 mg capsules	Clomifen	Increase of gonadotropin levels
Contraspasmin 0.02 mg tablets	Clenbuterol hydrochloride	ß1 (cardiac stimulation) tablets and ß2 (anabolic) effects

See text for further details. i.m., intramuscular.

dium showed enlargement and nuclear polymorphism of the LV muscle fibers. Additionally, disseminated focal necroses with loss of nuclear staining, interstitial fibrosis, and dehiscense of intercalated discs (Fig. 1A,B) were found. Capillary hyperemia, platelet aggregations and several fibrinous clots were found in the lungs, liver and kidneys (Figs. 2 and 3). Several small, cystic, blood-filled spaces were scattered throughout the liver parenchyma, partly lined by sinusoidal cells, and the hepatocytes showed nuclear fat-free vacuoles (Fig. 4A,B). A urine sample was analyzed for anabolic steroids and narcotics by an enzyme immunoassay and gas chromatography-mass spectrometry after derivatisation with trimethylsilyl. Significant concentrations of substances with effects on the central nervous system were not detected but mesterolone, methandienone (synonymous: mathandrostenolone), testosterone, nandrolone, and clenbuterol were detected in the urine sample. The testosterone: epitestosterone ratio in urine was 64:1 (IDAS, Doping Laboratory, Kreischa).

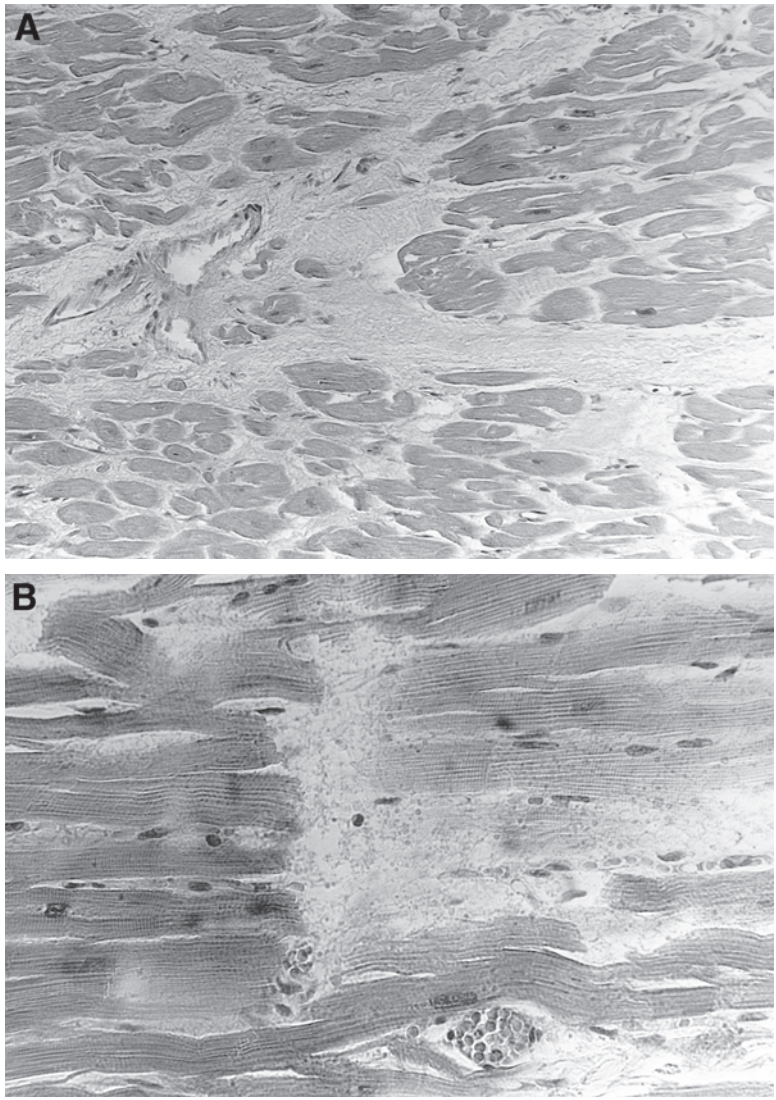

Fig. 1. Left ventricular myocardium of a 23-year-old body builder (hematoxylin & eosin). **(A)** Massive interstitial fibrosis. **(B)** Dehiscense of intercalated discs.

Because gross inspection and histology revealed no other relevant pathological alterations, a sudden CA was assumed to be the actual cause of death. For this, the following effects of the enhancing drugs detected are of particular interest: (a) anabolics cause a deep prolonged depression of the stimula-

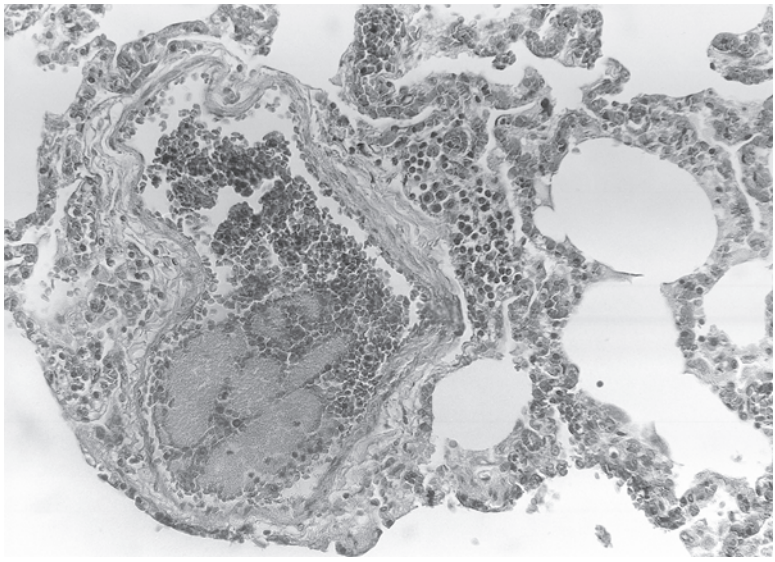

Fig. 2. Lung tissue from a 23-year-old body builder. Capillary hyperemia and platelet aggregations in a pulmonary artery (hematoxylin & eosin).

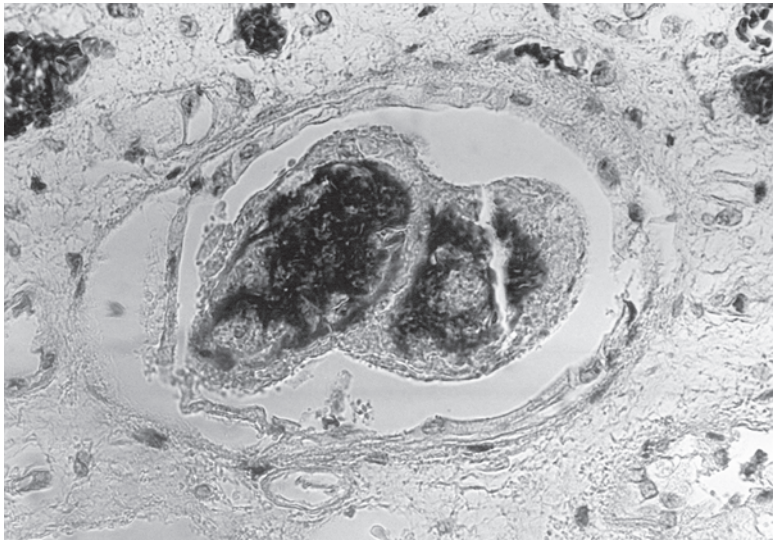

Fig. 3. Tissue section from the kidney of a 23-year-old body builder. A fibrin plug is seen in a renal blood vessel (fibrin staining according to Weigert).

