普通高等教育"十一五"国家级规划教材　卫生部"十一五"规划教材

全国高等学校双语教材

毒理学基础

ESSENTIALS OF TOXICOLOGY

主编　黄吉武

Chief Editor　Huang Jiwu

人民卫生出版社

PEOPLE'S MEDICAL PUBLISHING HOUSE

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PREEACE

前　言

采用双语（英语及汉语）进行专业课教学，是学生创新能力培养、全面素质教育的一个重要内容，也是我国教育与国际接轨，参与国际竞争，贯彻“教育要面向现代化，面向世界，面向未来”教育方针的一个主要途径。随着现代人类事物的全球化趋势，我国对外开放进程的加速，特别是近年来各个层次基础英语教学的显著进步，为双语教学提供了一定的前提条件。然而推广双语教学对广大师生来说，依然是一个巨大的挑战。当前开展英汉双语教学面临的最大困难，仍莫过于英语水准的欠缺，也只有突破这一瓶颈，才能保证双语教学的效果。为了适应面向英语程度一般的学生进行双语教学的需要，我们进行了毒理学专业课与专业英语课相结合教学模式的探讨。希望通过有限学时的教学，使学生一方面掌握毒理学的基础理论与基本知识，另一方面获得专业英语实际运用的技能。

然而，双语教学依靠适合学生水平和教学要求的教材，其关键在于内容适当、语言适宜、难度适中。我们一直认为使用原版教材是最终的理想选择，但是理想的并不一定是现实可行的，对于多数学校多数师生来说，原版教材内容往往过多，语言艰深，与当前学生和教师的实际英语水平不符合，阅读和掌握困难较大。我们希望将来某一天，国内教学和世界多数先进国家一样，也能普遍用上英语原版教材。武断地说，或许这需要八年十年时间的过渡。而从实际角度考虑，编写英汉双语教材，在当前不失为一个较好的补充过渡措施。2002 年，通过人民卫生出版社国际出版中心购买版权，从美国麦格劳 - 希尔（McGraw-Hill）公司引进了由克莱埃森（Klaassen CD）主编的优秀图书《卡萨瑞特 • 道尔 毒理学：毒物的基础科学（英文版）》（第 6 版）。同时，有幸得到全国 30 多位专家教授的协助和支持将此书翻译成汉语，于 2005 年出版（中文版，人民卫生出版社）。2003 年该公司还出版了本书的缩写本，缩写本精华依旧，但篇幅压缩，利于对全书实质内容的领会掌握。实际上，早在 1999 年本书第 5 版就曾出版过配套的袖珍手册。对此我们都进行了认真的研读，以了解当前毒理学理论的主流观念，熟悉毒理学英语文献的词汇体系、语言特点和表达规律。此前，通过编写《英汉毒理学词汇》（科学出版社，2002 年），在毒理学专业名词的规范方面也作了一些努力。这些都为双语教材的编写作了铺垫。在此基础上，我们联合国内 10 所高等院校的教授，并邀请疾病预防控制中心有实际工作经验的专家参加，主要参照缩写本的《卡萨瑞特 • 道尔 毒理学基础》（Casarett & Doull’s Essentials of Toxicology），此外，还参考了其他多部英语原版教材，完成了本书的编写。

编写中素材主要取自英文原版专著或教科书，针对情况作了不同的处理，例如，对于重要的定义、原理和法则等内容尽可能保持原作语言风格特色，力求原汁原味；做到语言平易规范、术语准确无误；除了语言表达方式忠于原文外，在内容的编写顺序及阐明论点的方式上也与原文保持一致。而对于说明解释、事例陈述、分析推理方面的课文，技术处理以缩写与节录方法为主，采用同义转换、等值取代、衔接润色等方法组织编排，以减少层次，精简内容，着重帮助学生理解专业知识，降低双语教学难度。

