药物流行病学

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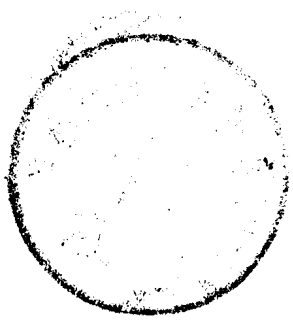

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推广药物流行病学知识，为人民健康服务

陈敏章

九六年八月

加強药品流行病学
研究為确保人民群
众用药安全服务

張文康

一九九五年四月

多学科人员共同参
力运用药物流行病
学研究成果改善患
者生存质量提高
人民健康水平

祝中国药学会药物流行病
学专业委员会成立

郑筱萸

一九九五年四月廿

国家医药管理局局长郑筱萸题词

加强对药品不良反应
的监察，为人民健康
作出贡献

张鹤铺

丙子年秋

开展药物流行病学工作，

保证人民合理用药。

潘学田

一九九年八月

前　言

药品的安全性与有效性是病人、临床医师、药师、制药企业和药政管理部门共同关心的问题。近百年来，相继发生于世界各国的一系列药害事件，导致了数以万计用药者的残疾和死亡，人类为建立药品安全性、有效性的评价方法，以寻求安全、有效的药物，付出了巨大的代价。

药物流行病学是运用流行病学的原理和方法，研究人群中药物的利用及其效应的应用科学；是临床药理学和流行病学等学科相互渗透形成的一门边缘学科，其研究对象为广大用药人群，其研究目的是使药物的治疗更为有效。近十年来，随着全球药品安全监察工作的不断发展，本学科的理论与方法渐趋完善，目前，国际上已成立了国际药物流行病学学会(ISPE)与欧洲药物安全监察学会(ESOP)等学术组织，编辑出版了《Pharmacoepidemiology》等专著及《Pharmiacoepidemiology and Drug Safety》等专业期刊，并建立了药物流行病学研究的大型数据库，一些著名大学如美国哈佛大学、加拿大 Mc Gill 大学，日本东京大学、荷兰 Utrecht 大学等均开设了药物流行病学课程并招收博士研究生。由于得到政府、企业、大学间多学科专家的共同参与，药物流行病学的研究已在全球呈现出前所未有的发展景象。

我国于 1989 年成立卫生部药品不良反应监察中心，负责组织开展 ADR 监察报告工作，并于 1992 年底在武汉正式创办了《药物流行病学杂志》，以广泛传播药物流行病学的知识和研究成果。创刊 4 年来，虽发表了一些高质量的研究成果和论著，但多数来稿的质量仍反映出我国药物流行病学的研究与发达国家之间尚存在一定的差距，因而激发了杂志社为促进药物流行病学学科在我国卫生事业中的发展而组织编写一部符合我国国情的药物流行病学专著的强烈愿望。1994 年 6 月，杂志社组织国内 20 多位相关学科的专家聚会湖北陆水，讨论制定了编写提纲与工作计划，旨在借鉴国外有关资料，全面系统地介绍药物流行病学的基本理论、方法及最新进展，并尽可能介绍国内的研究成果和实践经验，使之成为药政管理部门、药品生产与经营企业、临床医师和药师在开展药物流行病学研究工作时的一本工具书，并为医药院校、各级药品不良反应监察中心或重点监察医院组织开展药物流行病学培训和药品不良反应监察报告提供教材或参考。

全书分五个部分：第 1～2 章为概论，第 3～8 章介绍有关药物流行病学研究的方法学，第 9～12 章为研究工作的范围和内容，第 13～19 章为药物流行病学的应用和前景，最后为附录和索引。

本书的编写，得到国际药物流行病学学会执行主席 Edlavitch S. A. 教授、卫生

部药政管理局和国家医药管理局有关领导的支持和鼓励，并承中国药品生物制品检定所周海钧研究员和天津医科大学耿贯一教授主审了本书的主要章节。在编写出版过程中，由于全体作者的共同努力，药物流行病学杂志社颜敏华、周立文、陈佐佳等同志的精心组织，编务组汪桂清和蔡大勇同志对组稿、统稿和秘书工作的辛勤劳动，以及中国医药科技出版社的积极配合，使得本书在较短时间内能与读者见面，谨在此表示衷心的感谢！