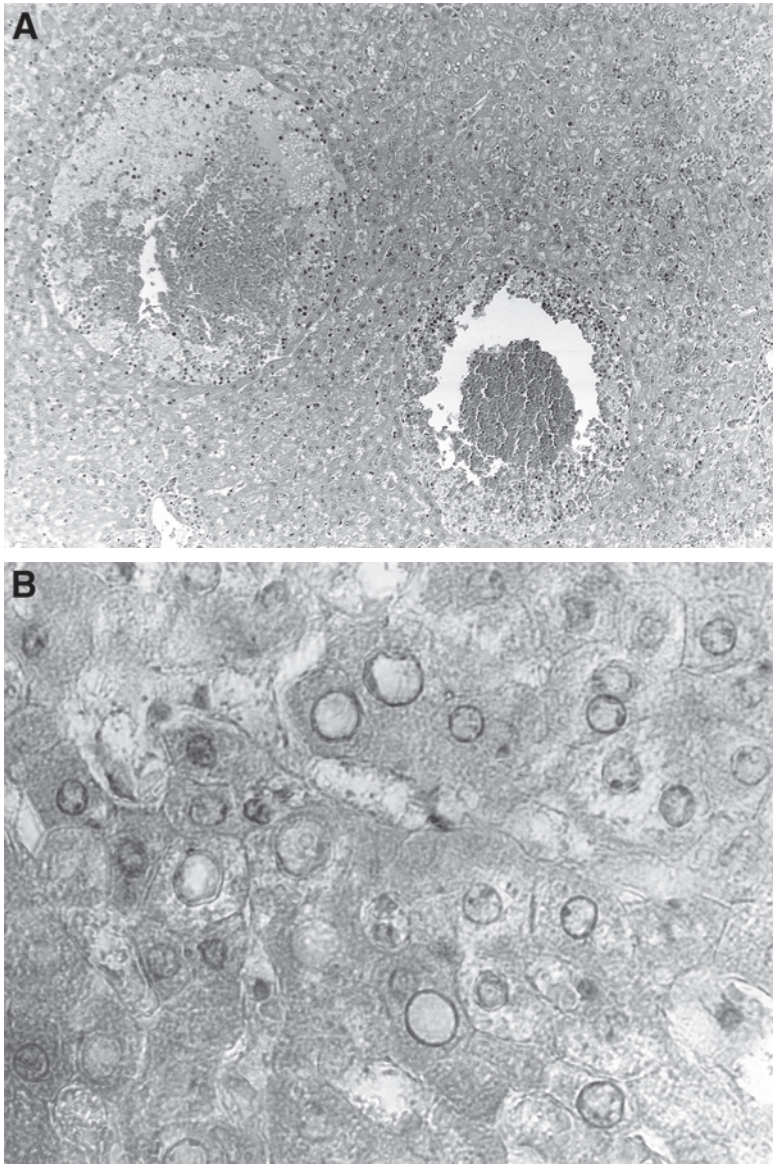

Fig. 4. Liver changes associated with anabolic-androgenic-steroid abuse by a 23-year-old body builder. **(A)** Peliosis hepatis with several small, blood-filled cystic spaces. **(B)** Fat-free vacuoles in the liver parenchyma.

tion threshold of the human heart; (b) AAS, mesterolone, and clomifen may elevate the levels of sodium, potassium, calcium, and phosphate and thereby increase the risk of atrial and ventricular fibrillation; and (c) clenbuterol accelerates the heart rate by ß1- and ß2-receptor stimulation, thus raising the cardiac oxygen demand in combination with the effects of trijodthyronine.

The various effects of these substances on cardiac function itself and on electrolyte concentrations that also influence the cardiac system were thought to explain death as a result of sudden myocardial dysfunction on the basis of AAS-associated alterations of the myocardium. This case report illustrates well the adverse effects of performance enhancing drugs on different organ systems.

7. Medicolegal Aspects of Performance-Enhancing Drug Abuse

In 1976, steroids were added to the list of doping agents banned by the International Olympic Committee. Nevertheless, steroid abuse appears to be increasing among professional athletes and amateur sportsmen of all age groups. Because steroids must be prescribed by a physician, a black market has developed as a result of the increasing popularity of body building. Many "anabolic dealers" do not seem to know whether their products are authentic or counterfeit (containing substituted ingredients) *(60)*. Another problem is the doubtful purity and sterility of these products generating a potential health risk for the consumer. Furthermore, anabolic steroids are often used in combination with other drugs such as stimulants, diuretics, or different kinds of hormones. The complex pathophysiological interactions arising from such a polytoxicomaniac drug abuse together with steroid-associated structural alterations of various organ systems can be held responsible for fatal outcome in some cases. The use of an increasing broad variety of steroid products, taken in various forms and in different temporal combinations and sequences, makes interpretation of pathological findings extremely difficult. Moreover, the identification of performance-enhancing drugs in postmortem blood can be complicated by autolytic processes. Thus, the proof of causality between the use of performance-enhancing drugs and death might turn out difficult in a given forensic autopsy case. The overwhelming majority of fatalities reported in the literature so far is attributed to myocardial pathologies such as ventricular hypertrophy, myocardial fibrosis, or acute MI. Even though steroid-associated myocardial lesions were demonstrated in animal studies, there are no steroid-specific pathological findings in humans that can be considered as pathognomonic or specific. Consequently, other possible reasons such as an underlying intoxication or infection have to be clarified by extensive histological exami-

nation and toxicological analysis, taking also the precise circumstances of death as well as the previous medical history into account.

References

1. Salke RC, Rowland TW, Burke EJ. Left ventricular size and function in body builders using anabolic steroids. Med Sci Sports Exerc 1985;17:701–704.
2. Sachtleben TR, Berg KE, Elias BA, Cheatham JP, Felix GL, Hofschire PJ. The effects of anabolic steroids on myocardial structure and cardiocascular fitness. Med Sci Sports Exerc 1993;25:1240–1245.
3. Liang MTC, Paulson DJ, Kopp SJ, Glonek T, Meneses P, Gierke LW, Schwartz FN. Effects of anabolic steroids and endurance exercise on cardiac performance. Int J Sports Med 1993;14:324–329.
4. Yesalis C, Anderson W, Buckley W, Wright J. Incidence of non-medical use of anabolic-androgenic steroids. NIDA Res Monogr 1990;102:97–112.
5. Yesalis C, Kennedy N, Kopstein A. Anabolic-androgenic steroid use in the United States. JAMA 1993;270:1217–1221.
6. Dawson RT. Drugs in sport—the role of the physician. J Endocrinol 2001;170:55–61.
7. Mußhoff F, Daldrup T, Ritsch M. Anabole Steroide auf dem deutschen Schwarzmarkt. Arch Kriminol 1997;199:153–158.
8. Yesalis C, Bahrke MS. Doping among adolescent athletes. Baillieres Best Pract Res Clin Endocrinol Metab 2000;14:25–35.
9. Graham S, Kennedy M. Recent developments in the toxicology of anabolic steroids. Drug Safety 1990;5:458–476.
10. McNutt RA, Ferenchick GS, Kirlin PC, Hamlin NJ. Acute myocardial infarction in a 22-year-old worldclass weight lifter using anabolic steroids. Am J Cardiol 1988;62:164.
11. Bowmann SJ. Anabolic steroids and infarction. Br Med J 1989;299:632.
12. Luke JL, Farb A, Virmani R, Sample RH. Sudden cardiac death during exercise in a weight lifter using anabolic androgenic steroids: pathological and toxicological findings. J Forensic Sci 1990;35:1441–1447.
13. Lynberg K. Myocardial infarction and death of a body builder after using anabolic steroids. Ugeskr Laeger 1991;153:587,588.
14. Ferenchick GS, Adelman S. Myocardial infarction associated with anabolic steroid use in a previously healthy 37-year-old weight lifter. Am Heart J 1992;124:507,508.
15. Kennedy MC. Myocardial infarction in association with misuse of anabolic steroids. Ulster Med J 1993;62:172–174.
16. Kennedy MC, Lawrence C. Anabolic steroid abuse and cardiac death. Med J Aust 1993;158:346–348.
17. Huie MJ. An acute myocardial infarction occurring in an anabolic steroid user. Med Sci Sports Exerc 1994;26:408–413.
18. Delbeke FT, Desmet N, Debackere M. The abuse of doping agents in competing body builders in Flanders (1988–1993). Int J Sports Med 1995;16:66–70.
19. DuRant RH, Escobedo LG, Heath GW. Anabolic steroid use, strength training and multiple drug use among adolescents in the United States. Pediatrics 1995;96:23–28.

