GENERAL PHARMACOLOGY

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THE LAW OF CAUSALITY is neither true nor false. It is rather a heuristic principle, a signpost to help us find our bearings in a bewildering maze of occurrences, and to show us the direction in which scientific research must advance in order to achieve fertile results. The law of causality remains a lifelong companion of the scientist and confronts him incessantly with new problems. For science is not a contemplative repose amidst knowledge already gained, but is indefatigable work and an ever progressive development.

Max Planck, *"Scientific Autobiography";* Philosophical Library, New York, 1949, p. 149.

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DEVELOPMENT AND SCOPE OF PHARMACOLOGY

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FROM THE LABORATORY TO THE WARD

After Claudius Galen and for eighteen centuries, physicians and apothecaries gravely debated the taste, the color, and the consistency, of their recipes (*Note 1*). The therapeutic inefficacy of these mixtures and the misuse of a few active empirics were artfully hidden from the believers who admired the magistral scrawls of oddly latinized names and the picturesque signs of troy weights. The names, forms, compositions, and indications of official preparations varied with the edicts of the most renowned faculties. The rationale of their clinical applications was fantastic, and caused vehement but futile controversies. Materia medica, a venerable discipline, described and codified the curious specifications of mineral and animal products, of roots, bulbs, barks, leaves, flowers, and seeds—and of their multitudinous combinations.

The classifications of materia medica were so perfect that they remained the undisputed law from the time of Dioscorides until empirical medicine was shaken by the spectacular development of organic chemistry. Morphine (1805), salicylic acid (1844), and digitoxin (1869) were then isolated from their natural sources. These pure substances were several hundred times more potent than the familiar preparations from which they had been extracted; their biological activities did not vary from sample to sample. Artificial chemicals (ethyl ether, 1842; chloroform, 1847; amyl nitrite, 1867), which nature had never made, were found to elicit prodigious effects in man.

Organic synthesis not only isolated the natural substances, but also modified their chemical structures and their biological properties; it even

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(*Note 1*) A pamphlet of *Eli Lilly, Manufacturing Pharmacist,* carried in 1879 the following advertisement: "My elixirs will be found True to the Strength represented on the Label. In elegance of Flavor and Appearance they are not surpassed by any made."

created new series of pharmaceutical products (barbiturates, 1903; conduction anesthetics, 1905; arsenicals, 1906). The old remedies lost their magic; the poisons were stripped of judicial or political role; the traditional panaceas were slowly discarded after centuries of faithful and worthless prescription (*Note 2*). All these advances upset many traditions and excited several passionate polemics (*Note 3*). Most theologians and physicians affirmed that the harmony of creation required every natural disease to be treated with a natural product; others proclaimed that pure substances could never be so effective as the complex mixtures from which they had been isolated.

The biological properties of the new synthetic compounds were not suggested, as in the past, by medicinal lore. The therapeutic and toxic effects of every new drug had to be discovered and determined by laborious tests, and such evaluations required arduous accumulations of experimental data. Frogs, rodents, and dogs became the inseparable collaborators of biologists. It was then discovered that any drug could give sets of responses that might not always be consistent in different species. And after all these preliminary investigations, the drug sometimes elicited quite different effects in man, the last species to be tested.

Some investigators grew dissatisfied with the collections of incomprehensible phenomena that accumulated so rapidly; they would not content themselves with fabricating a jargon that could hide their ignorance (*Note 4*). They tried to rationalize the problems of selectivity, specificity, resistance, dependence, synergism, and intolerance. They endeavored to penetrate the secrets of the events they observed; they searched for the principles that connect biological effects and physicochemical structures. But little could be done as long as anatomy remained the only exact discipline. First physiology, then enzymology began to unravel the dynamics of life; certain mechanisms of drug action were soon related to selective inhibitions of definite metabolic pathways.

These studies exploded the botanical, mineralogical and zoological descriptions of materia medica. A new discipline was born that created new medicinal substances and explained their functions—all with the assistance of physics, physiology, chemistry, and enzymology. A great therapeutic nihilist, Sir William Osler, witnessed this revolution, and wrote (*Note 5*) in January 1910: "Pharmacology is making rapid strides, and the subject is

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(*Note 2*) The British Pharmacopeia did not discard clove, fennel, nutmeg, and quassia until 1958.

(*Note 3*) Louis Pasteur wrote to J. Paget in May 1887: "I cannot understand why every scientific discovery angers some individuals, and confuses others." (From the "Memoirs and Letters of Sir James Paget," S. Paget, ed.; Longmans, Green & Co., London, 1902, p. 372.)

