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SOME CHEMICAL BEARINGS OF PHARMACOLOGY[1]

PROBABLY the best definition of pharmacology is that which describes it as the study of the action of chemical substances upon living things. Pharmacological problems, therefore, fall into three groups, namely, those which relate (1) to the chemical substances (usually drugs or poisons), (2) to the living things (which may be anything from simple cells to highly complex organisms), and (3) to the reaction between the one and the other. Evidently then a pharmacological problem without a chemical bearing must indeed be superficial.

With regard to the problems of the first group—those relating solely to the chemistry of pharmacological agents—I will call your attention to a chemical classification of drugs which appears to differ from any which have previously been suggested. It should be of interest to every chemist desiring to advance our knowledge of drugs. In the following classes are included only substances whose value in the treatment of disease is at present above question, or likely to be soon established. Suggestiveness rather than completeness is the intent of this presentation.

A CLASSIFICATION OF PHARMACOLOGICAL AGENTS ACCORDING TO THE STATE OF PRESENT KNOWLEDGE OF THEIR CHEMISTRY

1. Substances from which no pure chemical principle has as yet been isolated:
   - Pituitary
   - Insulin
   - Secretin
   - Anti-venoms
   - Anti-toxins
2. Substances which contain definitely isolated chemical principles, but which are employed by preference in impure forms empirically found more effective:
   - Digitalis
     - (Digitoxin

[1] An address before the McGill Chemical Society, December 8, 1922.

Digitalin
Digitalein
Digitsaponin)
Vegetable purgatives
Emodin
Chrysophanic acid
Resins

3. Definite chemical entities the details of the structure of which are incompletely known:
Morphine
Quinine
Strychnine
Eserine
Thyroxin

4. Substances of definitely known structural formula:
Simpler compounds
Inorganic
Organic
Natural alkaloids
Animal
Vegetable
Synthetics
Barbitone
Novocaine
Salicylates
Atophan
Phenacetine
Chloramines
Acriflavine
Atoxyl
Salvarsan
"Bayer 205"

In every one of these groups the synthetic chemist should find attractive problems. In the first three these relate evidently to the promotion of the substances to a higher category, especially the fourth. But once a drug has attained the final group the chances are still overwhelmingly against being ideally suited to its purpose, and so the synthetic chemist must consider converting it into something a little different but more perfect. This means cooperation between chemistry and pharmacology.

To better illustrate the nature of the problems involved a number of substances from each of the four classes may be discussed. The first category includes three of animal origin. They are known as "endocrine" substances or "internal secretions" because they are elaborated by some organ of the body, and poured directly into the blood stream. Excess or deficit of endocrine principles means disease. In the latter instance the supply may often be satisfactorily maintained by administration of the required active principle.

The first drug which I have noted is the secretion of a part of the pituitary gland (attached to the center of the lower surface of the brain) which has the power of causing contractions in the muscular walls of many so-called involuntary organs. It is used particularly in obstetrical work for its effect in stimulating contractions of the uterus. A well-known chemical substance exhibiting similar pharmacological characters is histamine, but Abel has recently prepared an extract of the pituitary exhibiting twenty times the strength of histamine.

Insulin is the term applied by Banting, Best and Macleod, of Toronto, to their new pancreatic extract which is unquestionably able to lower the blood sugar content of both normal and diabetic organisms, regardless of how high a place it may ultimately take among the remedies for diabetes. The chemist who first succeeds in identifying the active substance in this preparation will have made a contribution of great value to pharmacology.

Secretin is an extract of the duodenal mucosa which, as Bayliss and Starling show, is normally absorbed into the blood stream and carried to the pancreas, where it stimulates the digestive function of that organ.

Antivenoms and antitoxins present difficulties to the chemist on account of the comparatively small quantities available. Profound effects in the body result from the introduction of solutions which contain but fractions of a milligram of pure principle.