由于药物流行病学尚为发展中的新兴学科，加之编写时间仓促，编者专业知识有限，其中缺点和错误在所难免，欢迎广大读者提出修改意见，以供再版时修正。

最后，谨以此书献给为中国药物流行病学事业的发展而默默奉献的人们！

《药物流行病学》杂志社

1996 年 5 月

序　言

药品是人们防病治病、调节生理功能、提高健康水平的重要武器，必须安全有效。但是国内外的实践表明，许多经过严格审批的药物，即使在质量检验合格、正常用法用量的情况下，仍会在一部分用药者身上出现不良反应，严重的能致伤致残，甚至引起死亡。

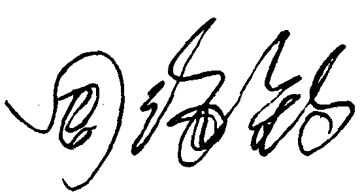
本世纪50年代以后，许多国家建立了药品不良反应(ADR)监察报告制度，收集了大量的ADR病例报告，但是这种制度下的漏报率很高，大多数病例的因果关系难以确定。药品管理部门对有关药物如何加强管理，难以决策。

在这样的情况下，国际上许多学者把流行病学的原理、方法应用到ADR监察工作中，解决了药品安全性监察方面的许多难题，使药品管理部门能迅速对有关药物采取新的管理措施，确保人民用药安全有效。

我国的ADR监察报告工作起步较晚，但是近年来，在卫生部和各省、自治区、直辖市卫生厅的关怀下，这项工作在我国已经取得了一定的进展。开展药物流行病学的调查研究就成了一个紧迫的任务。

几年来，《药物流行病学》编写组的同志们收集了国内外大量的文献资料，终于编写出我国第一本药物流行病学的专著，我表示衷心地祝贺。我有幸参加了本书的审稿工作，发现这本书在编写过程中，注意把国外的经验和我国的国情结合起来，系统地介绍了药物流行病学的基本理论、研究方法及国内外的进展，内容很丰富，是药品监督管理人员、药品安全性监察人员、药品生产经营企业和医疗卫生单位的医、药、护专业人员工作中很好的参考书。

当然，由于这门学科的历史不长，我们国家在这方面还缺乏实际经验，这本书内容上难免有这样那样的缺点甚至错误，欢迎广大读者多多地批评指正，以便再版时修正、补充。



中国药品生物制品检定所所长
中国药学会理事长　周海钧

1996年5月1日

PREFACE

Pharmacoepidemiology is a relatively young applied science which uses the scientific knowledge and approaches of epidemiology to study the utilization and effects of pharmaceuticals in human populations. It is generally accepted that pharmacoepidemiology was launched as a distinct discipline approximately 30 years ago, as scientists, clinicians, legislators, and regulators reacted to the worldwide public and professional outcry following the thalidomide disaster of the 1960s[1,2,3].

Individually, drug therapy and epidemiology have long and rich histories. According to earliest written history, drug therapy has played a central role in health care. Until the mid 19th century, drug therapy consisted of "natural" preparations. The oldest known pharmaceutical document tells how the Sumerians prepared botanical drugs (approximately 2,000 years B. C.), and there is written evidence that drugs were sold commercially in Babylonia, 2111 B. C.. During the next 1,000 years, there are Egyptian and Greek accounts of the use of drugs from the plant, animal, and mineral kingdoms, with botanical drugs dominating[4].

The oldest Chinese review of medicinal materials, Shennong Bencao Jing (100～200 A. D.), covered 365 herbal drugs. By 1578 A. D., as many as 1898 crude drugs of plant, animal and mineral origin (Li Shi-zhen) were documented. Today, more than 500 species and subspecies of herbal drugs, from 130 genera and 3,000 chemical constituents, have been described[5].

