Toxicology

The Basic Science of Poisons

EDITED BY

Louis J. Casarett, Ph.D.

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毒理学：毒物的基本科学

本书虽是为培训毒理学工作者而编写的一本毒理学教科书，但它的内容与编写方式，与传统的毒物学分类教科书不同，除将毒物按其化学性质及使用特点分类叙述外，还按人体器官和系统分类介绍毒物的作用部位，其中讨论了毒物在特殊器官或系统中引起的生理、生化、病理等变化，及导致这些变化的因素是什么，最后还介绍了毒理学研究结果在各领域中的应用。本书内容丰富，对在工业、农业、医学、食品、药剂、兽医等领域，从事毒理学和卫生工作的人员，是较实用的参考书。

目次：(一)毒理学的一般原理：①毒理学的起源和范围，②毒理学的评价，③毒物的吸收、分布和排泄，④毒性物质的代谢，⑤影响毒性的因子。(二)系统毒理学：⑥中枢神经系统毒理学，⑦肝脏毒理学，⑧肾脏毒理学，⑨呼吸系统毒理学，⑩血液中有形成份的毒理学，⑪骨骼系统毒理学，⑫生殖系统毒理学，⑬眼的毒理学。(三)毒性因子：⑭致畸物，⑮化学性致癌物，⑯射线和放射性物质，⑰农药，⑱金属，⑲溶剂和蒸汽，⑳空气污染物，㉑食品添加剂，㉒动物性毒物，㉓植物毒理学，㉔塑料毒理学，㉕社会性毒物。(四)毒理学的应用：㉖临床毒理学，㉗法医毒理学，㉘工业毒理学，㉙兽医毒理学，㉚毒理学和法律。索引。

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FOREWORD

THOSE of us who honor sources consider ourselves to be privileged spectators of the emergence of one of the new sciences, toxicology. Other closely related disciplines, now established, had their beginnings in the not-distant past. Just over a century and a quarter ago, pharmacology began in a home-basement laboratory of a physiologist-physician who rejected the empirical use of medicinals in favor of research to explain how drugs act, to find a "scientific" drug therapy, and to develop new and better drugs. A. V. Hill's whimsical account of the origin of another sister science—biochemistry—has the charm of a legend. Years ago in the department of physiology, as he told it, it was the custom late every afternoon for the staff members to leave their laboratories and gather in the library for a cup of tea and for discussions of the day's troubles and triumphs. Over the years the group enlarged, as from time to time a scientist and then another joined the department, until one day the number was so large that all could no longer get into the room for a cup of tea. So some moved down the hall and began their own tea, and biochemistry was born.

The origin of modern toxicology was neither so discernible as that of pharmacology nor so orderly as that of biochemistry. A generation or so ago, the toxicologist was the coroner's chemist. In that day, poisonings were not unknown; in fact, 60 years ago in the United States they seem to have been accepted and tolerated. The pioneer industrial physician Alice Hamilton found primitive methods of manufacture in the "dangerous trades" that engendered widespread poisonings of workmen as they earned their livelihood. Contemporaneously, Harvey Wiley and his "poison squad" presented incontrovertible evidence of the filth contaminating food grains as they were harvested and shipped to the mills. The "brown fogs" of London were accepted as a curious natural phenomenon. Calomel was the child's laxative; sodium fluoride, the household ant poison; Paris green, the garden and orchard insecticide. World War I brought new agents of chemical warfare—chlorine and mustard gas—that maimed and killed. Who could have foreseen that the slowly mounting concern over poisonings, which initially called forth almost trivial attempts to control and prevent injuries, would provide the impetus for efforts that grew in breadth and intensity until from their confluence sprang a new science, toxicology?

It took a "grass-roots" outcry to force the first legislative act of protection for the consumer, the Pure Foods Act of 1906. Public pressure, as it waxed and waned in the intervening years, has accounted for the passage of certain other measures, e.g., the Food, Drug, and Cosmetic Act of 1938 that requires toxicity testing of new drugs before marketing. Only in the last decade have major pieces of legislation appeared, one after another, dealing with toxic hazards from many sources as they threaten the health, comfort, or quality of life of workman, housewife, patient, or consumer. Toxic hazards are being defined and to a growing degree controlled or eliminated.

