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The Scientific Status of Pharmacology

Through pharmacology, a subject of ancient interest but a young science, important generalizations are emerging.

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Current custom suggests that the retiring president of the American Association for the Advancement of Science give an informal, informative, and interesting review of the status of his professed scientific discipline. This custom is tough on me. As a scientist, I make pretense at being a physiologist and a pharmacologist. On the other hand, I am humanistically interested in the history and philosophy of science. It may be that I can combine these interests and say something that will be appropriate on the history and philosophy of physiology or pharmacology (*1*).

Since pharmacology is currently attracting so much attention, what with congressional hearings and spectacular business developments, it would seem appropriate to consider what pharmacology is about. What is the scientific status of pharmacology? What are the characteristic and unique features that distinguish it from other sciences? What are the theoretical concepts on which pharmacology, as a science, may rest? It what ways may pharmacological knowledge be applied in a worth-while way to human welfare?

It is helpful occasionally to examine the basic concepts of an intellectual scientific discipline and to explore its theoretical foundations. This is becoming increasingly important in the biological sciences. Apart from such great theoretical generalizations as the principle of evolution, the biological sciences are not as satisfactorily explored from the standpoint of theoretical background as the physical sciences are. The significance of the theoretical development of the physical sciences is clear when one considers the many dilemmas confronting us in regard to nuclear power. It has been the *applications* of mathematical, physical, and chemical theory which have made possible so much of our current comfort and so many of the conveniences of civilization.

Americans generally seem to be reluctant to undertake basic theoretical studies. However, if we are to maintain any satisfactory world position in the applications of science to human welfare, we must always supply some of the essential theoretical nourishment on which practical applications thrive. The essential food for our very practical culture is scientific theory. So it would seem helpful to give some attention to the theoretical aspects of pharmacology.

Most people who are concerned with pharmacology are interested in it as a practical matter by which new drugs may be developed, some of which may be very important, saving many lives, promoting much health, and incidentally bringing in much money to those who are responsible for the development and use of these drugs. The great drug industry itself might benefit from taking a hard look at some of the theoretical bases on which pharmacology may rest.

In order to assist in an appreciation of the current status of pharmacology, my discussion will deal in turn with its traditional background (protopharmacology), the origin of its fundamental scientific problems, an analysis of the factors influencing the intensity of drug action, and finally a consideration of its practical applications. Apologies are offered in advance for what may seem to be dogmatic assertion on the one hand, or overemphasis of trivialities on the other.

Protopharmacology

Pharmacology is a subject of ancient interest, but it is a relatively new science. Pharmacology is the study of the interaction of chemical agents (drugs) with living material, whether the action is good or bad for the living material, or whether the living material is plant or animal in origin. If the action is harmful to living material, the field of inquiry is called toxicology and the action of the chemical is said to be "toxic."

The Greek-derived term *pharmacology* comes from *pharmacos*—something to be cast out, a harmful thing, a scapegoat—and *logos*—the word, or the truth about, or (as we indicate now) the study of. *Toxikon* means a poison or a poisoned arrow.

These distinctions between the possible useful action of a drug and its possible toxic effect were recognized anciently. Peoples everywhere on earth tried the plant, animal, and mineral materials in their environment for possible use as food, and as a result they noted what the actions of these materials may be. Many observations were also made on what animals eat in their environ-

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ment. In these ways, many of the plant purgatives came into use, as well as natural products for expelling worms, relieving pain, producing exaltation, or treating bruises.

There seem to have been many keen associations in these ancient observations. The old Egyptians, as indicated in the Ebers papyrus, written around 1550 B.C., recommended that moldy bread be applied to skin bruises. It took around 3500 years of social development before penicillin was finally derived from molds.

Folklore about the action of crude drugs has accumulated for centuries. This rough information was applied chiefly to the relief of symptoms of disease. From the medical folklore of all primitive peoples, through the old Egyptian medical papyri, through the magnificent compilation of Nero's surgeon Dioscorides, through the writings of Galen (A.D. 130–200), Avicenna (980–1037), and the medieval compilers, and through the Renaissance herbals and the complexities of the 18th-century pharmacopeias this empirical method continued. It probably began with chance observations on the gross effects of plant, animal, or mineral materials as they may have been tried for food, or as they may have come into contact with the skin. The Ebers, Hearst, London, and Berlin Egyptian medical papyri, dating from around 1500 B.C., contain hundreds of prescriptions which seem to be quite natural applications of such chance observations to the relief of the symptoms of various diseases.

These Egyptian medical papyri represent the earliest compilations of empirically obtained and empirically applied pharmacological knowledge. They are composed on the basis of rough classifications of diseases to be treated, and they recommend prescriptions for such diseases on the assumption that the diagnosis has been made. The folklore of all peoples is rich with similar material, but in comparison with the Egyptian medical papyri, the medical lore of other peoples is not as well organized, codified, or conventionalized, particularly with respect to dosage, to detailed directions for preparation and administration, or to combinations (polypharmacology).

Complex prescriptions containing many ingredients probably developed in the process of compilation and transcription of medical writings when the compiler was trying several materials recommended for the same purpose, with no indication of their relative effectiveness. What would be more natural than to combine them all in the same prescription? This tendency reached its climax among the Arabian compilers of the Middle Ages, such as Avicenna, and the mysterious Mesue, who attempted to condense the vast accumulation of medical recipes from ancient Egypt, the extensive Coptic literature, and the Greco-Roman writers.

On the basis of medical application of the botanical work of Aristotle's pupil Theophrastus (370–286 B.C.), Dioscorides, in Nero's time, originated a different system. This was to describe as carefully as possible the individual crude materials of plant, animal, and mineral origin as used in medicine, so that they might be identified, and then to indicate how each was to be prepared and administered and for what purpose each was to be used. This method of organization, on the basis of the materials used rather than of diseases to be treated, was subsequently followed in the development of modern pharmacopeias. The earlier formulary type of reference continued, however, and is currently exemplified in such a volume as the popular *Merck Manual.*

Pharmacopeias, or reference books of standardized and legally authorized medicinal preparations, arose in the 16th century. They met the obvious need of making uniform the various modifications of the same recipe made by different apothecaries. They thus enabled physicians ordering various formulas to expect some reasonable degree of uniformity in the preparations used, so that there might be some resulting uniformity in the effect produced in response to dosage.

A fundamental problem of pharmacology, the relation of dosage to effect, was thus recognized. This problem was early implicit, especially in poisonous materials. Even though three-fourths of the crude drugs recommended for oral use in the old Ebers medical papyrus were quantitated, no toxic dosages were ever recommended.

As the art of distillation was taken over by the medieval alchemists from the Arabs, the standardization of drugs again became important, in the production of "elixirs"—those pleasant but temporary answers to the pathetic quest for eternal youth. The rebellious Paracelsus (1493–1541) also aided in the development of standardization of drugs by popularizing "tinctures," and by using relatively simple preparations of such substances as sulfur, arsenic, and iron. The intricate letter of the famed anatomist Andreas Vesalius (1514–64) on the "China Root" (1546) was also influential in emphasizing the need for drug regulation and standardization.