Epidemiology may be defined as the study of the distribution and determinants of health-related states in human populations. Some definitions of epidemiology include the application of this study to the control of health problems[6]. The written history of epidemiology appears to begin with the terms epidemic and endemic. The concepts of the distribution of disease in time, space, and people are recorded in the writings of Hippocrates in the 5th century B. C.. By the 19th century, the term epidemiology appears in Spanish literature. Early in the 19th century, studies of the impact of environment, diet, and economic status made important contributions to public health in France, England, and Japan. Late in the 19th century, the germ theory of disease was discovered, and by the early 20th century, important investigations of infectious and chronic diseases were completed, including studies of cholera, pellagra, scurvy, beriberi, and lead poisoning[7].

Current Western pharmacotherapy is approximately 100 years old and is often considered to be based on the substantive work of Paul Ehrlich (1854～1915), who is recognized as the founder of chemotherapy[6]. Since Ehrlich's early work, the success in the laboratory of synthesizing compounds for testing has been phenomenal. Modern Western pharmacopeia include an excess of 30,000 single and combination drug products. In the 1900s, a new generation of biotechnologic approaches to discovering and manufacturing effective pharmaceutical

interventions is emerging. These approaches promise major therapeutic breakthroughs in the next decade. These therapies will pose new challenges to pharmacoepidemiologists as they become part of normal clinical practice.

Western pharmacologists and medical practitioners are also becoming more aware of the long and rich history of Chinese Traditional Medicines. There are efforts underway to better understand the role that Western medicines may play in China, as well as the lessons that can be learned from Chinese traditional therapy applied in other countries.

Drugs and biologics (Western or Traditional) may be used to treat, prevent or alleviate the symptoms of disease. Vaccines, for example, are used in healthy individuals to prevent disease. In some instances, such as with infections, drugs and biologics may cure disease. Frequently, drugs and biologics are used in people who have developed symptoms of one or more disease processes with the intention of limiting disease progression in order to improve the patient's quality of life and ability to function in society.

The pre-approval drug process in most countries follows a similar framework of typical approval based on safety and efficacy evidence from animal and human studies. Randomized clinical trials are considered pivotal to the approval process. The pre-marketing randomized clinical trials are typical placebo controlled and are limited in size. The majority are relatively short term. Patients are restricted to volunteers with the disease of interest and few complications. The physician must treat study participants according to a written fixed protocol, and patients are followed according to strict guidelines.

Unintended drug effects (UDEs) are defined as desirable or undesirable outcome associated with the use of a drug that is not an intended pharmacologic outcome of the therapy. After regulatory agency approval, pharmaceuticals are used in large populations and UDEs are inevitably observed, particularly when drugs are used chronically. The important research of modern pharmacology has led to greater understanding of how many drugs are metabolized in the body and the role that metabolic pathways, genetic and environmental factors play on pharmacokinetics and pharmacodynamics. This knowledgs helps to explain some of these UDEs.

Other UDEs initially cannot be distinguished from underlying disease (s). Factors such as patient self-selection, patient adherence to medication schedules, physician selection, patient habits (e. g. smoking, diet and alcohol consumption), the interactions of multiple drugs and multiple disease states are often unknown from pre-approval studies. In addition, some UDEs are predictable based on the drug's known pharmacologic activity. Others are indiosyncratic and are not based on the pharmacologic mechanism and dose and may be observed only after a large number of patients have used the medication. Pharmacoepidemiologic studies and reasoning are central to understanding the contributions which drugs and underlying disease make to patient outcomes.

The key to conducting sound pharmacoepidemiologic studies is the adherence to sound research principles and their understanding of the critical role that pharmaceutical therapy (Western and traditional) plays in the course of disease. In Western society, the concept of

"natural history of disease"is no longer applicable. This has been replaced with the"history of treated disease". When disease becomes clinically identifiable, medical practice is to treat the symptoms of the disease and when possible to limit or reverse disease progression through pharmaceutical and non pharmaceutical intervention. Almost all of these studies require multidisciplinary teams using the expertise of epidemiologists, pharmacoloists, pharmacists, clinicians, statisticians, health care administrators, sociologists, and pathologists.