As a result, toxicologists today are serving in many specialized areas. Clinical toxicologists diagnose, treat, and help prevent adverse drug reactions. When a promising new drug is synthesized, before the first dose can be sold to a patient, the toxic potentialities must be assayed first in animal tests and later, if justified, in rigorously safeguarded human exposures. Forensic toxicologists identify causative agents in poisonings—accidental, homicidal, or occupational. Vigorous attempts to reduce air and water pollution and to re-create a healthy human environment claim the attention of toxicologists who define the requisite purity. The enormous problems of toxic disturbances and distortions of our biosphere have called into being ecologic toxicologists. The dangers of the indiscriminate overuse of pesticides have been so dramatized that some beneficial substances, irreplaceable at present, are banned rather than controlled. Large sums of money are expended to guarantee the safety of a useful food additive or of a pesticide before use is permitted. Household chemicals receive safety evaluations. Occupational toxic exposures are systematically controlled in many large industrial companies that have developed excellent industrial hygiene and preventive medical practices; small companies frequently cannot afford such services. Nor is the end in sight in the efforts to forestall some unforeseen toxic catastrophe; studies are currently projected on hundreds of compounds, tests of unprecedented breadth, variety, and duration.

Few of today's toxicologists were trained primarily in toxicology. In the past, to carry on toxicologic activities, biomedical scientists were recruited from closely related disciplines, such as biochemistry and pharmacology, and for the most part had to be willing to learn by doing. Until recently, almost no formal training programs, few graduate courses, and no Ph.D. degrees in toxicology were offered. The recognition of pressing toxic hazards called scientists to tasks that sooner or later transformed them into toxicologists. Today, unrealistically large demands for trained toxicologists are being created by sweeping new federal legislation designed to safeguard against poisonings. Contemporaneously the toxicology training programs of the National Institutes of Health, which had made a promising start in developing specialists, are being terminated despite the obvious discrepancy.

Our educational problems traditionally have turned for solutions to the universities, and for this field not in vain; across the United States, formal training in graduate toxicology is being offered by a growing number of schools. In the first courses in toxicology, textbooks introduce the beginning student to concepts and principles as well as to descriptive summaries of the great poisons. The few available textbooks of toxicology differ in their approach: some are mainly descriptive; others base their presentations on pharmacokinetic or other theories. This is a time for exploring the avenues of instruction in toxicology. Drawing from teaching experience, Drs. Casarett and Doull have pooled their special interests and added contributions from other specialists in this volume, *Toxicology: The Basic Science of Poisons*. A useful plan of organization became apparent to them, grouping toxic phenomena according to organ systems. Dr. Casarett fervently brought this book to completion, conceding nothing to his terminal illness, because he bore the conviction that this form serves its purpose well, a conviction shared by Dr. Doull. Their choices are commended; toxicology needs such a textbook.

HAROLD C. HODGE

PREFACE

THIS volume has been designed primarily as a textbook for, or adjunct to, courses in toxicology. However, it should also be of interest to those not directly involved in toxicologic education. For example, the research scientist in toxicology will find sections containing current reports on the status of circumscribed areas of special interest. Those concerned with community health, agriculture, food technology, pharmacy, veterinary medicine, and related disciplines will discover the contents to be most useful as a source of concepts and modes of thought that are applicable to other types of investigative and applied sciences. For those further removed from the field of toxicology or for those who have not entered a specific field of endeavor, this book attempts to present a selectively representative view of the many facets of the subject.

Toxicology: The Basic Science of Poisons has been organized to facilitate its use by these different types of users. The first section (Unit I) describes the elements of method and approach that identify toxicology. It includes those principles most frequently invoked in a full understanding of toxicologic events, such as dose-response, and is primarily mechanistically oriented. Mechanisms are also stressed in the subsequent sections of the book, particularly when these are well identified and extend across classic forms of chemicals and systems. However, the major focus in the second section (Unit II) is on the systemic site of action of toxins. The intent therein is to provide answers to two questions: What kinds of injury are produced in specific organs or systems by toxic agents? What are the agents that produce these effects?

A more conventional approach to toxicology has been utilized in the third section (Unit III), in which the toxic agents are grouped by chemical or use characteristics. In the final section (Unit IV) an attempt has been made to illustrate the ramifications of toxicology into all areas of the health sciences and even beyond. This unit is intended to provide perspective for the nontoxicologist in the application of the results of toxicologic studies and a better understanding of the activities of those engaged in the various aspects of the discipline of toxicology.