Of the second class of drugs—those yielding unsatisfactory chemical principles, the most important members are the digitalis bodies and some of the vegetable purgatives. Of the former the alcohol-soluble crystalline *digitoxin* exhibits the required therapeutic properties, that is to say strengthening and regularizing the action of the diseased heart, but in its pure form presents undesirable side actions, so that the Galenical preparations, which are of course impure mixtures, are found much more efficient in safe doses.

From the vegetable purgatives such as cascara and rhubarb have been isolated emodin and chrysophanic acid—derivatives of anthraquinone. Other vegetable purgatives contain

definite resinous principles, but here again the crude drugs are preferred, as they delay absorption of these purgative principles from the bowel into the blood stream, and thus prolong their action in the former region where it is desired.

In the third class have lingered for about one hundred years a number of the most important alkaloids. The chemical isolation of these early in the nineteenth century is associated particularly with the names of Pelletier and Sertuerner.

Morphine, quinine, strychnine, eserine and others still defy the structural chemists; witness, for example, the conflicting views of Knorr and Pschorr concerning the first of these alkaloids.

Thyroxin is the second of the endocrine principles to have been isolated chemically; this was brilliantly accomplished in recent years by Kendall. The assigned structural formula has however not yet been substantiated, but the drug appears to be a trihydro, tri-iodo derivative of indol propionic acid. It has a content of about sixty-five per cent. iodine, which element has long been recognized as essential to the action of the thyroid principle, although of itself unavailing. Crude thyroid extract has for thirty years occupied a most prominent place in therapeutics. Its constant use keeps in a normal condition those who are unfortunate enough to exhibit a deficiency in the function of this gland.

The large fourth class contains, of course, all the simpler inorganic and organic drugs. Acids, bases and even elements are used in therapy, as well as ether, chloroform, phenol and numerous other organic chemicals. It is surprising how many of these present new chemical problems for the pharmacologist. Attempts, for example, have been made to prove that certain of the metals should preferably be introduced in the colloidal state. At the present time one hears reports of the possibility of colloidal lead as a cancer cure. Again, pure ether has been called into question in recent years. The so-called "Cotton process" ether has been widely advertised as containing impurities to which the anesthetic effects are really due. Chemically pure ethoxy-ethane, however, has been vindicated within the last year by Drs. Stehle and Bourne both clinically and in our laboratory.

SYNTHETIC DRUGS

The natural alkaloids.—Many of the natural alkaloids can now be imitated synthetically, for example, atropine and cocaine, and among the animal alkaloids, the first endocrine drug to be isolated, adrenaline or epinephrine, a powerful circulatory stimulant and hemostatic. Improvements over the first two alkaloids named are seen in the synthetics homatropine and procaine (novocaine) respectively. Procaine in turn is being replaced for some anesthetic purposes by Hirschfelder's saligenin, an instance of an old chemical adapted to a new use.

Countless other synthetic drugs have been developed. Among the most useful of these are barbitone of the hypnotics, acetyl salicylic-acid (aspirin) of the anti-rheumatics, atophan and phenacetine which resemble aspirin in so far as they possess antipyretic and analgesic properties. Such antiseptics as the chloramines and flavines and such agents as atoxyl and salvarsan suggest most interesting chapters in so-called chemotherapy.[2]

Among the newest of synthetics is "Bayer 205" now widely quoted as having been described in Hamburg as the "key to colonial possessions." Its significance lies in its curative value in tropical "sleeping sickness," in which it is said to exhibit the unusual therapeutic ratio of curative dose to toxic dose of 1 to 60.

The chemistry of pharmacological agents concerns itself further with their fate in the body. Nature's laboratory can transform them in many ways. Oxidations, reductions, decompositions and syntheses of drugs all occur, and the resulting products exhibit sometimes less and sometimes more pharmacological activity than the original substance. Thus the conversion to something else in the body may be essential to bring out the real action of a drug, or the result of the change may be to detoxify, as for example, when an excess of morphine is oxidized in the body.