According to the 1972 WHO definition, an adverse drug reaction(ADR)may be described as a drug response which is unintended and at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function. In most countries, a government health agency manages a spontaneous adverse drug reaction or drug event reporting system. Medical practitioners, pharmacists, and patients are encouraged to identify and report suspect ADRs to the drug manufacturer or the drug regulatory authority using a brief standardized reporting form. In most countries, the company manufacturing and selling the drug is required to submit periodic reports summarizing these spontaneous reports for each pharmaceutical they sell. They also must identify changing trends in safety reports and submit"immediate(3, 10, or 15 days)"reports when a new serious suspected adverse drug reaction is identified. The majority of countries which have such reporting systems contribute a copy of their reports to the World Health Organization(WHO)reporting system in Uppsala, Sweden. The suspect ADRs from a single country and the accumulated suspect ADRs reported to WHO may signal a possible undesirable drug association. Drug associations which appear to have clinical and biologic merit may be comfirmed or rejected through the conduct of epidemiologic studies.

Epidemiologic study designs may be descriptive, analytic, experimental or a combination of designs. Epidemiologists rely heavily on observational data and pay a great deal of attention to understanding the possible roles of biases and confounders in explaining the etiology of UDEs, as well as comparing alternative therapies for effectiveness and safety. Epidemiologic studies of the effectiveness and safety of alternative therapies in disease outcome should be conducted according to a written protocol. The written protocol should include a clear statement of the research objective(s), specific aims and rationale, appropriate literature review, and a description of research methods with the limitations of the approach selected. In the protocol and the eventual study report, the investigators need to consider potential biases and confounders and to explicitly state how exposures and outcomes will be measured and evaluated.

In addition to assessing the effectiveness and safety of drugs in actual use, additional information is wanted by the physician, health care administrator and the patient to make informed risk/benefit assessments in order to choose between alternative therapies. Each stakeholder has their own reason for the additional information. Health care administrators need adequate information regarding the cost-effectiveness of alternative approaches to treating disease in order to make informed budgetary decisions. Patients and physicians are concerned about the quality of life, the patient will experience with one therapy versus another. In most

countries, the patient is required to pay increasingly larger proportions of their health care costs. As a result, the patient is also concerned about the cost-effectiveness, cost-benefit, and cost-utility of alternative therapies.

Large computerized data bases play an increasingly important role in conducting studies of drug utilization, effectiveness and safety. When concerns about drug safety require quick answers, large computerized data bases have the potential to provide answers about drug exposure and treatment outcomes faster than initiating new longitudinal studies. Also, safety questions about marketed drugs are frequently related to rare unintended drug effects which can only be observed in very large populations.

Many of the accessible large data bases were established to provide administrative data. The quality of the captured information is often limited to address clinical questions. At times, patients must be contacted to collect information on confounders, such as smoking, diet, alcohol consumption and self-medication with non-prescription or prescription drugs. Often, medical records must be accessed to confirm diagnoses and exposure information, or the physician must be contacted to confirm diagnoses. However, "clinical information systems" that exist have proven useful to answer drug utilization, safety, and effectiveness questions. In the United States and Europe, a small number of clinical information systems have been established, and others are under development. Pharmacoepidemiologists need to have a working knowledge of the strengths and limitations of these resources, as well as developments to create additional data bases which could be useful for research purposes. A number of European and emerging Asian data bases are becoming available for use, and more of these resources are expected in the near future.

In the United States and several other countries, the quality, comprehensiveness, and availability of computerized medical information is improving. The clinical information which health care researchers need to evaluate the clinical significance of alternative therapies is also needed by health care administrators to develop more cost-effective health care delivery systems. As a result, additional clinical information systems are being developed in order to conduct these analyses through efficiently using computerized data bases. Pharmacoeconomics, outcomes research, and disease management are areas receiving substantial attention because of the international initiatives to better manage the costs of health care. Pharmacoepidemiologists are frequently involved in the design, implementation and analyses of these economically generated studies. Moreover many of the developing pharmacoeconomics and outcomes research programs are directed by pharmacoepidemiologists.