It will be obvious to the reader that the contents of this book represent a compromise between the basic, fundamental, mechanistic approach to toxicology and the desire to give a view of the broad horizons presented by the subject. While it is certain that the editors' selectivity might have been more severe, it is equally certain that it could have been less so, and we hope that the balance struck will prove of be appropriate for both toxicologic training and the scientific interest of our colleagues.

L. J. C.
J. D.

Although the philosophy and design of this book evolved over a long period of friendship and mutual respect between the editors, the effort needed to convert ideas into reality was undertaken primarily by Louis J. Casarett. Thus, his death at a time when completion of the manuscript was in sight was particularly tragic. With the help and encouragement of his wife, Margaret G. Casarett, and the other contributors, we have finished Lou's task. This volume is a fitting embodiment of Louis J. Casarett's dedication to toxicology and to toxicologic education.

J. D.

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UNIT I

GENERAL PRINCIPLES OF TOXICOLOGY

Chapter 1

ORIGIN AND SCOPE OF TOXICOLOGY

Louis J. Casarett

WHAT IS TOXICOLOGY?

In contrast to the apparent simplicity of this question, there is no simple answer. Because toxicology has evolved as a multidisciplinary field of study, definitions of toxicology often reflect the area of study from which the definition derives. For example, a pharmacologist might view toxicology as a study of drugs, a chemist might view the subject from a chemical or analytic viewpoint, whereas those concerned with a particular interest in an organ or system might have a still different definition of toxicology.

Toxicology is broader than the more parochial definitions. It is more than the science of poisons. Further, the discipline of toxicology is still in its most rapid evolutionary stage and a proper definition must include its breadth and take account of its probable future development. As an example, toxicology, for many, is considered a branch of pharmacology. A typical definition of pharmacology (Fingl and Woodbury, 1970) includes all chemical agents as drugs but recognizes certain implicit distinctions. It is recognized that the treatment of the noxious effects of therapeutic agents is quite properly a part of the pharmacologic considerations in therapy. However, the breadth of interest of the toxicologist extends well beyond therapeutic agents and embraces more biospheric systems than are customarily the province of the pharmacologist.

An understanding of what toxicology is may be gained by considering who its practitioners are, what they do, and how they do it. Although not truly definitive, this approach is informative. There is clearly a body of scientists who designate themselves as "toxicologists." Furthermore, there are those who do not so designate themselves but who, in fact, are engaged in activities and have points of view closely aligned with those of toxicologists. In short, there is an area of study properly called toxicology, growing numbers of scientists who can and do identify themselves as toxicologists, a toxicologic literature, and a thread of basic agreement about what toxicologists do.

The activities and contributions of toxicologists are many and varied. Some of these have been selected for fuller treatment elsewhere in this volume. The most obvious role of the toxicologist is in the biomedical area concerned with intoxications by drugs and other chemicals and the demonstration of the safety or hazard of drugs prior to their entry on the market. The recognition, identification, and quantitation of relative hazard from occupational or public exposure to toxicants comprise another major function. This relates closely to private and governmental responsibilities to assure safety of workers and the general public in their contact with industrial and commercial products, in ensuring air and water purity, as well as the safety of foods, drugs, and cosmetics. The assessment of hazard of such widely used materials as pesticides or other "economic poisons" is also the responsibility of the toxicologist. On the other hand, the development of such poisons with a selective toxic action on weeds, insects, and other unwanted organisms is also the province of toxicology.

Chief among the roles of toxicologists, whether they be academically, commercially, industrially, or governmentally employed, is that of prediction. The toxicologist is charged with garnering sufficient data on the toxicity of materials and adequate knowledge of the mechanisms by which they produce their effects to make reasonable predictions of their hazard and impact on the human population. The assessment of hazard and the rational projection of effects in a population are such overriding functions of toxicology that an alternate definition might be "the science that defines limits of safety of chemical agents."

Some insight into the development of the scope of toxicology, the roles, points of view, and activities of the toxicologist is offered by an examination of the historic evolution of the discipline.