20. Cembrano J, Lillo M, Val J, Mardones J. Influence of sex differences and hormones on elastin and collagen in the aorta of chickens. Circ Res 1960;8:527–529.
21. Gaynor E. Effect of sex hormones on rabbit arterial subendothelial connective tissue. Blood Vessels 1975;12:161–165.
22. Wolinsky H. Effects of androgen treatment on the male rat aorta. J Clin Invest 1972;51:2252–2555.
23. Fischer GM, Swain ML. Effect of sex hormones on blood pressure and vascular connective tissue in castrated and noncastrated male rats. Am J Physiol 1977;232:H616–H621.
24. Greenberg S, George WR, Kaclowitz PJ, Wilson WR. Androgen-induced enhancement of vascular reactivity. Can J Physiol Pharmacol 1973;52:14–22.
25. Horowitz KB, Horowitz L. Canine vascular tissues are targets for androgens, estrogens, progestins and glucocorticoids. J Clin Invest 1982;69:750–758.
26. Tischer KH, Heyny von Haussen R, Mall G, Doenecke P. Koronarthrombosen und -ektasien nach langjähriger Einnahme von anabolen Steroiden. Z Kardiol 2003;92:326–331.
27. Melchert RB, Welder AA. Cardiovascular effects of anabolic-androgenic steroids on primary myocardial cell cultures. Med Sci Sports Exerc 1995;24:206–212.
28. Behrendt H, Boffin H. Myocardial cell lesions caused by an anabolic hormone. Cell Tissue Res 1977;181:423–426.
29. Kinson MC, Lyberry R, Herbert B. Influences of anabolic androgens on cardiac growth and metabolism in the rat. Can J Physiol Pharmacol 1991;69:1698–1704.
30. Takala T, Ramo P, Kiviluoma K. Effects of training and anabolic steroids on collagen synthesis in dog heart. Eur J Appl Physiol 1991;62:1–6.
31. Appel HJ, Heller-Umfenbach B, Feraudi M, Weickert H. Ultrastructural and morphometric investigations on the effects of training and administration of anabolic steroids on the myocardium of guinea pigs. Int J Sports Med 1983;4:268–274.
32. Soares J, Duarte J. Effects of training and anabolic steroid on murine red skeletal muscle—a stereological analysis. Acta Anat (Basel) 1991;142:183–187.
33. Touchette N. Meeting highlights. "Roid Rage at FASEB." The J NIH Res 1990;2: 42–44.
34. McKillop G, Todd IC, Ballantyne D. Increased left ventricular mass in a bodybuilder using anabolic steroids. Brit J Sports Med 1986;20:151,152.
35. Madea B, Grellner W. Langzeitfolgen und Todesfälle bei Anabolikaabusus. Rechtsmedizin 1996;6:33–38.
36. Karch SB, Billingham M. Myocardial contraction bands revisited. Hum Pathol 1986;17:9–13.
37. Melchert RB, Welder AA. Cardiovascular effects on androgenic-anabolic steroids. Med Sci Sports Exerc 1995;27:1252–1262.
38. Urhausen A, Kindermann W. Sports-specific adaptation and differentiation of the athlete's heart. Sports Med 1999;28:237–244.
39. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. N Engl J Med 1991;324:295–301.

40. Dickerman RD, Schaller F, McConathy WJ. Left ventricular wall thickening does occur in elite power athletes with or without anabolic steroid use. Cardiology 1998:90:145–148.
41. Baumstark MW, Berg A, Frey I, Rokitzki L, Keul J. Analphalipoproteinemia in bodybuilders induced by anabolic steroids (abstract). Int J Sports Med 1988;9:400.
42. Ferenchick GS. Anabolic/androgenic steroid abuse and thrombosis—is there a connection? Med Hypotheses 1992;35:27–31.
43. Frankle MA, Eichberg R, Zachariah SB. Anabolic androgenic steroids and a stroke in an athlete: case report. Arch Phys Med Rehabil 1988;69:632,633.
44. Mochizuki RM, Richter KJ. Cardiomyopathy and cerebrovascular accident associated with anabolic-androgenic steroid use. Phys Sports Med 1988;16:108–114.
45. Laroche GP. Steroid anabolic drugs and arterial complications in an athlete—a case history. Angiology 1990;41:964–969.
46. Recant L, Lacy P. Fanconi's anemia and hepatic cirrhosis. Am J Med 1965;39:464–475.
47. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. Lancet 1977;2:262,263.
48. Antunes CMF, Stolley PD. Cancer induction by exogenous hormones. Cancer 1977;39:1896–1898.
49. Overly WL, Dankhoff JA, Wang BK, Singh VD. Androgens and hepatocellular carcinoma in an athlete. Ann Int Med 1984;100:158,159.
50. Goldmann B. Liver carcinoma in an athlete taking anabolic steroids. J Am Osteopath Assoc 1985;?:85, 56.
51. Creagh TM, Rubin A, Evans DJ. Hepatic tumors induced by anabolic steroids in an athlete. J Clin Pathol 1988;41:441–443.
52. Kalra TM, Mangla JC, DePapp EW. Benign hepatic tumors and oral contraceptive pills. Am J Med 1976;61:871–877.
53. Zak F. Peliosis hepatis. Am J Pathol 1959;26:1–15.
54. Burger R, Marcuse P. Peliosis hepatis: report of a case. Am J Clin Pathol 1952;22:569–573.
55. Karch SB. Anabolic steroids. In: Karch SB, ed. The Pathology of Drug Abuse. CRC Press, Boca Raton, New York, London, Tokyo, 1996, pp. 409–429.
56. Leong SS, Cazen RA, Yu GS, LeFevre L, Carson JW. Abdominal visceral peliosis associated with bacillary angiomatosis. Ultrastructural evidence of endothelial destruction by bacilli. Arch Pathol Lab Med 1992;116:866–871.
57. Paradinas FJ, Bull TB, Westaby D, Murray-Lyon IM. Hyperplasia and prolapse of hepatocytes into hepatic veins during longterm methyltestosterone therapy: possible relationships of these changes to the development of peliosis hepatis and liver tumors. Histopathology 1977;1:225–246.
58. Friedl KE. Reappraisal of the health risks associated with the use of high doses of oral and injectable androgenic steroids. NIDA Res Monogr 1990;102:142–177.
59. Phillips MJ, Oda M, Funatsu K. Evidence for microfilament involvement in norethandrolene-induced intrahepatic cholestasis. Am J Pathol 1978;93:729–744.
60. Foss G, Simpson S. Oral methyltestosterone and jaundice. Br Med J 1959;1:259–263.