During these past 30 years, pharmacoepidemiology has developed into a substantive applied science. The scientific standards for pharmacoepidemiologic studies are now quite high, and a great deal has been learned about how to select the best approach to evaluate the risks and benefits of alternative therapies. Pharmacoepidemiologic investigations have proven important to developing public health policy. Three of the areas which will receive increased attention in the future are: pharmacogenetics, drug metabolism and drug-drug interactions and the role of non-prescription (over the counter) and other patient selected therapies on disease

outcome. It is reasonable to expect that in the not too distant future, the practitioner will be better able to predict the response of an individual patient to alternative therapies.

Academic interest in pharmacoepidemiology continues to increase. Currently there are several graduate pharmacoepidemiology programs which grant degrees in pharmacoepidemiology and an increasing number of academic programs offering pharmacoepidemiolgy courses. The International Society for Pharmacoepidemiology (ISPE) begins 1996 with 1150 members in 45 countries and national ISPE chapters in Argentina and Belgium. In addition, there are new Pharmacoepidemiology Societies which have formed in Canada, Sweden, the Netherlands, Japan and the People's Republic of China.

Despite the demonstrated importance of pharmacoepidemiology to assessing the risk/benefit of alternate therapies and the worldwide interest in pharmacoepidemiology, the support for pharmacoepidemiology has sometimes been less than desirable by the pharmaceutical industry and regulatory agencies. This is also changing for the better. The regulatory agencies of a number of countries are working together to adopt common standards for drug approval and safety submissions.

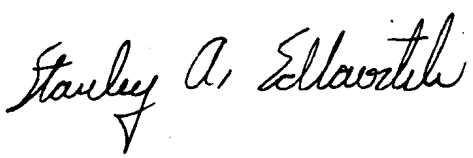
These standards that recognize pharmacoepidemiologic data and analyses are critical to the approval and risk/benefit assessment of alternative drugs. The regulatory agencies in the European Union, Japan, and the United States have addressed these and other areas through the International Conference on Harmonization (ICH). The ICH and efforts of the European Agency and the World Health Organization endorsed CIOMS working groups have resulted in proposals for common criteria for some aspects of drug approval and safety reportion. Areas of safety reportion include: suspect adverse drug reaction reporting formats, common definitions for serious reports and expedited reporting, worldwide birth dates for all marketed drugs, common definitions of adverse reaction terms, and criteria and formats of periodic safety reports.

I expect that pharmacoepidemiology will play an increasingly important role in worldwide drug approval and drug safety assessment. Significant advances in approaches to design meaningful studies, interpretation of epidemiologic data on drug use and safety, the increased availability of computerized data bases, multiple efforts to coordinate drug reporting requirements by regulatory agencies, the growth of academics teaching and research programs and the close relationship between pharmacoepidemiology and pharmacoeconomics are some of the reasons for the continued healthy growth of this discipline. Society demands safe, effective, and cost-effective drugs. The startling case of international communications through phone, satellite, and computer makes these goals easier to attain within individual countries and internationally.

This first Chinese textbook on pharmacoepidemiology is comprehensive. It contains 19 chapters which include discussions of the topics mentioned above, including: general epidemiology; analytic techniques; biases, confounding, and interactions; drug utilization; adverse drug reaction reporting and international efforts at harmonization; pharmacoeconomics; randomized clinical trials; and examples of important pharmacoepidemiologic investigations.

During the past four years, I have had the privilege of lecturing in Tianjin, Beijing, and Wuhan, and holding discussions with the Ministry of Health in Beijing. In 1995, I was honored to lecture at the 1st Chinese Conference on Pharmacoepidemiology, held in Wuhan. During these visits, I have had the opportunity to meet with a number of the scholars who have written chapters in this textbook. In addition, several of the these scholars have either visited my institution in the United States or have participated in the International Conferences on Pharmacoepidemiology, sponsored by the International Society for Pharmacoepidemiology (ISPE)in North America and Europe.