(*Note 4*) R. Asher: Lancet, *2*:359 (1959). Protoplasmic poison, tachyphylaxis, effector cell, target organ, antiphlogistic action, are a few of the many expressions which may be descriptive, but have not introduced any essential concept or fundamental explanation of biological phenomena.

(*Note 5*) Harvey Cushing: "The Life of Sir William Osler;" Oxford University Press, New York, 1940, p. 894.

universally recognized as of the first importance in university work. Moreover, it is one of the hopeful progressive disciplines, with great possibilities for public service."

This prediction could not have been better substantiated than by the discoveries of the following years. The arsenicals (1906) drastically reduced the dangers of syphilis; the sulfonamides (1935), penicillins (1941), streptomycin (1944), and the tetracyclines (1948) transformed the prognosis of the most severe bacterial infections. Twenty years have been added to the average life expectancy of man since the Victorian era. The effective chemotherapy of plague, typhus, cholera, malaria, trypanosomiasis, and many other pestilences have opened new continents to man's industry.

Pharmacology does not claim credit, however, for all medicinal advances. Immunology contributed the vaccines, toxoids, and antitoxins; physiology introduced the transfusions of blood, plasma, and its substitutes. Biochemistry discovered the vitamins and explained the coenzymic roles of these vital molecules. Biochemistry and physiology together investigated the hormones that regulate the homeostatic mechanisms. Radiology studied the biological effects of ionizing radiations, whether emitted by isotopes or by machines. Nevertheless, pharmacology contributed to some of these advances, or extended their applications. Many steroids and the thyroid inhibitors, for example, were developed after the same principles as many other series of drugs. The distribution, localization, and excretion of inorganic elements had been studied long before the investigation of radioactive isotopes benefited from and later perfected the cold data. The hormonal management of allergies and of some malignancies, and the vitamin treatment of certain disorders of calcium metabolism are pharmacological extensions of the strictly physiological role of hormones and vitamins.

The spectacular achievements of pharmacology may not be considered with complacency: viral infections, neurological and mental disorders, malignant diseases, atherosclerosis, and the injurious effects of radiations have yet to be subdued.

Pharmacology studies the biological effects of chemical substances, regardless of their therapeutic, diagnostic or mechanistic applications—just as anatomy studies every part of the body regardless of its surgical importance; bacteriology, the microorganisms regardless of their pathogenicity; and biochemistry, the reactions of life regardless of their clinical applications. Pharmacology, because of its wide scope, has split into specialties that emphasize the application of certain techniques or methods of research. Chemical pharmacology studies the metabolic interactions of drugs and tissues; pharmacodynamics examines the responses of intact or isolated physiological systems of the body. Special pharmacology scrutinizes the chemical and pharmacodynamic properties of individual agents; general pharmacology considers the major principles and characteristics of the different classes of drugs; comparative pharmacology collates the metabolism and effects of drugs in different species. None of these specialties can or should be autonomous: limited investigations may exaggerate the signifi-

cance of highly artificial observations. Partial studies may fail to realize the importance of isolated phenomena; several drugs have remained many years on the useless list before being rediscovered. The dangers of specialization are preached by most scientists, but avoided by few.

Pharmacology also contributes to two socially opposite disciplines. Toxicology studies the properties and effects of substances that would not be administered to man, unless accidentally or criminally. Toxicology is therefore important in public health and in forensic medicine. Therapeutics uses the pharmacodynamic effects of drugs to correct or restore functions that are altered by pathological or toxic processes. Therapeutics and surgery constitute the two main branches of treatment in modern medicine.

General pharmacology describes the main classes of agents, their biochemical characteristics, and their pharmacodynamic effects. The large number and rapid obsolescence of modern drugs forbid the inclusive study of every substance, except as a lifetime endeavor. Several encyclopedias and the literature contain detailed descriptions of all the agents that practicing physicians and research workers prescribe or administer. The particular properties of these substances, which come and go, are but single cases in a solid whole; the study of the exceptions completes, but cannot be substituted for, that of the rules.

General pharmacology emphasizes the pragmatic aspect of pharmacology rather than its whimsical side. Every drug has peculiarities that may offer a lead to the original investigator but that seldom contribute to the comprehension and application of the biochemical and pharmacodynamic properties of the drug.

The text that follows will emphasize human pharmacology because clinical experience has repeatedly shown that the best animal data cannot always be transferred directly to man. Animal results will be presented only when they complement or illustrate corresponding human results.

Pharmacology prepares for, but does not include the study of therapeutics. The clinical applications of drugs will therefore be indicated only as far as they represent an extension of pharmacological principles. For the same reason, supplemental therapies are not extensively covered; they provide the organism with natural vitamins and hormones that are lacking because of dietary, environmental, or endocrine deficiencies. The rationale of such treatments is physiological rather than pharmacological.