61. Hausmann R, Hammer S, Betz P. Performance enhancing drugs (doping agents) and sudden death—a case report and review of the literature. Int J Legal Med 1998;111:261–264.
62. Musshoff F, Daldrup T, Ritsch M. Black market in anabolic steroids—analysis of illegally distributed products. J Forensic Sci 1997;42:1119–1125.

Forensic Differential Diagnosis

13

Subendocardial Hemorrhages

Stephan Seidl, MD

Contents

Summary

Subendocardial hemorrhages (SEH) occur after cardiac injuries and resuscitation as well as secondary to noncardiac injuries comprising head injuries, infectious diseases, intoxications, hemorrhagic diathesis, abdominal trauma, asthma, and hypovolemic shock. In particular, the common incidence of SEH in intracranial lesions led to the suggestion that the phenomenon is mediated by the autonomic nervous system via hypersecretion of catecholamines. Other modes of SEH induction are also discussed, especially a sudden hypotension followed by subendocardial myocardial cell necrosis. Furthermore, animal experiments with adult miniature swine led to the suggestion that high-impact accelerations could provoke the formation of SEH. Human experiments, however, point out that humans do not appear to have catecholamine levels (cardiac or systemic) as high as those observed in miniature swine

From: *Forensic Pathology Reviews, Vol. 2*
Edited by: M. Tsokos © Humana Press Inc., Totowa, NJ

during high-impact acceleration exposure and it is widely accepted that the lesions in miniature swine develop as a consequence of a somewhat unique form of the porcine stress syndrome. SEH are located in the upper part of the interventricular septum, the opposing papillary muscles, and adjacent trabeculae carneae of the free wall of the left ventricle. A part of the conducting system is located in the subendocardium, and the left branches of the atrioventricular bundle are localized in the region in which SEH are most commonly seen at autopsy. Therefore, the predisposition of the subendocardium to ischemia may suggest a mechanism for the explanation of ventricular arrhythmia and sudden death. Additionally, ischemic lesions of the papillary muscles of the left ventricle can cause mitral insufficiency, thus contributing to heart failure.

Key Words: Subendocardial hemorrhage; noncardiac injury; head injury; catecholamines; hypovolemic shock.

1. Introduction

Hemorrhage beneath the endocardium, predominantly found in the ventricle of the left heart, is a striking feature seen in many forensic autopsy cases *(1,2)*. These so-called subendocardial hemorrhages (SEH) can appear extremely rapidly, within a few heart beats *(1)* and occur after cardiac injuries and resuscitation as well as secondary to noncardiac injuries, head injuries, infectious diseases, intoxications (e.g., heroin, cocaine, or heavy-metal poisoning like arsenic), hemorrhagic diathesis, abdominal trauma, asthma, and hypovolemic shock *(3–7)*. Therefore, they were sometimes termed "shock lesions," or, named after Harold L. Sheehan who studied SEH in the 1930s in cases of abortion and acute hemorrhage associated with pregnancy, as "Sheehan's hemorrhages" *(1,2,8–11)*.

In particular, the common incidence of SEH in intracranial lesions like head injuries, cerebral edema, surgical craniotomy, large cranial tumors, stroke, and sudden intracranial decompression led to the suggestion that the phenomenon of SEH is mediated by the autonomic nervous system via hypersecretion of catecholamines *(1,12–21)*. To support this theory, SEH is known to be part of Virchow's triad of pulmonary edema, gastric erosions, and subendocardial hemorrhage seen in head injuries and cases of raised intracranial pressure *(1)*.

In addition to the theory that SEH are mediated by hypersecretion of catecholamines, some authors prefer other modes of SEH induction, especially a sudden hypotension followed by subendocardial myocardial cell necrosis *(1,22)*. A part of the conducting system is located in the subendocardium and the left branches of the atrioventricular (AV) bundle are localized in the region

in which SEH are most commonly seen at autopsy *(2)*. Hypoxia, hypotension, tachycardia, anemia, inotropic agents, and other noxious factors, particularly ventricular fibrillation in the presence of an inadequate perfusion, may interact to produce subendocardial ischemia and necrosis despite the fact that the coronary arteries are not occluded *(2,23)*. Therefore, Guy and Eliot termed the subendocardium of the left ventricle the "weakest link in the chain of survival" and a "physiologic enigma" *(23)*.

Harruff found that the time interval between injury and death did not appear to be a factor important for the occurrence of SEH *(4)*. As SEH were believed earlier to represent an agonal phenomenon without any particular reference to the cause of death, the relevance of this special form of hemorrhage was discussed controversially for a long time *(2)*. Sevitt, however, discussed a potential functional importance of SEH in their anatomical relationship to the distribution of the Purkinje fibers, although he believed that SEH occur shortly before death rather than soon after the trauma *(15)*. Sheehan argued that even minor lesions may have an influence on cardiac function and may be involved in the mechanism of death *(2,10)*.

2. The Localization and Appearance of SEH

SEH are located in the upper part of the interventricular septum, in the opposing papillary muscles (Figs. 1 and 2A,B), and in the adjacent trabeculae carneae of the free wall of the ventricle of the left heart *(1,2,4,22,24)*. SEH are flame-shaped and confluent, not petechial, and tend to occur in one continuous sheet rather than patchy *(1)*. Severe bleedings may lead to a separation of the subendocardium from the ventricular wall and raise the endocardium into blood-filled blisters *(1,2)*. In cases of intracranial lesions, Smith and Tomlinson found that SEH were located directly beneath the endocardium and between the inner layers of myocardial fibers *(6)*. This finding was supported by Burton and MacKenzie, who saw SEH localized in the immediate subendocardial region, frequently surrounding Purkinje's fibers; in severe cases, hemorrhages penetrated several millimeters into the heart muscle and sometimes penetrated Purkinje's fibers *(25)*. Keil and coworkers, however, noticed that the erythrocytes were primarily located between the myocardial fibers and most seldom reached the endocardium *(24)*. As they found no cellular reaction in the surrounding of the hemorrhage, the authors concluded that SEH were signs of agonal-vital events.

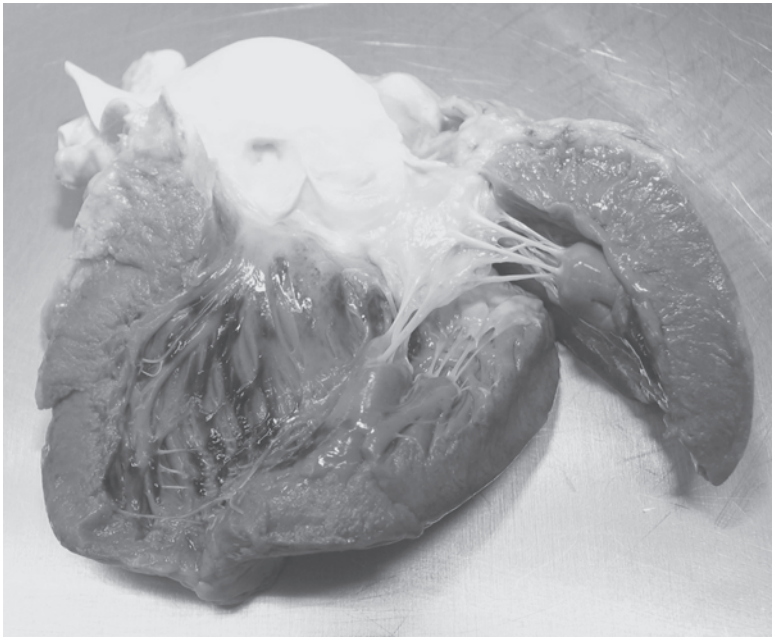

Fig. 1. Pronounced subendocardial hemorrhages in the left ventricle of the heart in the case of a 23-year-old man who died of central failure as a result of blunt head trauma. (Courtesy of Dr. Michael Tsokos, Hamburg, Germany.)