由于预防医学专业独立的毒理学教学在我国已有30年的历史，各校之间虽有差异，但在教学体系以及教学内容上大体一致，已形成特定的体制和惯例。教材的编写必须适应这一国情。遵循这个原则，我们以国内毒理学课程基本要求、教学大纲以及国家执业医师资格考试大纲为依据，同时参考卫生部规划教材，确定了教材的组织框架，内容的深度、广度和侧重点，使其密切结合专业培养目标，同时符合我国学生的实际接受能力。因此，本书是以参考国外一部权威教材为主，同时经过多本英文原版教材验证的，并结合国内学科特点和发展方向，由我国自行出版的毒理学双语教材。

教材中还提供了一些教辅资料和学生互动材料内容，如测试题、课文注释和课文汉语翻译，词语解释也尽可能用英汉两种语言。另外，为了利于重复学习，加强记忆和便于查找，对于生词在不同章节的课文注释中出现重复有意做了保留。特别是阅读窗等形式的资料，从身边的琐事谈起，一方面丰富了版面，另一方面使课文显得生动活泼，从已知导入未知，提高了教材的可读性和趣味性。更使学生产生一种亲切感，避免了一本书从头到尾通篇都是英文可能给学生带来的那种冰冷的生疏感。我们觉得这样有利于降低双语教学在短时期内对教学质量和学习效果可能带来的负面影响。同时也使学生亲历感受毒理学并非是科学家关起门来搞出的空洞高深的理论，纯科学的东西，而是和每个人息息相关，普通百姓的衣食住行都离不开的实用科学。

本教材分为两大部分。这两部分在内容编排方式、教学的重点上有所不同。第一部分内容为普通毒理学，涉及毒理学基本原理，包括毒理学常用概念、毒物生物转运与生物转化、毒作用机制及其影响因素、一般毒性及其测试、非特异靶器官毒性（致突变、致癌、致畸）以及管理毒理学共11章；第二部分内容为靶器官毒理学，包括血液、免疫、肝、肾、呼吸、神经、心血管、皮肤和生殖毒理学共9章。以上总共20章。教材第二部分将每章分成3个单元：内容精要、专业词汇和重点详述。其中内容精要又包括结构功能、常见毒物、毒作用及其机制、毒性测试评价方法4个段落。教材第一部分侧重毒理学基础以及专业英语过渡学习；第二部分侧重毒理学基础理论运用，毒理学专业词汇掌握及专业英语的提高。全书最后附有常见毒理学英语词素以及英汉名词对照索引。本教材适合预防医学、药学等相关专业的本科教学使用。此外，还可以将本教材变通使用，例如单纯使用英文或中文部分作为教材，也可满足研究生和专科教学需要。实际上，对于从事任何专业的医学工作者，本书在基础医学以及专业英语的学习掌握上都是有帮助的。

直到搁笔合上书稿之时，编者也没有如释重负的感觉，原因是仍觉得有许多可以改进完善之处。然而木已成舟，绝无可能从头再来。毕竟这是在国内第一次由中国教师用英语来编写毒理学

教材，应该说尚属于一种尝试性工作。虽然事前做了许多精心的策划和设计，但有许多的原则是在编写的过程中逐渐形成的，有许多技巧也是在这样一个较长的时期中一点一滴掌握的。我想假如再给我们多一次机会的话，一定会做得更好，为此也颇觉遗憾。如果说我们在编写过程中是怀着一种如履薄冰、小心翼翼的心情，生怕出现任何错误和纰漏的话；那我们现在则依然是怀着一种忐忑的心情来期待着读者的批评。一方面希望得到大家的肯定，另一方面期盼能及时指出不妥及错误之处，使我们有可能加以修正。

最后本书的出版特别要感谢北京大学周宗灿教授，感谢他将卫生部国家医学考试中心组织修订的最新执业医师毒理学考试大纲提供给我们，并且在本教材最初的设计策划过程中提出了很好的建议，对我们很有启发。此外，中国毒理学学会理事长庄志雄教授应邀推荐了编者，对本教材的编写也给予了关心和支持。当然更要感谢各位编者在本书编写过程中所付出的辛勤劳动和持有的严谨治学态度，以及对我的信任和支持。本教材的定稿会在秀丽的苏州金鸡湖畔召开，会议得到苏州大学的全力支持。苏州大学的张增利老师也参与了书稿的编写。在此一并表示衷心的感谢！