The first real pharmacopeia was the formulary authorized by the Senate of the City of Nuremberg. It was compiled by the brilliant youngster Valerius Cordus (1515–44) and was published in 1546. This example was soon followed in other European centers, and physicians were now able to prescribe preparations of uniform composition. The important principle was realized of furnishing a standardized and uniform complex formula under a relatively simple name. By specifying standards for the ingredients and for the methods of compounding, the pharmacopeias made it possible to detect adulteration, and thus to protect on the one hand against ineffective materials and on the other hand against toxic effects from overdosage with unknown amounts of dangerous drugs.

Sporadic experiments began to be made for the purpose of studying the action of drugs on animals. These experiments were usually undertaken to test suspected toxic action. Thus, in 1676 Johannes Wepfer (1620–95) demonstrated nux vomica tetanus in dogs. The introduction of many new and exotic drugs from the New World in the 17th century stimulated much experimentation on crude preparations. The experiments seem chiefly to have been made in order to get some idea as to the possible toxic dosage of such strange drugs as tobacco, nux vomica, ipecac, cinchona bark, and coca leaves.

By the 18th century many such systematic studies were being made. Anton Störk (1731–1803) critically examined the actions of hemlock, stramonium, aconite, and hyoscyamus. An extensive toxicological survey (1765) by Felice Fontana (1730–1805), in which more than 6000 experiments were made, led him to the fundamental opinion that general symptoms of drugs are produced by actions on particular organs. Thus was the way prepared for modern pharmacology.

Development of Pharmacology as a Science

Pharmacology as a significant science could not develop until the rise of modern chemistry at the end of the 18th century, largely under the influ-

ence of the French martyr A. L. Lavoisier (1743–94). By that time it had become possible to obtain pure chemical compounds of unvarying physical-chemical properties. Some could be synthesized by the beginning of the 19th century. Methods then became available for the isolation, in chemically pure form, of biologically active principles from crude drug sources. The contributions of the great 18th- and 19th-century chemists made modern pharmacology possible.

Yet it should be noted that relatively pure inorganic compounds had already been empirically introduced in medical use, especially such saline purgatives as potassium sulfate (Paracelsus) and sodium sulfate (J. R. Glauber, 1604–88). Chemical elements had already been used, as in the remarkable Arab ointment containing mercury which was used for skin conditions and which later became so important in the treatment of syphilis as soon as that scourge was recognized, at the close of the 15th century. Elemental sulfur had also early been used medically.

The credit for being the first to isolate a chemically pure active principle from a crude drug should go to Friederich W. Sertürner (1783–1841). He reported his studies from 1803 to 1817. From opium, the old pain-relieving crude drug, which is the dried latex from excised unripe poppy-seed capsules, Sertürner obtained, by ammonia precipitation, a white crystalline substance which he found to be a powerful pain-relieving and sleep-producing agent. This he named morphine, from Morpheus, the Greco-Roman deity of sleep. By direct experiments in animals and on himself, he found that the new substance is effective in very small dosage. Since he found no other agent in opium which causes the same sleep-producing and pain-relieving effects, he concluded that the valuable medicinal properties of opium are due to the presence of this substance.

Sertürner's discovery stimulated the development of a new scientific approach to pharmacology; with chemicals of constant physical properties available for the first time, dosage could be measured accurately in terms of mass of chemical per mass of living tissue, and the concept of a quantitative relationship between drug dosage and biological effect could be developed. Practically, this is important in medical practice, but physicians were slow to grasp its significance.

In theoretical application, it was

François Magendie (1783–1855), pioneer experimental pharmacologist.

seized upon by the French, probably under the influence of Gay-Lussac (1778–1850) and that handsome and inspiring teacher François Magendie (1783–1855). Within a few years, the latter, with Pierre Pelletier (1788–1842) and J. B. Caventou (1795–1877), had isolated emetine from ipecacuanha root, strychnine from nux vomica bean, and quinine from cinchona bark. Thus, the new and exotic plant remedies from the New World were brought under scientific control in the Old World. Soon Magendie issued a pharmacopeial formulary (Paris, 1821), based entirely on pure chemical agents. Official pharmacopeias slowly followed this example. The useful current *Merck Index* is of this sort.

These same methods of analysis and subsequent critical study were followed with respect to all sorts of crude drugs and are now being extensively applied to the conventionalized crude drug lore of China and India. The distinguished American pharmacologists K. K. Chen and C. F. Schmidt introduced ephedrine from the anciently used Chinese drug mahuang *(Ephedra vulgaris),* for the treatment of asthma. Indian and Swiss pharmacologists introduced reserpine as a tranquilizer from the anciently used serpent root, which even Dioscorides had recommended as a remedy for quieting patients in a frenzy. Currently, also, the intricate complexity of initial crude preparations of "hormones," "vitamins," "enzymes," "coenzymes," and even "viruses" and "genes" are yielding to a similar technique. This will go on to include "vaccines" and other immunological preparations.

A recent dramatic example of the rapid isolation and identification of a biologically active compound from natural sources is afforded by the international study of quinones in electron transport. Enzyme studies on mitochondrial fractions involved in biological oxidation led Wisconsin scientists to discover that these active agents are quinones. Studies in England on coenzyme factors related to vitamins A and K led to the same conclusions. Further fractionization in commercial drug laboratories in Switzerland and the United States showed that these quinone coenzymes have terpene side chains and are found extensively in all kinds of living material. Soon it was recognized that these agents may be involved in photosynthesis. By means of the new techniques of chromatography, spectrophotography, and nuclear magnetic resonance, the specific chemical structure of these compounds was established within 4 years after their existence was first suspected. The one most widely found in nature is appropriately called "ubiquinone," and since it is a coenzyme essential for growth and repair of living material, it is highly likely that appropriate pharmacologic studies will establish clear indications for its possible usefulness in medicine or some other aspect of applied pharmacology.

A notable further development occurred when attempts were made to improve on the naturally occurring materials. These attempts began with the rise of structural organic chemistry. The high price of quinine and the great demand for it in the mid-19th century led to the synthesis of a number of valuable antipyretics and analgesics whose structure was affirmed by the evidence existing for that of quinine. The recognition of Kekule's then newly proposed ring structure in such complex chemicals as quinine and salicin (from willow bark, anciently used in the treatment of arthritis) prepared the way for the synthesis of salicylates. Then the discovery that acetylation of an organic compound would frequently reduce its toxic biological action led to the development of aspirin, the most widely used of all present-day drugs, apart from alcohol.

Willstätter (1872–1942) revealed the chemical structure of cocaine, isolated from coca leaf in 1856 by F. Wöhler and introduced as a local anesthetic by Carl Koller, of Vienna and later of New York, in 1884. Knowledge of the chemical structure of a natural product made possible synthesis for the desired purpose of obtaining substances less toxic and more efficient than the natural product. Cocaine is an excellent local anesthetic, but it produces addiction, as

was so dramatically recognized by the great American surgeon William Halsted (1852–1922) when he became addicted to its use as a result of contact with it in surgical practice and then courageously freed himself from the addiction. Willstätter's work with cocaine made it possible for synthetic organic chemists to make a flood of new local anesthetics less toxic than cocaine, free from its addictive properties, and often more efficient than the parent compound.