Chapter 1

From the Laboratory to the Ward

The discovery and the development of an original class of drugs depends on many allied but dissimilar methods and techniques—and also on chance. The chemist, the pharmacologist, and the clinician accumulate all the information that their specialties can provide; they evaluate the significance of their results; they exchange their conclusions quickly, freely, and in terms that the others can understand. A delay in communication, or the transmission of a misleading conclusion, may retard or even quash the decisive experiment.

The discovery of a new drug is only sometimes planned. More often it is accidental, this second alternative being but an intelligently exploited digression from a systematic investigation. Whether from design or chance, the first active product is delivered by the chemical laboratory.

¶ 1–1 Chemical Synthesis. Investigators do not have any other guide than their theories until they find a compound that shows some promising effect; the chemist then prepares a few close analogs of the first agent. This preliminary trial indicates which structural alterations enhance or decrease the potency of the substance, and the process is repeated until a fairly satisfactory product has been obtained.

As soon as the results are announced or published, the chemists of competing laboratories prepare other series of analogs. After years of research, and when all the data have been released by the patent departments, the essential structural requirements of the new group of drugs are analyzed. These "structure-activity relationships," however, are merely suggestive because of three common limitations. First, synthetic investigations are rarely directed toward the preparation of compounds that should be inactive; all efforts tend consequently to prove rather than disprove the structural hypotheses. Second, the pharmacodynamic activity of all the substances is esti-

mated in different laboratories, often by different techniques; their results are seldom strictly comparable. Third, the potency of a large number of agents is usually determined by a specialized, simple, and inexpensive procedure; the results rarely even suggest the relative activities of different substances in intact animals or in man. Despite these restrictions, the analysis of structural requirements contributes often to the improvement of certain classes of drugs; and it explains those aberrant pharmacodynamic effects known as side effects.

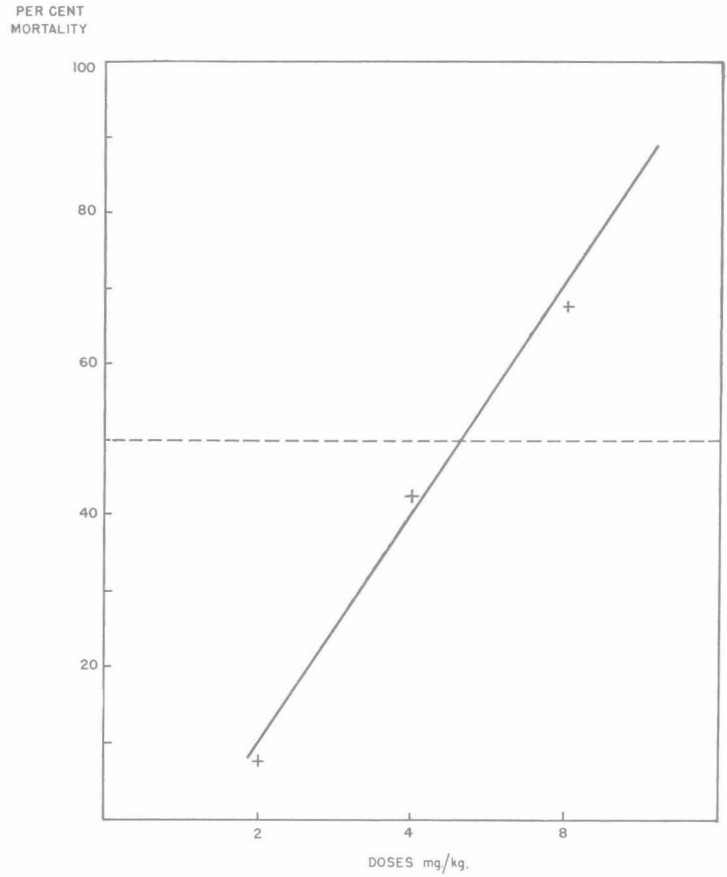

Figure 1.1. Graphic determination of the LD_{50}.

¶ *1–2 Animal Toxicity.* The acute toxicity of every new substance is determined before any other biological test. An approximate LD_{50}—a dose that theoretically is lethal for 50 per cent of the animals—is measured in a few mice (Fig. 1.1). This provisional value is used only as an indication of what is the highest tolerated dose of the substance.

The LD_{50} is later carefully determined if preliminary pharmacodynamic results warrant an extensive study of the new compound. This chemical is then administered orally and parenterally in at least three species, of which