主　编

2008 年 4 月

HOW TO USE THIS COURSE
如何使用本书

本教材第一部分是毒理学传统核心内容，也是实际应用毒理学原理及方法的基础。学好这部分内容，应把毒物剂量 - 机体反应作为贯穿全书的主线，深入理解**毒理学基本概念**，如毒物、毒性的相对性。毒理学研究机体和毒物在一定环境条件下相互作用及其结果。剂量是最关键的**毒作用影响因素**。机体如接触毒物将进行**毒物处置**（**生物转运与生物转化**），而毒物若损害机体则通过一定**毒作用机制**产生毒效应，表现为**一般毒性作用**（三性）和**特殊毒性作用**（三致）。而评定毒物何种暴露对人体产生实际危害，据此规定使用条件提出限用、禁用的建议则是**管理毒理学**的内容。第二部分涉及可能成为毒作用靶子的九大器官系统，是第一部分所学知识的延伸、应用和深化。每章的 3 个单元（section）中，第 1 单元内容精要以纲要与提示的方式简略表达。这一单元的学习，应在复习各靶器官系统的**结构与功能**特点的基础上，重点分析掌握其对毒物敏感的原因以及**毒反应的类型和机制**，并以此为线索分类记忆**常见的毒物**，而**毒性测试评价**，从某种意义上来说不过是通过体内外试验再现毒作用形式而已。第 2 单元专业术语列出了该靶器官系统的生物医学基本词汇。第 3 单元重点详述着重对毒反应及其机制给以较详细的论述，英文课文语言程度稍难，附有汉语译文。

本双语教材的编写贯彻了调动教师主导作用、学生主体作用以及师生互动的教学原则。编写依据规定的教学内容和要求，选择素材组织课文，同时针对课文提供了详实的诠释资料。为此，除了课堂学习外，学生还应进行必要的预习和复习。预习主要是了解毒理学各章节的学习目标，内容要点，并了解英语词汇的意义和读音。课后复习可参照教材提供的课文注释及汉语译文，结合教师课堂讲授透彻理解英语课文，掌握毒理学基本理论和基本概念；每章学习结束后，尝试着用对所学到的新知识做一下内容概括，并和课本上的本章小结进行对照；最后再通过测试题，评价自己学习的效果。总之，学生只有发挥主观能动性，主动学习，才能通过本教材，收到较好的学习效果。

课文注释是针对教学难点和重点，特别是在英语阅读方面的困难进行的解释和说明，学生应充分利用。生词与词组注释，是课文注释的主要内容，按条目列出，分为重点掌握词汇和一般掌握词汇注释。重点掌握词汇（条目前有圆点标示）是毒理学文献乃至科技英语中出现频率较高，而在词语辨析、搭配习惯、汉语翻译上较难掌握的词汇。为此提供了英汉双语的贴切而详细的解释。对于词汇的注释并非简单罗列一般词典上现有的释义，而是给出由课文上下文情境确定的特定含义，必要时还给出发生转换或引申后的词义；此外重点掌握词汇还提示了联想记忆的线索与

方法；列出在音或形方面相近的易混淆词汇以及需注意的关联词语。【名词解释】是对毒理学专业名词术语、概念的定义和解释。【句子解析】是对长句难句的句型、语法结构及习惯用法作详细分析。【词素学习】表示词素（词根、词干、词缀）及其释义，其后列举同根词、衍生词以及可通过本词联想记忆的其他词汇。

此外，应了解课文注释中以下注释符号的意义：①圆括号，（ ）—— 表示补充性说明解释，在汉语行文中表示可取代前面字或词，在英语行文中表示可省略的字母或词，另外还用来注明构词方法；②方括号，[ ] ——在汉语行文中表示可省略的字或词，或注明国际音标；③ <例> ——表示例举、实例、例子；④ <记> —— 记忆法，表示可通过本词联想记忆的其他同根词词汇；⑤ <注> ——列举同形异义词、异形近义词、词形近似的异根异义词等，或表示“提示”、“注意”、“比较”等含义；⑥ [同] —— 表示同义词；⑦ [反] —— 表示反义词；⑧箭头，→ ——表示词汇来源与引申、推论、转义等。