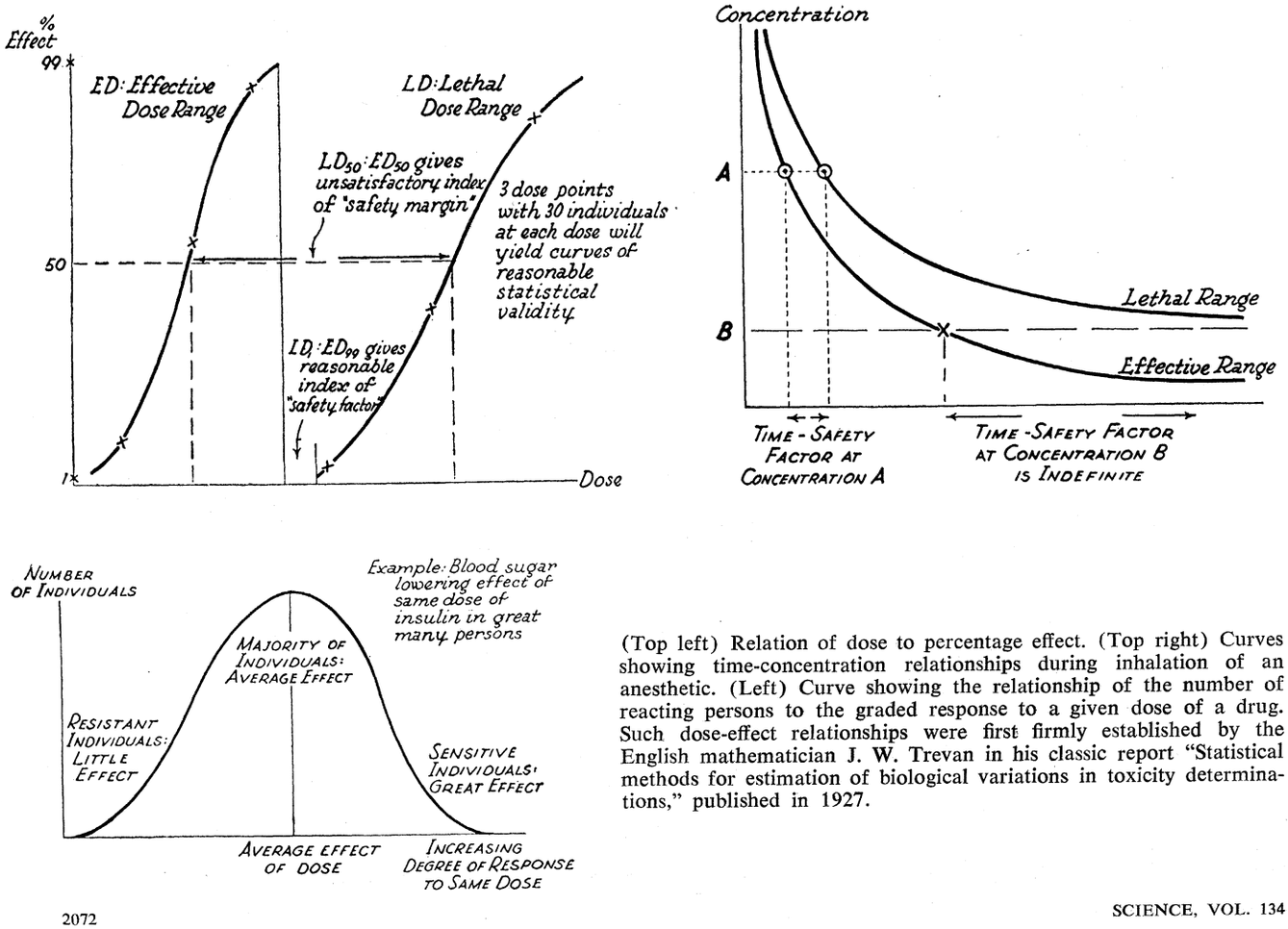
While a consideration of the relationship between chemical constitution and biological action or "biochemorphology," is fundamental in such efforts as these, few satisfactory generalizations or theories have been developed as guides in this field. Results are still achieved by laborious empirical testing of chemical relatives rather than by confident rational prediction of the properties of a specific compound. Nevertheless, there remains hope that such principles may develop; it was possible to predict, by a consideration of chemical and biological properties of related compounds, that the chemical agent divinyl oxide would have value as an inhalation anesthetic agent even before the compound had been prepared or was known.

The steps in a characteristic pharmacological sequence are as follows: (i) the recognition of the biological activity of a crude preparation, from which (ii) the biologically active substance is eventually isolated in chemically pure form, free from all contaminating material, so that its physical properties are constant and determinable; then, (iii) the establishment, painfully, of the chemical structure of the substance; next (iv) the synthesis of its chemical relatives; then, (v) the laborious pharmacological appraisal of all the related compounds; and then finally, (vi) the choice of the one best suited for the particular application one has in mind.

To be applicable to medicine, this pharmacological appraisal must be subject to controlled clinical evaluation, which now includes careful statistical control through the interesting method known as a "double-blind" study. In this, the drug to be tested is compared with some chemical like simple salt or sugar, prepared to taste or look like the drug to be tested; then the drug and the other compound are given to equal numbers of patients with the same disorder, without either the attending physicians, the nurses, or the patients themselves knowing what each patient is getting. With studies of this sort, it is not surprising to get scientific confirmation of the anciently recognized fact that the attitude of physicians toward their patients may profoundly influence the effect of the drugs they use: patients tend to get well with hope and gentle treatment, regardless of the drugs that may be given to them.

Scientific Problems Involving Pharmacology

Gradually the fundamental problems of pharmacology have been recognized and investigated. These are: (i) the relationship between the dosage of the chemical used and the biological effect produced; (ii) the localization of the site of action of chemicals on biological material; (iii) the mechanisms of absorption and distribution of chemicals through living material, and the mechanisms of the metabolism, destruction,



(Top left) Relation of dose to percentage effect. (Top right) Curves showing time-concentration relationships during inhalation of an anesthetic. (Left) Curve showing the relationship of the number of reacting persons to a given dose of a drug. Such dose-effect relationships were first firmly established by the English mathematician J. W. Trevan in his classic report "Statistical methods for estimation of biological variations in toxicity determinations," published in 1927.

or removal of drugs from living material; (iv) the specific mechanism of particular drug action; and (v) the relationship between chemical constitution and biological action.

Dose-Effect Relationships

Even in antiquity it was realized that there is a relationship between the amount of a drug that is given a person and the intensity of its effect. This dose-effect relationship was implicitly sensed for several millennia before any attempt was made to quantitate it. Indeed, the solid establishment of pharmacology as a quantitative science did not come until 1927, when the English mathematician J. W. Trevan (1887–1955) wrote his classic report on "Statistical methods for estimation of biological variations in toxicity determinations." Trevan was a consultant for a well-known drug company in London and had much to do with the development of methods for biological assay and standardization.

Trevan showed that there is a Gaussian distribution of variations in the intensity of response of biological material to a given dosage of a drug, and that if these intensities are summated for increasing dosage in accordance with the percentage of the total number of living specimens responding, the resulting relation is sigmoid if expressed graphically. Many refinements are possible with this sort of graphic representation, but the essential features were established by Trevan and extended by A. J. Clark (1885–1941). Clark not only analyzed various aspects of the dose-effect relationship but also established quantitation in time-concentration relationships. Time is an extremely important biological factor, but it may be neglected unless it is specifically emphasized.