Rajs found the site of the hemorrhages usually at the level of the junction of the Purkinje fibers and "typical" heart muscle; the Purkinje fibers were forced apart *(2)*. If the affected individual had survived the primary lesion for a few hours, the thebesian veins (Venae cordis minimae) and the lymph vessels adjacent to the hemorrhages in the subendocardium were markedly distended. Additionally, Rajs found a wide separation of myocardial fibers in these fulminant cases, indicating interstitial edema *(2)*. When the patient survived more than about 6 hours, however, minute necrosis of myofibers, as well as hemorrhages, and leukocytic infiltration were also observed in the subendocardium and around minor branches of the coronary arteries and focally in the interstice in other parts of the myocardium (Fig. 2C,D). The lesions were most pronounced in the subendocardial regions, within the apexes of the papillary muscles of the ventricle of the left heart, and in some cases in the upper part of the intraventricular septum, close to the aortic annulus fibrosus and bifurcation of the AV bundle *(2)*.

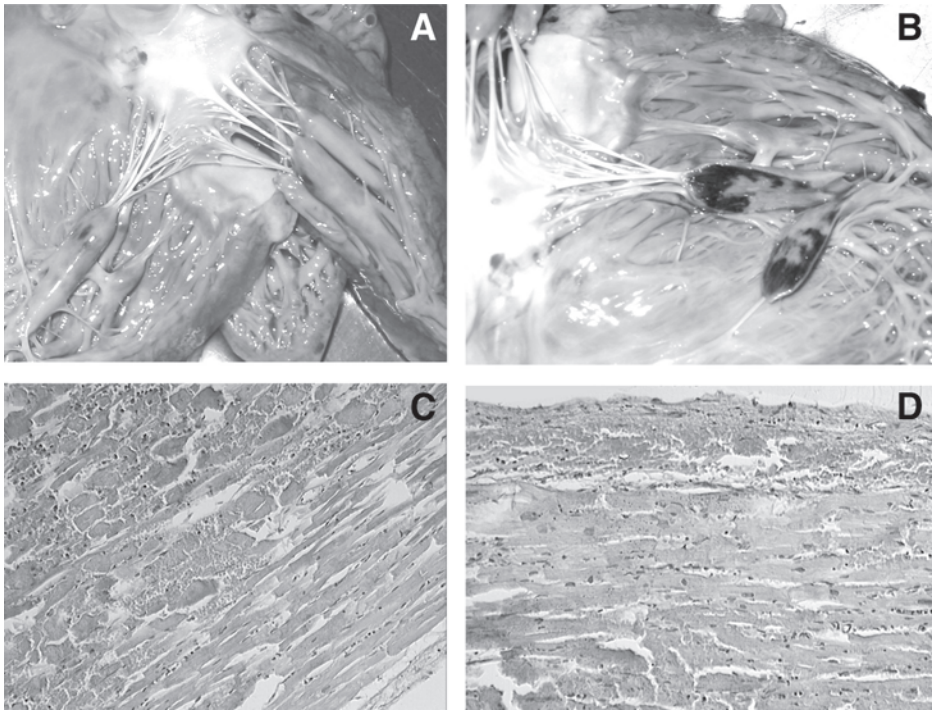

Fig. 2. Fatal heroin intoxication of a 22-year-old woman with a survival time of 20 hours following intravenous heroin injection. The actual cause of death was a severe cerebral edema. **(A)** Weak subendocardial hemorrhages (SEH) in the efflux path of the left heart ventricle and in the upper parts of the papillary muscles. **(B)** Massive hemorrhages on the cross-section of a papillary muscle. **(C)** Histology. High-power view of left ventricular subendocardium. The hemorrhages are located between the myocardial fibers and do not reach the endocardium. Necrosis of myofibers and leukocytic infiltration (hematoxylin & eosin, original magnification x40). **(D)** Histology. High-power view of papillary musculature. The SEH are located both directly beneath the endocardium and between the inner layers of necrotic myocardial fibers (hematoxylin & eosin, original magnification x40).

3. Causative Factors of SEH: An Overview

Already in the first decade of the last century Eppinger and Rothberger, as well as Berblinger, induced SEH by faradic excitation of vagal nerves in animal experiments and attributed them to cardiac arrhythmias resulting from elevated vagotonia *(22,26,27)*. In 1964, Mazzella and colleagues provoked SEH by carotid occlusion and section of the vagal nerves *(28)*. In the same

year, Gauer and Henry reported about SEH in hypotension treated with noradrenalin *(29)*. Some years later it was shown once more both clinically and experimentally that catecholamine administration causes electrocardiographic changes and cardiac degeneration *(30,31)*. Bove and coworkers demonstrated in animal experiments that the administration of noradrenalin alone led to moderate to severe SEH, although the administration of phentolamine simultaneously with noradrenalin afforded a protective effect on the myocardium *(32)*. Vormittag and Keiler saw beneficial effects of β-receptor blockage on the course of hemorrhagic shock in animal experiments with dogs and explained this phenomenon by the prevention of the catecholamine induced tachycardia and the thereby increased coronary perfusion and decreased myocardial oxygen consumption *(33)*. Cruickshank et al. showed that β-receptor blockage reduced tissue injury and supraventricular tachycardia induced by severe head injury in humans *(34)*. Additionally, epidermal growth factor (EGF) can prevent catecholamine-induced functional disturbances and heart injuries including SEH by activation of the EGF receptor ErbB1 *(35)*.

According to another explanation for the origin of SEH, the existing blood pressure in the coronary system is unsupported across the endocardium by an equal pressure within the ventricular lumen—if the intraventricular pressure drops precipitously, rupture of the superficial vessels occurs *(1)*. Knight has alluded to flaws in this theory, one being the common incidence of SEH in intracranial lesions *(1)*. A mechanical damage to the left ventricular (LV) endocardium as a result of the vigorous contractions of the relatively empty left ventricle also seems to be a less likely possible causative factor for SEH *(2,36)*.

Another formation theory for SEH is a sudden hypotension with its resultant decrease in perfusion pressure followed by necrosis in the subendocardium and papillary muscles, which are the most vulnerable parts of the heart to ischemia *(2,22,37–42)*. Hemorrhages and myocytic necrosis resulting from hemorrhagic shock are similar lesions as they both occur after excessive endogenous secretion or exogenous administration of catecholamines *(2)*. Accordingly, the animal experiments performed by Sherman and Grayson could argue for a combination of both theories, the hypersecretion of catecholamines and the pressure gradient across the endocardium *(43)*. The authors observed in experiments with dogs that adrenaline infusions raised systolic and diastolic levels of peripheral coronary pressure both when the systemic blood pressure was allowed to rise and in experiments in which rise in systemic arterial pressure was prevented by hemorrhage. This increase of coronary pressure is mediated by catecholamines via contraction of the coronary vascular walls and accompanied by a local increase in the oxygen consumption of the tissue by an oxidation promoting effect *(2,44)*.