从专业英语技能训练的角度出发，本书包括了阅读、词汇和翻译三方面的内容。阅读是最基本的训练，通过精读英语课文，可以熟悉毒理学及相关专业文献中常见的语言现象，逐步提高阅读的速度与理解程度。词汇学习可以随同课文阅读进行，也可利用教材中课文相关词汇和附录中的常用英语词素进行集中学习。为了便于掌握毒理学词汇的发音，本教材词汇尽可能加注了音标。至于课文中出现的属于一般词汇的生词有些未做注释，留给学生自己解决，以便锻炼借助工具书选择词义以及通过上下文猜测词义的能力。但最重要的是通过课文的阅读和文章翻译实践来掌握词汇。提供汉语译文的目的在于使学生更好地理解英语课文内容，同时通过模仿，英汉互译，实际操练。译文仅供参考，不主张依赖译文逐字逐句对照原文阅读。

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PART Ⅰ GENERAL TOXICOLOGY
第一部分 普通毒理学

CHAPTER 1
INTRODUCTION TO TOXICOLOGY

CHAPTER OUTLINE

DEFINITION OF TOXICOLOGY

Toxicology is the study of the adverse effects of chemicals on living organisms. It is a multidisciplinary subject which comprises many different areas. Regardless of the specialization within toxicology, a toxicologist is trained to perform one or both of the two basic functions of toxicology, which are to (1) examine the nature of the adverse effects produced by a chemical and (2) assess the probability of these hazards/toxicities occurring under specific conditions of exposure. Ultimately, the goal and basic purpose of toxicology is to provide a basis for appropriate controlling measures so that these adverse effects can be prevented.

In the world, more than 80 000 commercial and industrial chemicals are now in use and 500-1000 new chemicals are added each year. Because of this escalation in the numbers of chemicals to which humans may potentially expose, toxicology has become increasingly important in the area of quantitative estimates of the potential effects on human health and environmental significance of various types of chemical exposures (e.g., pesticide residues on food, contaminants in drinking water, and airborne dusts in the workplace).

SCOPE OF TOXICOLOGY

Three Main Specialized Areas

The professional activities of all toxicologists fall into three main areas: descriptive, mechanistic, and regulatory.

Descriptive Toxicology

A descriptive toxicologist is concerned directly with toxicity testing, which provides information for safety evaluation and regulatory requirements. The concern may be limited to effects on humans, as in the case of drugs and food additives, or to potential effects on fish, birds, and plants, as well as other factors that might disturb the balance of the ecosystem.

Mechanistic Toxicology

A mechanistic toxicologist is concerned with identifying and understanding the mechanisms by which chemicals exert toxic effects on living organisms. In risk assessment, mechanistic data may be very useful in demonstrating that an adverse outcome observed in laboratory animals is or is not directly relevant to humans. Mechanistic data are also useful in the design and production of safer alternative chemicals and in rational therapy for chemical poisoning and treatment of disease. An understanding of the mechanisms of toxic action contributes to the knowledge of basic physiology, pharmacology, cell biology, and biochemistry.

Regulatory Toxicology

A regulatory toxicologist has the responsibility for deciding, on the basis of data provided by descriptive and mechanistic toxicologists, whether a drug or another chemical poses a sufficiently low risk to be marketed for a stated purpose. Regulatory toxicologists also assist in the establishment of standards for the amount of chemicals permitted in ambient air, industrial atmospheres, and drinking water, often integrating scientific information from basic descriptive and mechanistic toxicology studies with the principles and approaches used for risk assessment.

Other Specialized Areas of Toxicology

In addition to the above categories, there are other divisions of toxicology which may be based on the classes of chemicals dealt with or application of knowledge from toxicology for a specific field:

- Forensic toxicology is concerned primarily with the medicolegal aspects of the harmful effects of chemicals on humans and animals, in establishing causes of death, and in determining their circumstances in a postmortem investigation.
- Clinical toxicology is concerned with disease caused by or uniquely associated with toxic substances. Efforts are directed at treating patients poisoned with drugs or other chemicals and at the development of new techniques to treat those intoxications.
- Environmental toxicology focuses on the

impact of chemical pollutants in the environment on biological organisms, most commonly on nonhuman organisms such as fish, birds, and terrestrial animals.