It is rather remarkable that it took so long for a firm scientific basis to be provided for such an ancient idea as the relationship between a dose of a drug and the effect it might produce. There still remain many aspects of dose-effect and time-concentration relationships which are not ordinarily understood by those who may employ chemicals for biological effect (whether physicians, dentists, or members of the other health professions), or by agriculturists, or indeed by scientists in general. The matter is of practical importance when a physician tries to evaluate the relative merits of similar chemical agents which may be recommended for the same purpose. The "safety factor" is involved. The idea is to develop a drug with as wide a spread as possible between the dosage which will produce the effect desired and the dosage which may produce some unwanted, even lethal, effect.

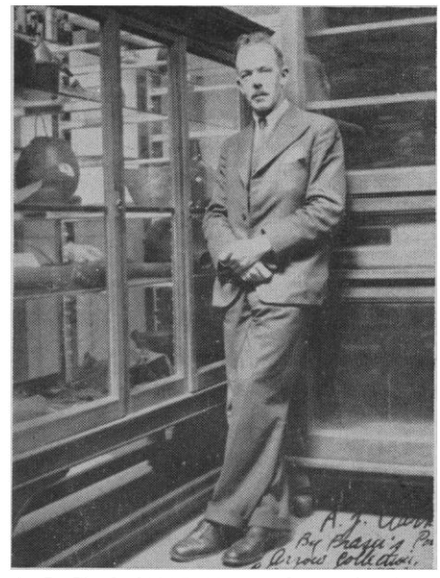
Even for scientific purposes, drugs are frequently compared on the basis of the ratio between the dosage which will produce 50 percent of the effect desired and the dosage which may kill 50 percent of the samples of living material. This is the familiar ratio of ED_{50} to LD_{50}. In a practical way, however, no physician is interested in the dosage which will give the effect he desires in only half his patients, and certainly no physician in his right mind gives a rap about the dosage which will kill half of his patients. Much more significant, practically, is the relationship between ED_{99} and LD_1. However, since this is not as readily obtained by experimental methods, new drugs are often introduced clinically on the basis of a "safety factor" represented by the ratio of ED_{50} to LD_{50}. This is dangerous.

Those who use chemicals to produce an effect on living material are concerned with the factors which determine the intensity of activity. These factors can be expressed in a shorthand manner:

$$I=(f)\ D\frac{rA}{rE},\ P,\ S$$

This statement indicates that the intensity of action of a chemical on biological material is determined by dosage *(D)* in terms of mass of chemical per mass of living material; the ratio of the rate of absorption and distribution of the chemical through the living material *(rA)* to the rate of detoxification or excretion of the chemical from the living material *(rE)*; the physical-chemical properties of the chemical *(P)*, which really determine the activity of the chemical on living material; and then *(S)*, the specific and peculiar characteristics of the living material concerned, including its organizational status (in terms of macromolecules or ecological milieus), its age, its metabolic state, its "allergic" sensitivity, its pathological status, and such integrating factors as enzyme systems, neurohormonal systems, and sex.

It is clear that there may be quite precise quantitation of such factors as dosage, rates of absorption, distribution, detoxification and excretion, and physical-chemical properties. These factors are capable of precise scientific study, with results that may be expressed quantitatively. The product of dosage and the ratio of the rate of absorption and distribution of a drug to the rate of detoxification and excretion will give the concentration of the drug in the living material involved at any specific time after its administration. It is this concentration, with its mass action effect, which is a predominant factor in drug action.

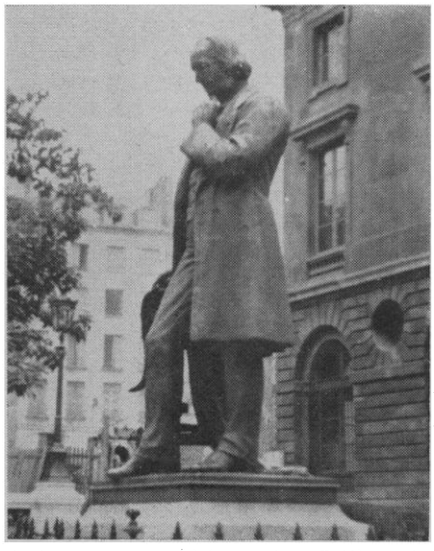


A. J. Clark (1885–1941), pioneer in pharmacological theory. The photograph, taken in Edinburgh in 1938, shows a case of arrow poisons collected by Clark's predecessor, T. R. Fraser.

On the other hand, because of the peculiarities of the specific living material concerned, many judgment factors are involved. The application of pharmacology to medical affairs involves the judgment of the clinician and is a matter of long experience and wisdom. We are beginning to realize that similar judgment factors are involved in applying pharmacological knowledge to such aspects of living material as are involved in social organization or ecological milieus.

Localization of Drug Action

Magendie and his keen pupils in Paris began the study of the localization of the place of activity of newly isolated chemicals in living material. Because of general orientation toward eventual human use, these experimental studies were mostly carried forward on mammals. The study of the localization of the place of action of chemicals in the complex mammalian organism followed naturally from a considera-



A bronze memorial at the Collège de France, Paris, of Claude Bernard (1813–78), pupil of François Magendie and pioneer in the study of mechanisms of drug action. This photograph was taken in 1938; the statue was reputedly melted by the Germans in World War II.

tion of the symptoms of acute poisoning, as suggested experimentally by Fontana with crude drugs. It was promptly extended by J. E. Purkinje (1787–1869) in skillful experiments on himself, and by Claude Bernard (1813–78), Magendie's brilliant pupil. Bernard showed that the exotic Amazonian arrow poison, curare, which paralyzes animals when arrows tipped with it are shot into them, acts by blocking the transmission of the nervous impulse from motor nerves to muscles.

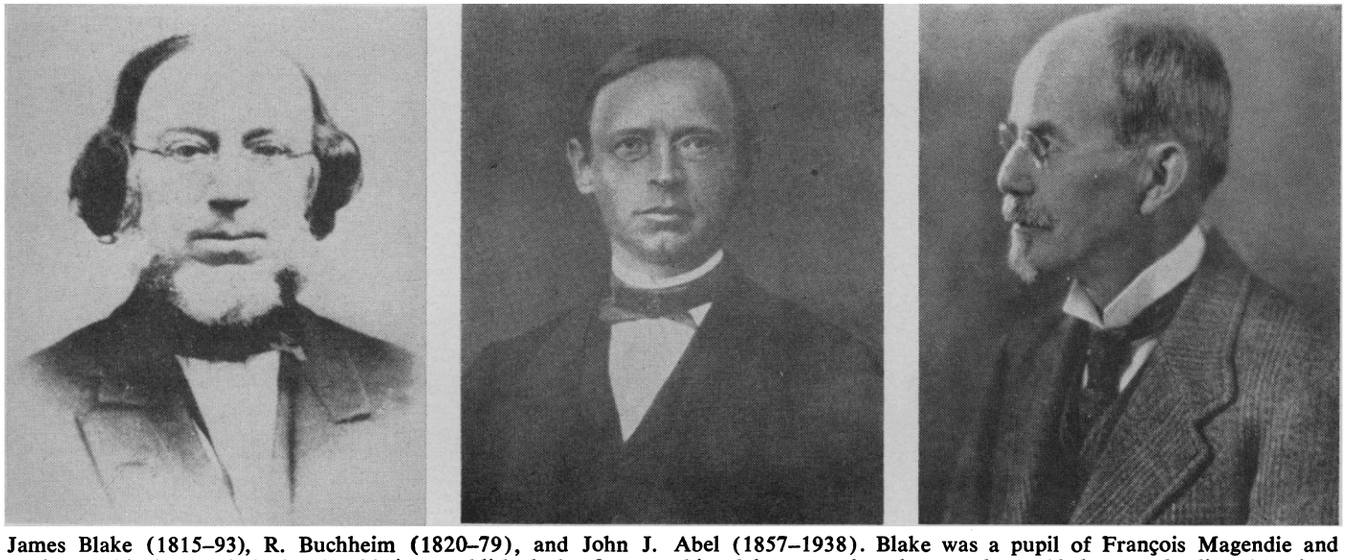
Since cells are considered to be the usual units of living material, and since molecules are taken as the units of chemical agents, it might be thought that pharmacology as a science would be chiefly concerned with the study of the interactions of molecules and cells. Indeed, about three decades ago this approach was carefully explored by A. J. Clark. While his study focused attention on pharmacology as an emerging quantitative science, the approach was clearly unsatisfactory, since molecules of chemical compounds can merely react with molecules of other chemical compounds. Actually, Clark's study showed that the amounts of drugs which are biologically active can be so small in some cases as to provide merely the possibility of activity of a single molecule of the drug on a single small isolated spot on the surface of a cell. These "active patches" have gradually been termed "receptors," and currently there is much study of the chemical characteristics of these highly localized areas on cell surfaces, at which chemical molecules may react. If molecules of drugs penetrate cells, it is to be expected that they will either interact with molecules within the cells, and thus disturb cellular activity, or interact with various aspects of the integrative mechanisms of cells, which probably are physicochemically based, and thus again alter the ordinary activity of the cell. Currently, it is recognized that there is a high degree of specificity of receptor sites on the surfaces of cells.