4. SEH Secondary to Noncardiac Injuries and Intoxications

4.1. Intracranial Lesions as a Result of Natural and Traumatic Causes

Traumatic head injuries, as well as intracranial bleeding of nontraumatic origin like subarachnoid hemorrhage from aneurysm rupture, hypertensive cerebral hemorrhage, and stroke, produce cardiac arrhythmias, heart block, low cardiac output, and myocardial necrosis *(4,22,30,45)*. Furthermore, electrocardiographic changes similar to subendocardial infarcts and elevations of the enzyme creatine kinase MB have been reported after head injury *(4,14,17,20,21,46,47)*. As a morphological correlate, lesions that include gross SEH and a variety of microscopical myocardial lesions were found in hearts of patients with head injuries and other internal injuries leading to shock *(4,13–16,48)*. In a rat acute stroke model, Cechetto et al. showed that the occlusion of the middle cerebral artery led to SEH, ischemic damage, or subendocardial congestion, although the mean blood pressure and pulse pressure of the animals did not change during the experiment *(19)*. However, Cechetto et al. recorded a significant increase of the levels of both norepinephrine and epinephrine.

4.2. Intoxications and Chemical Injuries to the Heart

Sympathetic hyperactivity and shock are likely to be the same mechanisms that operate in the cardiac toxicity of heavy-metal poisoning, cocaine or acetaminophen overdose fatalities, and other intoxications *(4,49,50)*. The induction of SEH and multifocal myonecrosis in the left heart ventricle by the β-receptor agonist fenoterol was shown in animal experiments by Pack et al. *(51)*.

In cases of acute arsenic poisoning, SEH manifesting in the LV wall and reddening of the gastric mucosa are the only lesions commonly seen at autopsy *(1)*. Knight points out that the most severe SEH he had ever seen were present in a suicidal overdose of arsenious oxide, in which the hemorrhages appeared as raised blood-filled blisters under the endocardium *(1)*. To date, however, it is not clear whether arsenic poisoning produces SEH by a direct mechanism or secondary to shock *(1,4)*.

Than et al. portrayed three cases of fatal envenoming by viper bites *(52)*. The clinical features included local swelling, spontaneous systemic bleeding, defibrination, shock, hypoglycemia, coma, and oliguria. An intractable cardiac arrhythmia was attributed to subendocardial and myocardial hemorrhages.

Bose and colleagues reported 300 cases of yellow oleander seeds ingestion *(53)*. In electrocardiogram, 138 cases (46%) revealed varying types of

arrhythmias, including sinus bradycardia in 68 cases (49.3%). Ischemic changes were present in 118 cases (39.3%). In all 14 fatal cases, subendocardial and perivascular hemorrhage with focal myocardial edema was present.

4.3. Infections

After inoculation with rat-adapted influenza A virus, 50% of rat pubs showed SEH presenting as small foci of red blood cells beneath the ventricular endocardium *(54)*. If the animals were dually challenged with an additional sublethal dose of endotoxin, the rate of SEH was 100%. Similar results were found when an endotoxin shock was induced with the bacterium *Escherichia coli* (B5, 4 mg/kg) in a canine model *(40)*. Gross examination of the hearts demonstrated diffuse to patchy SEH. Histological examination revealed diffuse intramyocardial hemorrhage that was more pronounced in the subendocardium than in the midmyocardium.

4.4. High-Impact Trauma and Acceleration

According to the results of earlier animal studies, high-impact accelerations were for a long time thought to provoke SEH (*25,55,56*). Following single exposures of +8 or 9 Gz (vertical acceleration) for 45 to 90 seconds, Burton and MacKenzie saw SEH of varying severity in adult miniature swine, involving both the wall and papillary muscles *(55)*. The severity of SEH was directly related to level and duration of G exposure, heart rate, and catecholamine activity *(25)*. Gillingham and Crump exposed a group of fighter aircraft pilots to high-G stress (three 40-second runs at 8 G and two 40-second runs at 10 G, all in one day) *(57)*. As the obtained noninvasive clinical cardiological data revealed just a preejection period shortened at 48 hours poststress and a rise of serum total creatine phosphokinase and lactic dehydrogenase, they concluded that the results of Burton and MacKenzie were not reproducible in humans. The discrepancy cleared up by experiments of Burns et al., who determined plasma levels of catecholamines and cortisol during +Gz exposures in miniature swine *(58)*. The authors recorded a clear increase of norepinephrine, epinephrine, and cortisol levels during +Gz exposure to the emotional stress of handling, restraint, and the unfamiliar environment of the centrifuge, and +Gz. Laughlin confirmed these results and concluded that the lesions in miniature swine appear to develop as a consequence of a somewhat unique form of the porcine stress syndrome *(59)*. For humans, however, +Gz exposure seems to be not as psychologically stressful and humans appear not to have catecholamine levels (cardiac or systemic) as high as those observed in miniature swine during +Gz exposure. Thus, Laughlin argues that the pathological findings

observed in miniature swine are not caused by an acceleration phenomenon *(59)*.

Hellerich and Pollak portrayed an airplane crash and described the morphological features of high-speed impact trauma in detail *(60)*. As a result of the immediate circulatory arrest in the victims, the authors attributed subepicardial and subendocardial hemorrhages, petechiae of the conjunctivae and of the serous membranes as well as petechial hemorrhages seen in the mucous membranes of larynx and trachea to mere local tissue bruising at the moment of impact.

Knight, however, pointed out that SEH can appear extremely rapidly, within a few heart beats *(1)*. He portrayed a case of well-marked lesions in a heart that was avulsed from its base during the crash of a military aircraft, obviously causing virtually instantaneous death. Tsokos and colleagues observed the presence of SEH in five out of eight suicidal cases of railway-related complete decapitations *(12)*. Because there were no other pathological autopsy findings attributable to a traumatic origin seen in the heart in those cases, the authors regarded SEH as a vital reaction but also advised caution with respect to the hypothesis of a hypersecretion of catecholamines as responsible for the occurrence of SEH in cases of complete decapitation.

5. SEH Secondary to Cardiac Injuries and Resuscitation Procedures

5.1. Heart Trauma

Zhu and colleagues portrayed a case of sudden death as a result of a cardiac conducting system injury from a blunt chest impact. A 20-year-old male who was kicked in the precordial region lost consciousness and was confirmed dead on arrival at a hospital emergency care unit. SEH in the region of the AV node and a contusion extending from the posterior wall of the left ventricle to the upper ventricular septum were observed at autopsy. Histological examination revealed injury of the AV node and the His bundle. Although the cardiac injury including contusion of the myocardium itself was not so extensive, it was considered that arrhythmia was induced by the cardiac conducting system failure, which was considered to be the actual cause of death *(61)*.

Plack et al. reported the observation of SEH in the outflow tract of dog hearts after aortic valve double balloon dilatation (*62*). Histological examination revealed definite injury to the myocytes of the left bundle branch, sometimes leading to electrocardiographic conduction disturbances. Subendocardial

valvular hemorrhages of the right heart ventricle were reported by Ford and Manley in patients with and without indwelling right heart catheters *(63)*.

5.2. Resuscitation Procedures

Cardiovascular resuscitation produces cardiac lesions and SEH. The administration of catecholamines during resuscitation significantly increases the frequency of myocardial lesions when compared with defibrillation alone *(4,64)*.