- Drug toxicology plays a major role in the preclinical safety assessment of chemicals intended for use as drugs, and studies potential effects of drugs after high doses. Drug toxicology also elucidates the mechanisms of side effects observed during clinical application.
- Occupational toxicology is the subdiscipline concerned with the chemical exposures and diseases found in the workplace. Both acute and chronic occupational poisonings have exerted a major influence on the development of toxicology in general. Occupational toxicology also helps in the development of safety procedures to prevent intoxications in the workplace and assists in the definition of exposure limits.

MULTIDISCIPLINARY NATURE OF TOXICOLOGY

Relationship to Other Sciences

Although generally accepted as a specific scientific field during last century, the practice of toxicology is not a discipline in its own right but comprises many different disciplines at present. Toxicology is highly eclectic interdisciplinary science with contribution from and to a broad spectrum of other sciences. At one end of the spectrum are those sciences that contribute their methods and philosophical concepts to serve the needs of toxicologists, either in research or in the application of toxicology to human affairs. At the other end of the spectrum are those sciences to which toxicology contributes.

In the first group chemistry, biochemistry, physiology, immunology, pathology, epidemiology, biomathematics, and ecology have long been important while molecular biology has, in the last two or three decades, contributed to dramatic advances in toxicology.

In the group of sciences to which toxicology contributes significantly are such aspects of medicine as public health, occupational health, internal medicine, forensic medicine, and pharmacy. Toxicology also contributes in an important way to veterinary medicine, and to such aspects of agriculture as the development and safe use of agricultural chemicals. The contributions of toxicology to environmental studies have become increasingly important in recent years.

The field most closely related to toxicology is pharmacology. In many countries, toxicology as a discipline has developed from pharmacology. Pharmacology and toxicology both study the effect of chemicals on living organisms and have often used identical methods. However, fundamental differences have developed with advances in these sciences. Pharmacology focused on chemicals with beneficial effects (drugs) at lower doses whereas toxicology studied the adverse health effects occurring with the same chemicals at high doses. Today, the main interest of research in toxicology has shifted to studies on the long-term effects of chemicals after low-dose exposure, such as cancer or other irreversible diseases; moreover, most chemicals of interest to toxicologists are not used as drugs.

Toxicology is a recognized scientific discipline encompassing both basic and applied issues. Few disciplines can point to both basic sciences and direct applications at the same time. Toxicology may be unique in this regard.

Toxicology Is Both a Science and an Art

Toxicology, like medicine, is both a science and an art. The science of toxicology is defined as the observational and data-gathering phase, whereas the art of toxicology consists of the utilization of the data to predict outcomes of exposure in human and animal populations. In most cases, these phases are linked because the facts generated by the science of toxicology are used to develop extrapolations and hypotheses to explain the adverse effects of chemical agents in situations where there is little or no information. For example, the observation that the administration of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) to female Sprague-Dawley rats induces hepatocellular carcinoma is a fact. However, the conclusion that it will also do so in humans is a prediction or hypothesis. It is important to distinguish facts from predictions. When we fail to distinguish the science form the art, we confuse facts with predictions and argue that they have equal validity, which they clearly do not. In toxicology, as in all science theories have a higher level of certainty than do hypotheses, which in turn are more certain than speculations, opinions, conjectures, and guesses.

HISTORICAL ASPECTS OF TOXICOLOGY

Antiquity and Middle Ages

Toxicology dates back to the earliest humans, who used animal venoms and plant extracts for hunting, warfare, and assassination. Primitive man was aware of natural poisons from animals and plants and indeed used these on his weapons. The word toxicology is derived from *toxicon* – a poisonous substance into which arrow heads were dipped and *toxikos* – a bow. The Ebers papyrus (circa 1500 BC) contains information pertaining to many recognized poisons. Hippocrates (circa 400 BC) in his writings showed that the ancient Greeks had a professional awareness of poisons and of the principles of toxicology, particularly with regard to the treatment of poisoning by influencing absorption. He also mentioned clinical toxicology principles pertaining to bioavailability in therapy and overdosage.