Drug Absorption and Detoxification

The important pharmacological problem of the mechanisms of absorption and detoxification of drugs was first investigated, in part, by Magendie but was systematically explored by Oswald Schmiedeberg (1838–1921) and J. von Mering (1849–1908). This became the special interest of M. von Nencki (1847–1901), and the study is being well extended currently by many brilliant investigations on pathways of absorption and detoxification. Many of these studies on the changes occurring in the chemical structure of drugs in contact with living material have revealed important metabolic pathways and enzyme systems. Tracing the direct avenue of absorption and metabolism of a drug has been made possible by extensive use of radioactive isotopes in key parts of the drug structure. The difficult matter of explaining how large molecules get inside cells and thus influence cellular activity seems partly to be explained by the process of pinocytosis, or "cell-drinking," as first described by Warren Lewis (1870–).

Mechanisms of Drug Action

Meanwhile, the practical achievements of Crawford Long (1815–78), W. T. G. Morton (1819–68), and J. Y. Simpson (1811–70) in demonstrating successful anesthesia for surgery by the use of ether and chloroform focused attention on the problem of the specific



James Blake (1815–93), R. Buchheim (1820–79), and John J. Abel (1857–1938). Blake was a pupil of François Magendie and a pioneer biochemorphologist. Buchheim established the first teaching laboratory for pharmacology. Abel was a leading American teacher of pharmacology, whose work stimulated the isolation of several biologically active chemicals from crude mammalian glands of internal secretion.

mechanism of particular drug action. This was skillfully probed by Claude Bernard. For many years his correct explanation of the mechanism of action of carbon monoxide on red-blooded animals (in making an irreversible combination with hemoglobin, so that hemoglobin cannot transport oxygen), remained the only successfully solved example in studies of this important scientific question.

At a macromolecular level, drug molecules may act directly with energy exchange, so that if the macromolecules are genes or viruses, mutations may occur. This may be a factor in cancer chemotherapy, whether the mutation be lethal or reversionary to healthy growth. At cellular, tissue, organism, social, or ecological levels of biological organization, introduced chemicals would seem to act chiefly by disturbing some essential aspect of the internal coordinated integration of the system, usually in relation to enzyme patterns, in such a way that the system shows increased or decreased functional activity; decreased activity may result in the disintegration or "death" of the system.

The complexities of mammalian organisms soon made it evident that the mechanism of action of chemicals on living things can more readily be studied on a more uniform population of simpler organisms. The practical importance of antiseptics, which were first tested on bacterial cultures during the latter part of the 19th century, stimulated this development. It has now been extended to tissue culture, with records made by time-lapse movies of the activities of the cells growing in culture under the influence of various introduced chemicals; phase-contrast microscopy is used so that no dyes or other extraneous material need be introduced. Studies of this sort can indeed be quantitated, as my former colleague Charles Pomerat has demonstrated so clearly. It is surprising that the possibilities of using simple plants as pharmacological test objects were so long in being appreciated.

Biochemorphology

The possible relationship between chemical constitution and biological action was first explored by another pupil of Magendie, James Blake (1815–93), that remarkable British nonconformist and pupil of Sharpey and Faraday who became a California pioneer. As a senior medical student, in 1839 he had already shown that drugs act in the mammalian body only after reaching the responsive tissue, and not indirectly by reflex nervous mechanisms. This was part of the problem of considering the absorption and distribution of drugs, and the rates at which these processes may proceed.

In 1841 Blake bravely announced his faith that there must be a relationship between chemical constitution and biological action, and he began to study the relationship by the use of inorganic salts, whose physical-chemical characteristics and structure were much better known than were those of the recently isolated alkaloids. Gross though his studies were, Blake concluded by 1846 that the characteristic pharmacological effect of an inorganic salt is due more to its electropositive ion than to its electronegative one; that there is a relation between the isomorphous properties of elements and the biological action of their compounds; and that with increase of atomic weight in isomorphous groups of elements there is an increase in the intensity of action of corresponding salts. Thus Blake was able to arrange the elements into groups on the basis of the biological effects of their salts. These groups roughly correspond to those of the periodic table, as developed later by the great Russian chemist D. Mendeljeff, although Blake disclaimed any anticipation. Subsequently in California, Blake offered evidence to indicate that molecular vibration rates, which may be correlated with absorption bands in spectrum analysis, may influence the biological activity of inorganic compounds.

Blake's fundamental approach to the relation between chemical constitution and pharmacological action was extended to organic compounds by A. C. Brown (1839–1923) and T. R. Fraser (1841–1920), who showed that various alkaloids with tertiary nitrogen and differing biological actions uniformly acquire a curare-like action through conversion to quaternary ammonium bases. In structure-action relations of organic compounds, some generalizations developed from the studies of B. W. Richardson (1828–96), P. Ehrlich (1854–1915), A. R. Cushny (1866–1926), A. S. Loevenhart (1878–1929), E. Fourneau (1872–1949), and S. Fränkel (1868–1939).

As part of this general problem of biochemorphology, the relation of the physical properties of such substances to their biological effects is also to be considered, as emphasized by Jacques Loeb (1859–1924). Current interest in biochemorphology is greatly stimulated by the discovery of ways and means of reducing the toxicity of existing compounds (as by acetylation of polar radicles) while, at the same time, more sharply developing desired biological effects. These studies have been greatly accelerated by current interest in antibiotics, "tranquilizers," and steroid compounds. F. Schueler is proposing generalized approaches to these matters in his consideration of chemobiodynamics and drug design.