HISTORY OF TOXICOLOGY

Antiquity

Toxicology predates man and, in a variety of specialized and primitive forms, has been a relevant part of the history of man (Figure 1–1). Earliest man was well aware of the toxic effects of animal venoms and poisonous plants. His knowledge was used for hunting, for waging more effective warfare, and, probably, to remove undesirables from the small groups of primitive society. The Ebers papyrus, perhaps our earliest medical record (circa 1500 B.C.), contains information extending back many centuries. Of the more than 800 recipes given, many contain recognized poisons. For example, one finds hemlock, which later became the state poison of the Greeks; aconite, an arrow poison of the ancient Chinese; opium, used as both poison and antidote; and such metals as lead, copper, and antimony. There is also an indication that plants containing substances akin to digitalis and belladonna alkaloids were known. Hippocrates, while introducing rational medicine about 400 B.C., added a number of poisons. He further wrote instructions that might be considered primitive principles of toxicology in the form of attempts to control absorption of the toxic materials in therapy and overdosage.

In the mythology and literature of classic Greek history one finds many references to poisons and their use, and it was during this period that the first professional treatment of the subject began to appear. For example, Theophrastus (370–286 B.C.), a student of Aristotle, included numerous references to poisonous plants in *De Historia Plantarum.* It remained for Dioscorides, a Greek physician in the court of Emperor Nero, to make the first attempt at a classification of poisons, which was accompanied by descriptions and drawings. His separation into plant, animal, and mineral poisons not only remained a standard for 16 centuries but is still a convenient classification today (see Gunther, 1934). Dioscorides also dabbled in therapy recognizing the use of emetics in poisoning and the use of caustic agents or cupping glasses in snakebite.

Poisoning with plant and animal toxins was quite common. Perhaps the best-known recipient of a poison used as a state method of execution was Socrates, although he was in distinguished company. Expeditious suicide on a voluntary basis also made use of toxicologic knowledge. Demosthenes, who took poison hidden in his pen, was only one of many examples. The mode of suicide calling for one to fall on his sword, although manly and noble, carried little appeal and less significance for ladies of the day. Cleopatra's knowledge of natural, primitive toxicology permitted her the more genteel method of falling on her asp instead.

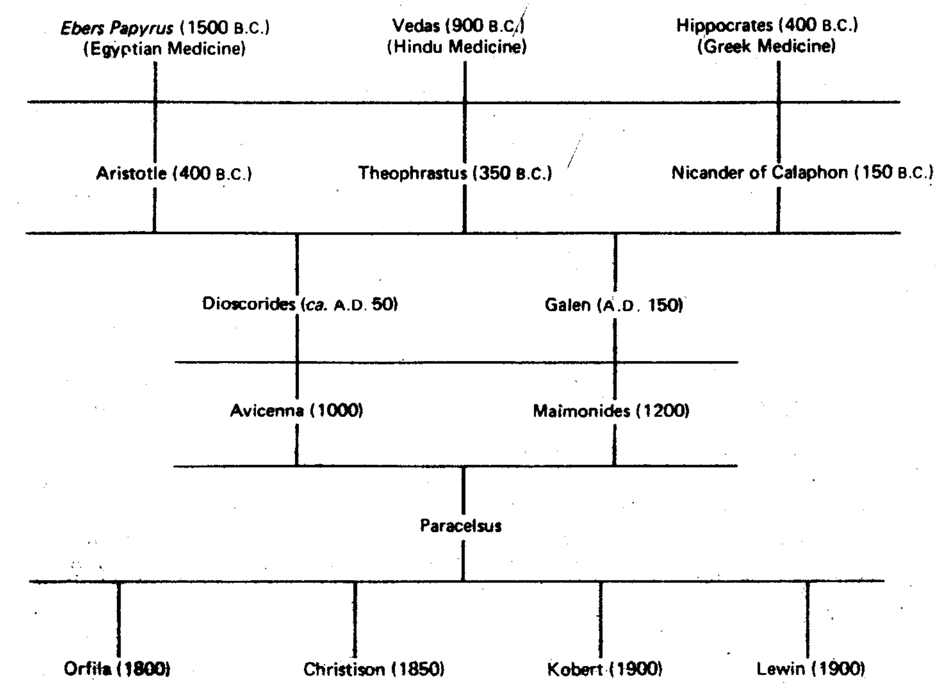

Figure 1–1. Major reference points in the evolution of toxicology as a science.