Using poisons for murder, suicide and political assassination was quite common. It is well known for example that Socrates (circa 470-399 BC) committed suicide by taking hemlock as state method of execution. King Mithridates VI (132-63 BC) of Pontus did numerous acute toxicity experiments on unfortunate criminals to search for antidotes to poisonous substances and regularly protected himself with a mixture of 50 different antidotes.

Dioscorides (40-90 AD), a Greek physician in the court of the Roman emperor Nero, made the first attempt at a classification of poisons, which was accompanied by descriptions and drawings. His classification into plant, animal, and mineral poisons not only remained a standard for 16 centuries but is still a convenient classification.

In the Middle Ages, especially in Italy, the art of poisoning for political ends developed into a cult. The Borgias were infamous among the families engaged in poisoning during the fifteenth and sixteenth centuries.

Age of Enlightenment

A significant figure in the history of science and medicine in the late Middle Ages was the renaissance man Philippus Aureoles Theophrastus Bombastus von Hohenheim-Paracelsus (1493-1541) Paracelsus (Figure 1-1). Between the time of Aristotle and the age of, there was little substantial change in the biomedical sciences. A view initiated by Paracelsus that became a lasting contribution held as corollaries that (1) experimentation is essential in the examination of responses to chemicals, (2) one should make a distinction between the therapeutic and toxic properties of chemicals, (3) these properties are sometimes but not always indistinguishable except by dose, and (4) one

Figure 1–1. P. A. Paracelsus (1493–1541).
This Swiss physician and scientist questioned and rejected the irrational medicine of his time. He realized especially the crucial importance of dose in relation to both the adverse and the beneficial.

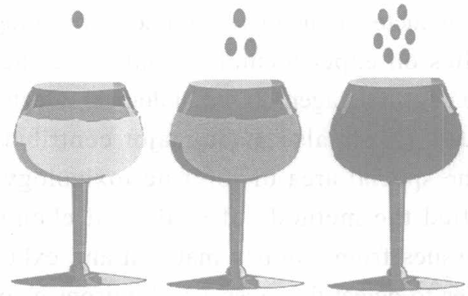

Figure 1–2. Effects of amount on response.
The greater the dose, the greater the effect. Fill three large glasses with approximately 3/4 water. This represents the approximate water content of an individual. Put one drop of blue food color in the first glass, three in the second glass, and then seven in the last glass. Stir with a pen and look at the change in color as a response to increased dose of food color in each glass. Think how some chemicals, caffeine being one, distribute throughout total body water.

can ascertain a degree of specificity of chemicals and their therapeutic or toxic effects. Paracelsus summarized his views in the following famous phrase: "All substances are poisons; there is none that is not a poison. The right dose differentiates a poison from a remedy. " This statement is properly regarded as a landmark in the development of the science (Figure 1-2).

The development of the industrial revolution stimulated a rise in many occupational diseases. During this period of time, occupational toxicology was established and advanced by the work of Bernardino Ramazzini. His classic, published in 1700 and entitled *Discourse on the Diseases of Workers*, set the standard for occupational medicine. Percival Pott's (1795) recognition of the role of soot in scrotal cancer among chimney sweeps was the first reported example of polyaromatic hydrocarbon carcinogenicity.

The nineteenth century dawned in a climate of industrial and political revolution. Organic chemistry was in its infancy in 1800, but by 1825 phosgene and mustard gas had been synthesized. These two agents were used in the World War I as war gases.

Another significant figure in toxicology was Mathieu Joseph Bonaventure Orfila (1787–1853), a Spaniard working at the University of Paris in the early nineteenth century, who is said to be the father of modern toxicology (Figure 1-3). He clearly identified toxicology as a separate science.