Theoretical Pitfalls in Pharmacology

The first exclusive pharmacological laboratory was operated in the basement of his home in Dorpat, Estonia, by R. Buchheim (1820–79), who also set the conventional tone of pharmacology texts in his 1856 *Lehrbuch,* based on mammalian organ systems. He defined the task of pharmacology as that of first determining at which point in the body a drug may act and then explaining the response on the basis of physical-chemical reactions between the cell constituents and the drug. Since then, many theories of drug action have been proposed without, however, any satisfactory agreement. Thus, there are many different theories of anesthesia, none of which seem adequate to explain the similar effects resulting from so many different kinds of chemical compounds, even including xenon, the chemically inert element. The most refined concepts of physical chemistry may enter into these theories, as is the case with the recent "molecular theory of general anesthesia," proposed by Linus Pauling, in which the anesthetic state is attributed to the formation in the brain of minute hydrate crystals of the clathrate type.

Pharmacology remains chiefly a descriptive science. It is largely a matter of accurate observation and ingenious experimentation, with an analysis of the actions of chemicals on living material in whatever terms are appropriate in current physics, chemistry, and physiology. This follows the procedures established by Buchheim, Schmiedeberg, Fraser, Karl Binz (1832–1913), H. C. Wood (1841–1920), A. Hefter (1859–1925), and John J. Abel (1857–1938) (*1*). The thorough survey of general

pharmacology made so carefully by A. J. Clark indicates the magnitude of the inherent difficulties in pharmacology, which have permitted little more than observational empiricism.

Unfortunately, pharmacology has been so traditionally allied to drug therapy that many fallacious ideas were sure to arise. These, however, are being corrected by statistical methods and "double blind" studies, through new recognition of the ancient principle of the healing power of nature itself and of the faulty reasoning embodied in the phrase *"post hoc ergo propter hoc."*

Again, quite apart from false analogies from drug therapy, there may be errors in interpreting the actions of chemicals in contact with living material on the basis of reactions that may occur in the test tube. When chloral hydrate was first introduced as a depressant drug, it was supposed to exert its narcotic effect by slowly liberating chloroform. Von Mering showed that it is reduced in the body to trichloroethanol, which conjugates with glycuronic acid and is excreted in the urine. The enzymatic mechanisms of these kinds of changes are now being studied.

Pharmacologists remember Ehrlich's disregard of the lack of correlation between in vitro and in vivo effects of drugs: he tried dihydroxyamino arsenobenzene in trypanosome-infected rats and found that it clears the organisms from the blood of the rats, although he knew that it does not kill the trypanosomes in vitro. It was this which suggested to him, with equal lack of direct evidence, that "Salvarsan," the famed "606," might be useful in syphilis, a disease caused by organisms which are only somewhat related to trypanosomes. With something of this same background in mind, my colleagues and I introduced the organic arsenical carbarsone for the effective treatment of amebiasis.

In spite of the rather careful delimiting of the particular scientific problems which differentiate pharmacology from other sciences, it has no characteristic methodology. The isolated perfused mammalian organ technique, used often for bioassay, is essentially a physiological method. Pharmacology is highly empirical and eclectic, using current techniques of biophysics, biochemistry, physiology, and cytology. Much of current interest in molecular biology, so dramatically evolved in genetics, now includes various aspects of pharmacology.

Contrary to frequent sensational news stories, drugs perform no miracles. Drugs can only make living material do more or less what that living material is already capable of doing. The environment of living material can be altered by taking essential chemical factors away from it or by adding abnormal chemical factors to it. Under these circumstances, there may be either increased activity on the part of the living material or decreased activity of the living material, which may go as far as its death.

Significance of Biological Organization Levels

Here it may be appropriate to pause for a moment to consider the significance of a couple of events in that remarkable year of 1847. About the time that Marx and Engels issued their manifesto to the effect that history and economics are explainable in materialistic terms, three young German physiologists, Carl Ludwig (1816–95), Emil Du Bois-Reymond (1818–96), and Hermann von Helmholtz (1821–94) issued a manifesto to the effect that all living processes, including consciousness, are explainable in terms of physics and chemistry. Much evidence has gradually accumulated meanwhile to justify this faith, but another factor, peculiar to living material, raises difficulties.

This factor, the organizational level of living material, was also recognized in 1847, by Rudolf Virchow (1821–1902), who sensed the scope of pathology, the science of disease, as involving deviation in form and function from the norm at cellular, tissue, organism, and social levels of living organization, and founded a great periodical to further this concept. Since then it has slowly been recognized that the characteristics of living material at different organizational levels may vary greatly, so that extrapolation of findings from one level of biological organization to another is precarious.

Meanwhile, we have extended Virchow's concept of organizational levels of biological material at both ends. Life begins with complex macromolecules, such as genes and viruses, and here the principles of physics and chemistry directly apply. Macromolecules may be organized and integrated with many other chemical materials to form cells, which at Virchow's time were thought to be the basic units of life. Cells, however, may be organized into tissues or organs, with specific integrations serving their specific functions. These tissues and organs may further be integrated into organisms, constituting individuals such as human beings. Human beings, and indeed many other organisms, are capable of further integration and organization into societies. These societies in turn may be integrated with a more or less limited ecological environment.

The gamut of biological organization thus runs from macromolecules to ecological milieus. The relatively unknown factor in these various organizational levels is the complex mechanism of integration. Of this we are only currently beginning to get a glimpse, largely by analogy with the techniques developed in cybernetics. Certain it is that chemical agents may produce wholly different results at different organizational levels of biological material. It is clear, for instance, that for amphetamine the effective and lethal dose ranges are quantitatively different at individual and social levels of biological organization. This situation probably exists for many drugs.

Applications of Pharmacological Knowledge

Pharmacology is a rapidly growing science, related to many other biological sciences. Currently, pharmacological studies are adding much excitement to our exploration of the ways in which our brains work. The new field of neuro- and psychopharmacology has blossomed richly as a result of general public acceptance of experimentation on brain activity.

Pharmacology has ties with biophysics, biochemistry, all aspects of physiology, pathology, psychology, and sociology. Like any other biological science, pharmacology is basically dependent upon advances in mathematics, physics, and chemistry.

Pharmacology has direct application in many aspects of professional and vocational endeavor. Its most obvious applications are in the health professions. Historically, pharmacology has long been associated with the medical profession. The obvious applications of pharmacological knowledge occur in the use of drugs to aid (i) in the diagnosis of disease, as in the use of chemicals in functional tests; (ii) in the prevention of disease, as with antiseptics or vitamins; (iii) in the "cure" of disease, as in the removal of infecting parasites by

the chemotherapy of antibiotics; (iv) in the alleviation of the symptoms of disease; and (v) in the promotion of optimum health. The greatest number of drugs are used by physicians for the alleviation of the symptoms of disease.

Similarly, many applications of pharmacology are made in dentistry. Notably, here the local anesthetics are most widely employed. Many drugs of antiseptic action are also used in dentistry, as well as various drugs that have a metabolic effect with respect to the teeth. The current furor over fluoridation of drinking water to prevent dental caries is essentially a pharmacological problem.

Pharmacology may be considered to be the basis for the art of pharmacy. After the biological action of the chemical has been established and some indication has been found for its use, it is up to pharmacists to prepare the chemical in an appropriate way for administration. This is a great and ancient art. It involves considerations of absorption, distribution, and removal of the drug from the body. Many brilliant new advances have been made, particularly in prolongation of absorption, prolongation of action, and promotion of palatability or ease of administration of drugs.