It is clear that the Greeks and later the Romans made considerable use of poisons, often political. Much legend and myth has grown out of the skill of poisoners and the occupational hazards of political life during the period. One such legend tells of King Mithridates of Pontus, who was so fearful of poisons that he regularly ingested a mixture of 36 ingredients (Galen reports 54) as protection against assassination. On the occasion of his imminent capture by enemies, his attempts to kill himself with poison failed because of his successful concoction and he was forced to use his own sword held by a servant. From this tale comes the term "mithridatic" referring to an antidotal or protective mixture. Another term from the Greek, "theriac," also has become a synonym for "antidote" although the word derives from a poetic treatise by Nicander of Colophon (204–135 B.C.) entitled "Theriaca," which dealt with poisonous animals. Another poem, "Alexipharmaca," was about antidotes.

This concern for antidotal measures or chemicals remained a preoccupation for centuries. In addition to the terms given above, others were applied such as Alexiteria and Bezoardica, the latter referring to concretions found in the goat bladder. The practice of medicine was based largely on an "antidoting" of disease, and descriptions of therapeutic agents also were so classified. For example, an early respectable forerunner of the modern pharmacoepia was the "Antidotarium of Nicolaus." It was not until the seventeenth century that a commission appointed by the Pope to Matthiolus opened the horizons to a search for "Antidota specifica."

In Rome, poisoning seemed to take on epidemic characteristics, which are described by Livy as being especially distressing to the public in the fourth century B.C. It was during this period that a conspiracy of women to remove those from whose death they might profit was uncovered, and similar large-scale poisoning continued from time to time until 82 B.C. when Sulla issued the Lex Cornelia. Consistent with the Roman tradition of law and structure, this appeared to be the first law against poisoning and it later became a regulatory statute directed at careless dispensers of drugs.

The history of poisons and their use is the basis of entertaining retrospective diagnosis as described by Meek in his essay *The Gentle Art of Poisoning* (1928) and in a book by Thompson entitled *Poisons and Poisoners* (1931). Although most poisons used during the period were of vegetable origin, the sulfide of arsenic and arsenious acid were known to be used. It has been postulated that arsenic was the poison with which Agrippina killed Claudius to make Nero the emperor of Rome. This postulate is supported by the later use of the same material by Nero in poisoning Britannicus, Claudius' natural son. The deed was under the direction of Locusta, a professional poisoner attached to the family.

The mixture of fact and legend surrounding that murder illustrates the practices of the times. A first attempt to poison Britannicus failed but the illness reported contained evidence of all the symptoms of arsenic poisoning. The failure led to suspicion and the hiring of a taster. The second, and successful, attempt involved a more devious scheme. The arsenic was placed in cold water and Britannicus was served excessively hot soup. The taster had demonstrated the safety of the soup, but it was not retested after the water had been added to cool the soup.

Here superstition and legend embellish the story. Nero claimed that Britannicus had died of epilepsy and ordered immediate burial to prevent others from seeing the blackening of the body believed to occur after poisoning. As the legend continues, the corpse was painted with cosmetics to hide the deed but, in a raging storm, the cosmetics washed off, revealing Nero's perfidy.

Middle Ages

Prior to the Renaissance period and extending well into that period, the Italians, with characteristic pragmatism, brought the art of poisoning to its zenith. The poisoner became an integral part of the scene, if not as a social being, at least as a political tool and as custodian of a common social expedient. The records of the city councils of Florence and particularly the infamous Council of Ten of Venice contain ample testimony of the political use of poisons. Victims were named, prices set, contracts recorded, and, when the deed was accomplished, payment made. The notation "factum" often appeared after the entry in the archives, indicating successful accomplishment of its transaction.

In less organized but more colorful ways, the citizens of Italy in the Middle Ages also practiced the art of poisoning. A famous figure of the time was a lady named Toffana, who peddled specially prepared arsenic-containing cosmetics (Agua Toffana). Accompanying the product were appropriate instructions for use. Toffana was succeeded by an imitator with organizational genius, a certain Hieronyma Spara, who provided a new fillip by directing her activity toward specific marital and monetary objectives. A local club was formed of young, wealthy, married women, which soon became a club of eligible young, wealthy widows, reminiscent of the matronly conspiracy many centuries earlier.