I am impressed with the intellectual calibre of the scientists contributing to this text and appreciate the generosity of these colleagues in inviting me to lecture, to serve as a contributing editor to the Chinese Journal of Phamacoepidemiology and now to preface this textbook. It is a great honor to make a small contribution to this very large and important work of over 550,000 Chinese characters. It will be my privilege to continue working with these and other scholars and to share experiences in evaluating alternative therapies to benefit patients in all countries.



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序

药物流行病学是一门新兴的应用学科。它采用流行病学原理和方法研究药物在人群中的利用和效应。在20世纪60年代沙利度胺(反应停)药害事件后，在世界各国公众及专业人员的强烈呼吁下，科学家、临床医师、药政立法管理人员共同努力使药物流行病学形成一门独立学科，迄今已有近30年的历史。

药物治疗学和流行病学各自都有悠久灿烂的历史。根据最早的历史记载，药物治疗在卫生保健中起着至关重要的作用。直到19世纪中叶之前，药物治疗主要依赖于各类天然制剂。早在公元前2000年左右的药物文献中就记载过索麦人制备植物药品；有记载表明公元前2111年在巴比伦王国已有药物进行商品销售。随后一千余年间，主要有埃及和希腊使用从植物、动物或矿物中提制的药物，而以植物药为主的记载。

最早的中文医药书籍《神农本草经》(公元100～200年)述及了365种草药。到公元1578年，李时珍详细记载了多达1898种的植物、动物或矿物生药。至今，西方已发行了一部有关植物性中药的专著，其中记载了从130种植物所得500多种草药和3000余种化学组份。

流行病学可以定义为是研究人群健康(或疾病)状况分布及其影响因素的科学。流行病学的某些范畴涉及到控制健康问题的应用研究。流行病学的形成过程是以研究流行病(epidemic)或地方性流行病(endemic)为开端的。疾病在时间、空间或人群中分布的概念曾记载于公元前5世纪希波克拉底的著作中。到19世纪，西班牙语文献中已有流行病学这一术语。19世纪初期，有关环境、食品或经济状态影响的研究对法国、英国及日本的公共卫生起到积极作用。19世纪后期，人们发现了引起疾病的病原体，到20世纪初期，流行病学家已完成了对霍乱、糙皮病、坏血病、脚气病和铅中毒等重要传染病或慢性病的调查研究。

现代西方药物治疗已有近100年的历史，其发展是以埃利希(Paul Ehrlich，1854～1915，化学药物治疗的奠基人)的重要工作为基础的。由于埃利希的早期工作，实验室化学合成药成功地用于试验已成为现实。现代西方医药已有3万余种单体药物或复合药物。在20世纪90年代，新的生物技术促进了有效药物制剂的发现和研制。这些研究途径有希望成为未来10年医药治疗学的重要突破。这些新的治疗措施作为常规临床治疗的一部分时，也是药物流行病学家研究的新课题。

西方药理学家及医务工作者已日益认清了传统中医药悠久灿烂的历史，并致力于更多地认识西医药在中国所起的作用及中国传统治疗学知识在其他国家的应用。

西方的或传统的药物或生物制品可用于治疗、预防或缓解疾病的症状。如疫苗成功地用于健康人体以预防疾病的发生。药物或生物制品可完全治愈某些疾病，如传染病。为了提高病人的生活质量及增强他们的劳动能力，药物或生物制品常用于已有临床症状的病人，以期阻止疾病的发展。

许多国家在药品审批前都要求提供动物实验和人体研究证据，用作审批药品安全性和有效性的依据。随机临床试验是审批过程的关键。上市前随机临床试验都是典型的安慰剂对照及仅限于小样本受试者。大多数研究观察期相对较短；受试者仅限于对所研究的疾病感兴趣并很少有并发症的志愿者。医师必须按临床试验规定的试验方案来处理受试者，受试者亦须遵循