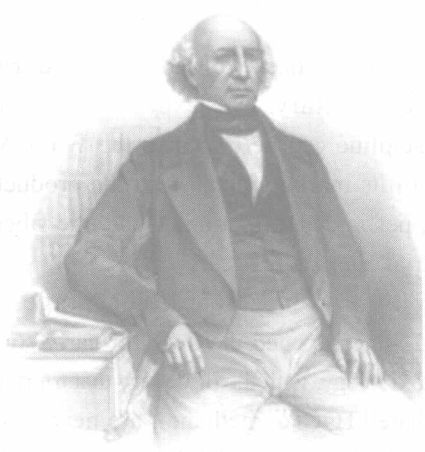

Figure 1–3. M. J. B. Orfila (1787–1853).
A Spanish chemist and physician, he can properly be called "the father of modern toxicology." His two-volume work, published as an English translation in 1817, was the first textbook of toxicology.

He conducted numerous quantitative toxicological studies on experimental animals, relating the dose of a toxic agent to the biological effects that ensued. Orfila also made major contributions to the special area of forensic toxicology. He applied the methods of analytical chemistry to tissues from autopsy material and exhumed bodies to detect the presence of poisons as proof of poisoning. Orfila also critically examined the procedures used at this time in the treatment of poisoning, many of which were ineffective. Many of his recommendations concerning the elimination of poisons from the body and the use of artificial respiration remain valid today.

Many German scientists contributed greatly to the growth of toxicology in the late nineteenth and early twentieth centuries. Among the giants of the field are Oswald Schmiedeberg (1838-1921) and Louis Lewin (1850-1929). Schmiedeberg's research focused on the synthesis of hippuric acid in the liver and the detoxification mechanisms of the liver in several animal species. Lewin made contributions to the chronic toxicity of narcotics and other alkaloids.

Modern Age

Toxicology has evolved rapidly during the twentieth century. The exponential growth of the discipline can be traced to the World War II era with its marked increase in the production of drugs, pesticides, munitions, synthetic fibers, and industrial chemicals.

Prohibition of alcoholic beverages in the United States opened the door for early studies of neurotoxicology, with the discovery that triorthocresyl phosphate (TOCP), methanol, are neurotoxicants. Mueller's discovery of DDT and several other organohalides such as hexachlorobenzene and hexachlorocyclohexane, during the late 1920s resulted in wider use of insecticidal agents. The tragic event of sulfanilamide in glycol solution led to the passage of the Copeland bill in 1938, the major bill involving the formation of the U.S. Food and Drug Administration (FDA). The sulfanilamide disaster played a critical role in the further development of toxicology, resulting in work by Eugene Maximillian Geiling in the University of Chicago that elucidated the mechanism of toxicity of both sulfanilamide and ethylene glycol. Studies of the glycols were simultaneously carried out at the U.S. FDA by a group led by Arnold Lehman. The scientists associated with Lehman and Geiling were to become the leaders of toxicology over the next 40 years.

More recently, in 1945, Sir Rudolph Peters studied the mechanism of action of arsenical war gases and so was able to devise an effective antidote known as British Anti-Lewisite. Another seminal event in toxicology that occurred during the World War II era was the discovery of organophosphate cholinesterase inhibitors. The importance of the early research on the organophosphates has taken on special meaning in the years since 1960, when these nonbioaccumulating insecticides were destined to replace DDT and other organochlorine insecticides. Toxicologists today owe a great deal to the researchers of chemical carcinogenesis of the 1940s. Much of today's work can be traced to Elizabeth and James Miller's seminal research on reactive intermediate of chemical carcinogenesis and mixed-function oxidases at Wisconsin.

The 1960 were a tumultuous time for society, and toxicology was swept up in the tide. Starting with the tragic thalidomide incident and the publication of Rachel Carson's *Silent Spring* (1962), the field of toxicology developed at a feverish pitch. The end of the 1960s witnessed the "discovery" of TCDD as a contaminant in the herbicide Agent Orange. The discovery of a high-affinity cellular binding protein designated the "Ah" receptor and work on the genetics of the receptor have revolutionized field of toxicology.