Pharmacology is a necessary part of the nursing profession. All nurses must have information regarding untoward or toxic action of drugs, so as to be able to inform the attending physicians whether or not anything is going wrong in drug medication. Nurses are usually responsible for the administration of drugs in hospitals and should, therefore, have clear knowledge of precise measurement and details of drug administration.

Pharmacology is widely applied in public health, particularly in the control of drinking water and in the mass use of disinfectants for control of infectious disease. The wide use of chemicals in all phases of industry makes it necessary for physicians and public health workers to know a great deal about the toxicity of all kinds of chemicals that may never be developed for specific medical use. It is necessary that this information on toxicity be obtained about all new chemicals in order to protect workers against the dangers of such chemicals if they are used industrially, and to treat such workers, or consumers, if toxic reactions occur.

A broad field for application of pharmacology is maintained in veterinary medicine. This involves not only the control of various diseases in domesticated animals and poultry but also such matters as increasing the rate of growth, modifying sexual development, and even controlling fertility.

Pharmacology is being increasingly applied in agriculture, agronomy, and forestry. Chemicals are being promoted for control of plant growth, whether for pest control or for direct nutrition. Some chemicals so accelerate the rate of growth of plants that they die, and thus these chemicals can be used to eradicate weeds. On the other hand, rate of growth of plants can be increased in such a way as to speed up the use of those plants as food.

By far the greatest use of chemicals in relation to agriculture is in pest control. Often this is directed toward prevention of disease in domesticated animals and humans. There are many effective insecticides as well as rodenticides. Nevertheless, their use always constitutes potential danger to humans as a result of accidental ingestion. Furthermore, the disturbance of the ecological balance in an area by destruction of insects or rodents may have wide-reaching results that are neither anticipated nor desired. Insect and rodent control by means of chemical agents requires great judgment if it is to be satisfactory and free from danger.

The use of chemical warfare agents of various sorts may be considered to be one form of pest control. Again, their use, as in the case of nuclear energy, is fraught with unexpected and often undesired complications and effects. It is unfortunate that general public ignorance of chemical warfare agents, or indeed of the facts on nuclear energy, causes intensive fear and thus lays the basis for mass hysteria.

Chemical warfare not only involves the use of tear gases, irritating vapors, or toxic skin-absorbable poisons, such as were used in World War I, but now includes the possibility of employing highly poisonous "nerve gases" which could be used on civilian populations as well as troops. These "nerve gases" are related to some of the insect toxins, which block the action of acetylcholine esterase, so that symptoms of accumulation of acetylcholine occur. These symptoms may be relieved by high doses of atropine. The extension of chemical warfare agents can go as far as the proposal that volatile tranquilizers be used to take the fight out of large masses of enemy troops or indeed of enemy people.

The applications of pharmacology to sociology are becoming very broad. Here are raised questions as to the ethical use of drugs under various circumstances: Are pain-relieving drugs justified in euthanasia? What is the best way to handle the social aspects of drug addiction? How about the use of drugs for criminal purposes? How far should governments wisely go in controlling the use of drugs, either on an individual basis or under the direction of physicians?

Perhaps the most important application of pharmacological knowledge to social levels of biological organization is that of fertility control. This is particularly important in human societies. Several steroid compounds have now been devised which can control ovulation in women, and it is likely that other chemical compounds may be developed which can control spermatogenesis in men. It is interesting that the steroid compounds controlling ovulation in women can be used both for the purpose of promoting satisfactory ovulation and for the purpose of suppressing it entirely. It now remains to develop these drugs economically in such a way that they may be used on national levels to keep population growth within reasonable bounds, not only for available food supplies but also for satisfying adjustment to land areas.

It has been the very success of applications of scientific knowledge in the control and prevention of disease which has resulted in the current terrifying human population growth all over the world. Also, in association with highly successful applications of scientific knowledge to industry and commerce and with promotion of comfort, convenience, and cleanliness in living, several unexpected and serious difficulties arise, such as extensive pollution of airs and waters, with resulting dangers to human life and welfare. Much of this pollution involves chemicals which may have harmful effects on living material, including humans. These products and effects involve various aspects of toxicology, whether they range from nuclear wastes to combustion fumes or exhausts, or from virus to detergent contamination of drinking and industrial water.

Another serious aspect of our overpopulation problem is the ever-increasing number of old people who are unprepared psychologically, economically, politically, or socially to take care of themselves. Further, there has been no fully satisfactory social means of taking care of them, either. To the often pathetic question of whether or not chem-

icals can maintain youth and bring rejuvenation, the answer so far must be a qualified "no." Chemicals and drugs, however, may help in providing comfort, relaxation, equanimity, and some degree of physical contentment even into advanced old age.

Pharmacology may become increasingly applicable in criminology and in law. This again usually involves some aspect of toxicology, in connection with chemicals or drugs that are used for homicidal or other nefarious or antisocial purposes. By virture of their widespread social use, many drugs, such as alcohol and various addictive drugs, are subject to extensive legal inquiry and well-meaning but often ineffective legal control. Here the psychological aspects of addiction must be better understood by the public generally in order that legal control that will be socially sound and socially effective and acceptable may be provided. Here again, as in many other aspects of the applications of pharmacology and toxicology to human affairs, economic factors intervene and must be considered if satisfactory application of current pharmacological knowledge is to be achieved.

The development of law covering pharmacological and toxicological problems is ancient and significant. The determination of whether or not poisoning has occurred has been a prime legal problem since the Renaissance. Broader aspects of legal control in pharmacology and toxicology concern restrictions on the manufacture, sale, distribution, and adulteration of drugs. It has been proposed that the current problem of "food additives" be handled legally.

While it is not likely that we will be so foolish as to apply pharmacological knowledge to social problems to the extent envisioned by Aldous Huxley in *Brave New World,* the capacity for doing so certainly exists. Fortunately, pharmacological studies on the brain are helping us to understand something of the complex way in which our amazing brains function. This is particularly important to us at this time, when our scientific knowledge of the world about us is increasing so rapidly. This verifiable information about our universe gives us the capacity to control our environment in many surprising ways. Chemicals can play an enormous role in this matter, not only in increasing sources of food for our ballooning populations but also in developing our environments in a manner that may be satisfying for us.

On the other hand, our knowledge of the ways in which our brains function has lagged. It may well be that the pharmacological studies which have resulted in tranquilizers, antidepressant drugs, and psychomimetic compounds are furnishing tools of the utmost importance in the analysis of the complexities of our integrated nervous systems. The more we understand the ways in which our brains work and are conditioned, the better able we may be to understand ourselves and our relation to our environment.

Actually it appears possible that chemicals can be developed which may have an important effect on our individual and thus on our social satisfactions. Pharmacological knowledge is indicating much of significance about the highly complex chemical integration within certain cells of the brain stem where increased activity leads to behavior directed toward self-preservation on the one hand, in the search for food, and to species preservation on the other hand, in the drive for sexual activity. Enhanced activity of these cells seems to be dependent upon the metabolic build-up within them of a considerable complex of many types of chemical agents. When these spill through the cells, depolarization occurs and cellular activity diminishes. This is reflected in the feeling of "satisfaction" which we feel as individuals when we ingest food or when a sexual orgasm occurs. Some tranquilizers, such as reserpine from the anciently used serpent root of India, can bring some of these chemicals, such as 5-hydroxytryptamine, out of the cells, thus depolarizing them and reducing their activity.