Matsuda et al. made resuscitation experiments in rabbits with countershock energies between 12 and 240 W-seconds discharge *(65)*. Epicardial alterations were found in electrode-shaped areas that confined to the superficial epicardium in all rabbits. The heart from rabbits that died within a few minutes after countershock showed epicardial alterations in the right and left ventricle and subendocardial alterations with focal hemorrhage were evident in the left ventricle. Subendocardial necrosis and interstitial edema were also found in the left ventricle 72 hours after countershock. These myocardial damages appeared in the transthoracic pathway between the electrodes.

6. Conclusions

Most investigators agree that SEH and related cardiac lesions are consequences of the massive sympathetic neural discharge and catecholamine secretion that occurs in shock and in certain types of head injury *(4,14,30,31,34)*. The excessive sympathetic activity produces or aggravates ischemia of the sensitive subendocardial zone, resulting in conduction disturbances as well as myocardial necrosis and hemorrhage in more severe cases *(4,14,17)*. The susceptibility of the subendocardium to ischemia may suggest a mechanism for the explanation of ventricular arrhythmia and sudden death. Additionally, ischemic lesions within the papillary muscles of the left ventricle can cause dysfunction resulting in mitral regurgitation thus contributing to heart failure *(2,23,66,67)*. Therefore, it is conceivable that these secondary cardiac lesions are part of the mechanisms of death in head injury. Clinical experience has indicated that a high proportion of deaths as a result of early failure in cardiac transplant recipients may in fact be related to the damaging effects of brain death in the donor *(4,14)*. Harruf comprehensibly supposes that there is a group of trauma victims who are unsuitable as heart donors for transplantation purposes because of the adverse effects of excessive catecholamine secretion precipitated by shock and certain types of head injury *(4)*.

The occurrence of SEH in cases of rapid circulatory arrest without any heart trauma, especially in cases with complete decapitation, prompted the

following questions: How does SEH develop? Should SEH be regarded as a vital reaction *(12)*? In suicidal, as well as accidental fatalities, an excessive endogenous secretion of catecholamines has to be assumed. Summarizing the theories mentioned here, one is tempted to speculate that the resulting raise of coronary pressure coincides with an abrupt drop of intraventricular pressure at the moment of disruption of major blood vessels. Thus, in such special cases SEH might be caused by the resulting pressure gradient across the endocardium and therefore could be looked on as a vital reaction.

References

1. Knight B. Forensic Pathology. Arnoldt, London, Sidney, Auckland, 1996.
2. Rajs J. Left ventricular subendocardial haemorrhages. A study of their morphology, pathogenesis and prognosis. Forensic Sci 1977;10:80–103.
3. Caesar R. Subendokardiale Blutungen. In: Remmele W, ed. Pathologie, Vol 1. Springer, Berlin, Heidelberg, New York, 1999, p. 243.
4. Harruff RC. Subendocardial hemorrhages in forensic pathology autopsies. Am J Forensic Med Pathol 1993;14:284–288.
5. Yoshida K, Ogura Y, Wakasugi C. Myocardial lesions induced after trauma and treatment. Forensic Sci Int 1992;54:181–189.
6. Smith RP, Tomlinson BE. Subendocardial haemorrhages associated with intracranial lesions. J Pathol Bacteriol 1954;68:327–334.
7. Matsui T, Baba M. Death from asthma in children. Acta Paediatr Jpn 1990;32:205–208.
8. Sheehan HL, Murdoch R. Postpartum necrosis of the anterior pituitary: pathological and clinical aspects. J Obstet Gynaecol Br Emp 1938;45:456–488.
9. Sheehan HL, Sutherland AM. The pathology of heart disease in pregnancy. J Obstet Gynaecol Br Emp 1940;47:597–668.
10. Sheehan HL. The pathology of obstetric shock. J Obstet Gynaecol Br Emp 1939;46:218–231.
11. Sheehan HL. Subendocardial hemorrhages in shock. Lancet 1940;1:831,832.
12. Tsokos M, Türk EE, Uchigasaki S, Püschel K. Pathologic features of suicidal complete decapitations. Forensic Sci Int 2004;139:95–102.
13. Weintraub BM, McHenry LC. Cardiac anomalies in subarachnoid hemorrhage: a résumé. Stroke 1974;5:384–392.
14. McLeod AA, Neil-Dwyer G, Meyer CHA, Richardson PL, Cruickshank J, Bartlett J. Cardiac sequelae of acute head injury. Br Heart J 1982;47:221–226.
15. Sevitt S. Reflections on some problems in the pathology of trauma. J Trauma 1970;10:962–973.
16. McGovern VJ. Hypovolemic shock with particular reference to the myocardial and pulmonary lesions. Pathology 1980;12:63–72.
17. Koskelo P, Punsar S, Sipilae W. Subendocardial haemorrhage and E.C.G. changes in intracranial bleeding. Br Med J 1964;5396:1479,1480.
18. Leslie JB. Incidence and aetiology of perioperative hypertension. Acta Anaesthesiol Scand Suppl 1993;99:5–9.

19. Cechetto DF, Wilson JX, Smith KE, Wolski D, Silver MD, Hachinski VC. Autonomic and myocardial changes in middle cerebral artery occlusion: stroke models in the rat. Brain Res 1989;502:296–305.
20. Vögelin HP, Jutzi H, Gertsch M. EKG- und kardiale Veränderungen bei akutem Hirnschaden. Schweiz Med Wochenschr 1989;119:461–466.
21. Marion DW, Segal R, Thompson ME. Subarachnoid hemorrhage and the heart. Neurosurgery 1986;18:101–106.
22. Varga T, Szabo A. Herzveränderungen bei akutem intrakraniellen Druckanstieg. Z Rechtsmed 1978;80:311–318.
23. Guy C, Eliot RS. The subendocardium of the left ventricle: a physiologic enigma. Chest 1970;58:555,556.
24. Keil W, Rothämel T, Tröger HD. Subendokardiale Hämorrhagien aus forensisch-medizinischer Sicht. Beitr Gerichtl Med 1991;49:45–53.
25. Burton RR, MacKenzie WF. Cardiac pathology associated with high sustained +Gz: I. Subendocardial hemorrhage. Aviat Space Environ Med 1976;47:711–717.
26. Fassbender H, Wengler G. Zur Aetiologie der subendokardialen Blutung. Virchows Arch 1952;321:138–141.
27. Eppinger H, Rothberger J. Über die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems. Z klin Med 1910;70:1–20.
28. Mazzella H, Acosta CB, Guemberena L. Subendocardial hemorrhages provoked by carotid occlusion and section of the vagus nerves. Acta Physiol Lat Am 1964;14:202–206.
29. Gauer OH, Henry JP. Subendocardial hemorrhage in hypotension treated with norepinephrine. Am Heart J 1964;67:713,714.
30. Reichenbach DD, Benditt EP. Catecholamines and cardiomyopathy: the pathogenesis and potential importance of myofibrillar degeneration. Hum Pathol 1970;1:125–150.
31. Neil-Dwyer G, Walter P, Cruickshank JM, Doshi B, O'Gorman P. Effect of propranolol and phentolamine on myocardial necrosis after subarachnoid hemorrhage. Br Med J 1978;2:990–992.
32. Bove EL, Argenta LC, Cimmino VM, Brown JW, Nishiyama RH, Kirsh MM. The morphologic effects of simultaneous infusion of levarterenol and phentolamine on the canine myocardium. J Thorac Cardiovasc Surg 1975;70:701–706.
33. Vormittag E, Keiler A. Die Wirkung von Oxprenolol auf die Herzfunktion im hypovolämischen Schock des Hundes. Arzneimittelforschung 1979;29:1534–1538.
34. Cruickshank J, Neil-Dwyer G, Degaute JP, et al. Reduction of stress/catecholamine-induced cardiac necrosis by ß1-selective blockade. Lancet 1987;2:585–589.
35. Pareja M, Sanchez O, Lorita J, Soley M, Ramirez I. Activated epidermal growth factor receptor (ErbB1) protects the heart against stress-induced injury in mice. Am J Physiol Regul Integr Comp Physiol 2003;285:R455–R462.
36. Chiu CJ, Mersereau WA, Scott HJ. Subendocardial hemorrhagic necrosis. The role of direct mechanical trauma on the endocardium. J Thorac Cardiovasc Surg 1972;64:66–75.
37. Balazs T. Cardiotoxicity of adrenergic bronchodilator and vasodilating antihypertensive drugs. In: Balazs T, ed. Cardiac Toxicology. CRC Press, Boca Raton, FL, 1981, pp. 61–72.