Among the prominent families engaged in poisoning the Borgias are the most notorious. Although there is no doubt that they were among the leading entrepreneurs in the field, they probably receive more credit than their due. Many deaths that were attributed to poison are now recognized as having occurred from infectious diseases. For example, many of those reported as poison victims probably died from malaria, which was sufficiently bad as to make Rome virtually uninhabitable during the summer months. It appears true, however, that Alexander VI, his son Cesare, and Lucretia were quite active. Aside from personal reasons, the deft application of poisons to men of stature in the Church swelled the holdings of the Papacy, which was the prime heir.

A paragon of the distaff set of the period was Catherine de Medici. Catherine, although not so thoroughly fabled as her Borgia relatives and ancestors, was in tune with her time, a practitioner of the art of applied toxicology. She also represented a formidable export from Italy to France. As appeared to be all too common in this period (or any period), the prime targets of the ladies were their husbands. However, unlike others of an earlier period, the circle represented by Catherine (and epitomized by the notorious Marchioness de Brinvilliers) depended on direct evidence to arrive at the most effective compounds for their purposes. Under guise of delivering provender to the sick and the poor, Catherine tested toxic concoctions, carefully noting the rapidity of the toxic response (onset of action), the effectiveness of the compound (potency), the degree of response of the parts of the body (specificity, site of action), and the complaints of the victim (clinical signs and symptoms). Clearly, Catherine must be given credit as perhaps the earliest untrained experimental toxicologist.

Culmination of the practice in France is represented by the commercialization of the service by a Catherine Deshayes who earned the title La Voisin. Her business was dissolved by her execution. Her trial was one of the most famous of those held by the Chambre Ardente, a special judicial commission established by Louis XIV to try such cases without regard to age, sex, or national origin. La Voisin was convicted of many poisonings, including over 2000 infants among the victims.

During the Middle Ages and on into the Renaissance period, poisoning seems to have been accepted as part of the normal hazards of living. It had some elements of sport with a code, unwritten rules of honor, and a fatalistic attitude on the part of the selected victim. Devices and methods of poisoning proliferated at an alarming rate. The Chambre Ardente created in France was but a mild deterrent, and it remained for the rise of scientific methods in modern times to make the practice more risky for poisoners. Meanwhile, a single figure stood as a part of the Middle Ages but far ahead of his time as the creator of the basic scientific discipline of toxicology. This was Paracelsus.

Age of Enlightenment

A truly monumental figure in the late Middle Ages was the renaissance man in the history of science and medicine, Philippus Aureolus Theophrastus Bombastus von Hohenheim—Paracelsus. Between the time of Aristotle and the age of Paracelsus there was little substantial change in the biomedical sciences. In the sixteenth century the revolt against the authority of the Church was accompanied by a parallel attack on the godlike authority exercised by the followers of Hippocrates and Galen. Paracelsus, personally and professionally, embodied the qualities that forced numerous changes in this period. He and his age were pivotal, standing between the philosophy and magic of classic antiquity and the philosophy and science willed to us by figures of the seventeenth and eighteenth centuries.

In the turbulent career of Paracelsus one can find signal influences on all of science and numerous examples of his contributions to the initiation of toxicology. During the Middle Ages, however, the development of these essential features of science was accompanied by a more suppressive influence derived from Aristotle, viz., his authoritative stature coupled with the firm establishment of the concept of a dominant, essentially divine intelligence controlling the external world. This view lent a rigidity to science that was incompatible with its further maturation.

The Aristotelian school was taken over by Theophrastus (after whom Paracelsus was named), whose chief contribution was a botanical compendium similar to the zoologic work of Aristotle. Strato, next in order in the school, departed from the Aristotelian tradition and offered the view that forces that govern the pattern of events lie in the objects themselves and that these forces operate by a natural necessity. This view, earlier presented by Democritus, failed in its revival by Strato and failed to emerge from the remarkable Arab school of science epitomized by Avicenna. It was further submerged by the theistic interpretations of the Scholastics, Albertus Magnus and Thomas Aquinas. The concept of laws residing within the external world was revived again by Paracelsus and, although it faded until the time of Galileo and Newton, there remained an under-