It remains for us, as our experience and wisdom and scientific information increase, to apply to ourselves, and thus collectively to the societies in which we live, the knowledge that may help us to adjust more satisfactorily to each other and to our environment. There are thus interesting philosophical overtones to pharmacological study, and they bring in many aspects of the ancient Greek concepts of logics, ethics, and esthetics.

Economic Aspects of Pharmacology

The applications of pharmacology in the health professions and in agriculture have been greatly stimulating to industry and have resulted in a phenomenal growth of drug manufacturing. This in turn has resulted in commercial influences of all sorts in stimulating increased pharmacological research, with further applications toward hoped-for benefits in practical affairs and profit. The remarkable possibilities for chemical manufacture inherent in the close relationships between chemicals used as drugs and those used as explosives or for other industrial purposes was apparent to the highly developed German industry before World War I. Many of the unfortunate characteristics of that development still exist.

There is great interest in our own country in some sort of control over excesses in the food and drug industry. The food and drug industry would be wise to regulate itself in a satisfactory way, so that governmental control would not be necessary. We have altogether too much bureaucracy as it is, and if we are to preserve our standards of individual freedom and responsibility in our social unity, we must do all we can to reduce government control and regulation. Admittedly this is difficult.

The German pharmaceutical industry before World War I learned to take advantage of patent and copyright laws. In most countries patent rights to a product run for a definite number of years, 17 in the case of the United States; on the other hand, copyrights may run indefinitely. This is the case with trade names. The German drug manufacturers learned early to advertise trade names for drugs, so that when patent rights expired and the product came into open competition, physicians would continue to call for the drug under its trade name, because this would be the name they would most easily remember.

As it is, most drug manufacturers now have trade names for the drugs they sell. In addition, there is usually some sort of public name, which represents a generally agreed upon word symbol usually designating some aspect of the chemical make-up of the new drug. The trade name, however, is quite commonly selected from the standpoint of suggesting the use of the drug.

There is great confusion regarding drug names. Some recently introduced drugs may have as many as three or four trade names, as a result of licensing. It would seem that this confusion over names could readily be avoided by general use of the public name for a drug (I have a personal antipathy toward the term *generic name*; this term is a misnomer). Public names could be used with the designation of the company that manufactures the drug after

the public name, so as to identify the product as coming from that manufacturing company. This would certainly guarantee the quality of the product and would help to advertise the position and distinction of the drug manufacturing company. It would seem that drug manufacturers could unite in developing this principle in the use of public names for drugs so as to reduce the appalling confusion now existing in this matter.

When I appeared before the Kefauver Committee in regard to the control of alleged abuses in drug manufacturing and advertising, I recommended that patents on drugs be extended to 25 years, so that the manufacturers could be sure to get a reasonable return on the heavy investments they make on their research and development programs. On the other hand, I proposed that if this were to be the case, then any trademark that might be granted in connection with a new drug be cancelled when the patents expire. I don't know whether this would help or not. There certainly was little interest in the idea!

I have been amused at the specious claims of drug manufacturers with regard to the significance of trade names for drugs as a guarantee of quality. It would seem to me that the public name of the drug, followed by the name of the company which manufacturers it, would give equal assurance of quality.

It does not seem in the public interest to have a lot of unnecessary minor modifications of well-known drugs, all of which have the same general actions, in order to achieve some economic advantage as a result of clever advertising. Nevertheless, this is constantly done. In an authoritarian state, such as Russia, this matter may be handled simply through the authority of some agency in selecting the best drugs available for particular purposes and allowing only those to be manufactured and made available. On the other hand, in Japan any drug, except for certain addictive ones, is readily available for open purchase in drug stores, even including vaccines and antisera for self-immunization. The people of Japan, however, are amazingly sophisticated in regard to matters of health, and the drugs available to them are carefully packaged with full pharmacological information included.

Our economic policies in relation to pharmacology often are in conflict with scientific ideals and tradition. Consider the advertising used with conventional hypocrisy by drug manufacturers in promoting the sale of their special products: in some cases, as in TV commercials on aspirin preparations, it is intellectually disgusting; in others, as in professional journals directed to members of the health professions, it is intellectually insulting. Usually it is not informative but is slickly persuasive, as if physicians were status-seeking housewives.

The economic aspects of pharmacology involve political considerations insofar as legal regulation is concerned. These matters can become extremely confusing and often seem to be tempests in teapots. Many fundamental principles are involved, however, and the economic aspects of pharmacology continually have to be reviewed, particularly by those who are in the actual business of devising and developing new drugs for a particular purpose.

In Prospect

Pharmacology is a broad scientific discipline, closely correlated with all other areas of scientific interest, from astronomy to zoology. It is becoming increasingly dependent upon mathematics, physics, and chemistry, and it is increasingly related to the character of the organizational levels of the biological material with which it deals.

The fundamental scientific problems which differentiate pharmacology from any other scientific discipline are concerned with the interrelations of chemical agents and living material from the standpoint of dosage of the chemical in relation to the effects produced on the biological material; the absorption, distribution, metabolism, and removal of chemicals from living material; the localization of the point of interaction between chemicals and living material; the ways in which chemicals can act upon living material; and the relationships between the physical constitution of chemical compounds and their biological actions. These basic problems of pharmacology were well outlined by the middle of the 19th century, largely under the influence of the great French biological scientist François Magendie.

Pharmacology, however, still remains chiefly an empirical science, in which the analysis of observed phenomena is the basis for study and experimentation. From such analysis it is certain that broad generalizations may emerge which may have significant consequences for related scientific disciplines, particularly biophysics, biochemistry, physiology, histochemistry, pathology, psychology, and by extension, sociology. Pharmacological knowledge is being increasingly applied not only in the health professions but also in agriculture, industry, law, and politics. The applications of pharmacology to practical human affairs frequently result in unforeseen consequences which require careful study and judgment if they are not to prove harmful in the long run to human beings and ecological environments.

Pharmacological knowledge has vastly increased during the past century. It has produced many important chemicals, which have aided materially in the control of disease and in the promotion of optimum health and good living. The increasing applications of pharmacological science may provide increasing advances in long-range human welfare. However, as in the case of other sciences, pharmacology must be well balanced by humanistic considerations: the humanities and the arts give training in judgment, in propriety, and in the fitness of things which are essential for the wise application of scientific knowledge for human benefit.

Pharmacology shares with all the other sciences responsibility for getting at the verifiable truth about ourselves and our environment. Pharmacologists share with all other scientists the responsibility for judging wisely to assure the least possible disturbance of the natural balance of our world, which has taken so many millions of years to evolve. Pharmacology as a science can aid us through its applications, if they are wisely made, to obtain those satisfactions in living which we all crave—satisfactions the drive for which is an inherent part of the built-in make-up of our integrating neurohumoral mechanisms for self-preservation and for the preservation of our human species, with its presumed humanity.

Note

1. In the 114 years of AAAS history, a pharmacologist has held the presidency only once before. This was the revered John Jacob Abel (1877–1938), long professor of pharmacology at Johns Hopkins University, Baltimore. He presided at the June 1932 meeting in Syracuse and at the December 1932 session in Atlantic City. As retiring president he addressed the December 1933 meeting in Boston on "Poisons and disease," in a review of his studies on tetanus toxin.