38. Mesfin GM, Higgins MJ, Robinson FG, Zhong WZ. Relationship between serum concentrations, hemodynamic effects, and cardiovascular lesions in dogs treated with minoxidil. Toxicol Appl Pharmacol 1996;140:337–344.
39. Martin AM, Hackel DB, Entman ML, Capp MP, Spach MS. Mechanisms in the development of myocardial lesions in hemorrhagic shock. Ann NY Acad Sci 1969;156:79–90.
40. Kleinman WM, Krause SM, Hess ML. Differential subendocardial perfusion and injury during the course of gram-negative endotoxemia. Adv Shock Res 1980;4:139–152.
41. Archie JP Jr., Mertz WR. Myocardial oxygen delivery after experimental hemorrhagic shock. Ann Surg 1978;187:205–210.
42. Hackel DB, Wagner GS. Acute circumferential subendocardial infarction. Clin Cardiol 1992;15:373–376.
43. Sherman IA, Grayson J. Function of the coronary arterial collateral network in healthy myocardium: studies of peripheral coronary pressure in the dog. Can J Physiol Pharmacol 1980;58:134–140.
44. Lorenzen I. Vascular connective-tissue changes induced by catecholamines and thyroid hormone. In: Asboe-Hansen G, ed. Hormones and Connective Tissue. Munksgaard, Copenhagen, 1966, p. 136.
45. Hernandez-Meilan O, Hernandez-Meilan M, Machado-Curbelo C. Capablanca's stroke: an early case of neurogenic heart disease. Cuban-world-champion of chess 1921–1927. J Hist Neurosci 1998;7:137–140.
46. Kaste M, Hernesniemi J, Somer H, Hillbom M, Konttinen A. Creatine kinase isoenzymes in acute brain injury. J Neurosurg 1981;55:511–515.
47. Kaste M, Somer H, Konttinen A. Heart type creatine kinase isoenzyme (CK MB) in acute cerebral disorders. Br Heart J 1978;40:802–805.
48. Fireman Z, Yust I, Zahavi J, Kahn Y, Abramov LA. Subendocardial infarction and thrombocytopenia. Postgrad Med J 1979;55:36–38.
49. Karch SB, Billingham ME. The pathology and etiology of cocaine-induced heart disease. Arch Pathol Lab Med 1988;112:225–230.
50. Price LM, Poklis A, Johnson DE. Fatal acetaminophen poisoning with evidence of subendocardial necrosis of the heart. J Forensic Sci 1991;36:930–935.
51. Pack RJ, Alley MR, Dallimore JA, Lapwood KR, Burgess C, Crane J. The myocardial effects of fenoterol, isoprenaline and salbutamol in normoxic and hypoxic sheep. Int J Exp Pathol 1994;75:357–362.
52. Than T, Francis N, Tin Nu S, et al. Contribution of focal haemorrhage and microvascular fibrin deposition to fatal envenoming by Russell's viper (Vipera russelli siamensis) in Burma. Acta Trop 1989;46:23–38.
53. Bose TK, Basu RK, Biswas B, De JN, Majumdar BC, Datta S. Cardiovascular effects of yellow oleander ingestion. J Indian Med Assoc 1999;97:407–410.
54. Blood-Siegfried J, Nyska A, Lieder H, et al. Synergistic effect of influenza a virus on endotoxin-induced mortality in rat pups: a potential model for sudden infant death syndrome. Pediatr Res 2002;52:481–490.
55. Burton RR, MacKenzie WF. Heart pathology associated with exposure to high sustained +Gz. Aviat Space Environ Med 1975;46:1251–1253.

56. Erickson HH, Sandler H, Stone HL. Cardivascular function during sustained +Gz stress. Aviat Space Environ Med 1976;47:750–758.
57. Gillingham KK, Crump PP. Changes in clinical cardiologic measurements associated with high +Gz stress. Aviat Space Environ Med 1976;47:726–733.
58. Burns JW, Laughlin MH, Witt WM, Young JT, Ellis JP Jr. Pathophysiologic effects of acceleration stress in the miniature swine. Aviat Space Environ Med 1983;54:881–893.
59. Laughlin MH. An analysis of the risk of human cardiac damage during +Gz stress: a review. Aviat Space Environ Med 1982;53:423–431.
60. Hellerich U, Pollak S. Airplane crash. Traumatologic findings in cases of extreme body disintegration. Am J Forensic Med Pathol 1995;16:320–324.
61. Zhu BL, Fujita MQ, Quan L, et al. A sudden death due to cardiac conduction system injury from a blunt chest impact. Leg Med (Tokyo) 1999;1:266–269.
62. Plack RH, Hutchins GM, Brinker JA. Conduction system injury after aortic valve dilation in the dog single- versus double-balloon catheters. Angiology 1990;41:929–935.
63. Ford SE, Manley PN. Indwelling cardiac catheters. An autopsy study of associated endocardial lesions. Arch Pathol Lab Med 1982;106:314–317.
64. Karch SB. Resuscitation-induced myocardial necrosis: catecholamines and defibrillation. Am J Forensic Med Pathol 1987;8:3–8.
65. Matsuda H, Seo Y, Takahama K. A medico-legal approach to the myocardial changes caused by transthoracic direct current countershock. Nippon Hoigaku Zasshi 1997;51:11–17.
66. Markiewicz W, Amikam S, Roguin N, Riss E. (1975) Changing haemodynamics in patient with papillary muscle dysfunction. Br Heart J 1975;37:445–448.
67. Gould L, Reddy CVR, Vecchiotti HJ, Gomprecht RF. Observations on papillary muscle dysfunction. Am Heart J 1974;87:674,675.

Index

D

E

F

G

H

I

K

L

M

N

O

P

R

S

T

U

V

W

Y

About the Editor

Dr. Michael Tsokos is a lecturer of forensic pathology and legal medicine at the University of Hamburg, Germany, and the Police Academy of the City of Hamburg, Germany. He is the primary or senior author of more than 100 scientific publications in international peer-reviewed journals and the editor of a number of books dealing with topics of forensic pathology. In 1998 and 1999, he worked for a time with the exhumation and identification of mass grave victims in Bosnia-Herzegovina and Kosovo under the mandate of the UN International Criminal Tribunal for the former Yugoslavia.

In 2001, Dr. Tsokos was honored with the national scientific award of the German Society of Legal Medicine for his research on micromorphological and molecularbiological correlates of sepsis-induced lung injury in human autopsy specimens.

He is a member of the International Academy of Legal Medicine and the German Identification Unit of the Federal Criminal Agency of Germany. Dr. Tsokos is assistant to the editor-in-chief of *Rechtsmedizin* (the official publication of the German Society of Legal Medicine) and a member of the Editorial Board of *Legal Medicine* and *Current Immunology Reviews.*