The second of the three suggested fields of pharmacology embraces the living things upon which the drugs and poisons act. The behavior of living organisms considered apart from drugs pertains especially to the realms of physiology

2 By usage the term "chemotherapy" is generally restricted to the employment of specific etiotropic agents.

and pathology. The chemical viewpoint is continually assuming larger proportions in these fields, and the pharmacologist is continually concerned with their problems.

PHARMACOLOGICAL REACTIONS

Let us pass, however, to our third division which constitutes pharmacology in its restricted sense, and discuss the reactions between chemical agents and living things. *What* are these pharmacological reactions, and *why* do they occur?

To answer the first question one measures the various manifestations of drug action by either chemical, physical or psychological methods. By chemical methods we may determine changes in the carbon dioxide output of the lungs, in the alkali reserve of the blood, or detect the presence of abnormal constituents in the urine, such as sugar or albumen; any of these things may be influenced by drugs. Examples of physical manifestations are seen in changes in the blood pressure, the pulse rate, the size of the pupil, the temperature of the body, and many others. More difficult of exact measurement are those pharmacological actions which are only subjectively appreciated. The psychical effects of caffein, for example, must be tested by the study of the abilities of perception, association, etc. Still more difficult is it to measure the relief of pain, and to decide in which cases this is really due to the action of the drug.

Although to demonstrate the existence of many pharmacological reactions we do not always need to invoke the aid of chemistry, this does become necessary when one approaches the more fundamental question of *why*. The rate and output of the heart are, for example, measured in physical units, but their ultimate basis is chemical or physico-chemical, as are the reactions between drug and cell which may alter them. In the study of these reactions comparatively little progress has been made. One fact, however, concerning changes in function produced by drugs appears to be certain, —they are never qualitative. While we may increase or decrease a cell's normal activity we can not alter its nature. By, however, stimulating certain functions, depressing others coincidently, and leaving still others untouched, drugs and poisons can elicit an endless variety of responses, as seen, for example, in the different types of behavior produced by various convulsants or by narcotics.

In seeking to determine why certain effects are produced by chemical substances, cells and tissues may be removed from the body and investigated while thus isolated, but such methods lead to wrong inferences as to the nature of the reaction *in vivo* unless many of the changed conditions are taken into consideration. Not the least important factor is the rôle of the medium in which the pharmacological agent is dissolved. What happens in an aqueous solution may be very different from the result in the presence of a complex of colloids, salts, etc., such as the blood. One of the chief foundations of pharmacology, therefore, is the chemistry of the blood.

Among the factors concerned in the reaction between drug and cell must be considered changes in osmotic conditions, surface tension, cell permeability, absorption, hydrogen-ion concentration and the like. The mechanism of narcotic action is partially elucidated in many cases by reference to the interesting parallelism between the lipoid-solubility and narcotic effects of a series of anesthetic drugs. But because the cells of the nervous system owing to their lipoid content exhibit an affinity for such drugs, does not tell us why the satisfaction of this affinity should necessarily alter their function. One may conceive of the molecule of chloroform, for instance, binding itself to certain constituents of the cell which normally function by a continual give and take of other substances. When this occurs function would become depressed or cease; but direct evidence in support of this and similar explanations is lacking.

As another example of pharmacological analysis, take the effects of certain poisons upon the heart. Straub has shown that while one of these will act only when a certain amount has penetrated into the interior of the cell, another merely requires contact with the cell surface. The latter appears to enter into no sort of reaction, for it can be recovered practically quantitatively from the fluid leaving the heart. A third poison exhibits its action only while passing in or out of the cell, that is to say, during the period in which chemical equilibrium is being established between the cell and the medium which surrounds it. Again we are at

a loss for definite knowledge of the nature of the reaction between drug and cell.

A few cases seem simpler and are perhaps better understood, among which may be mentioned the combination of pharmacological agents with the hemoglobin of the red blood cell. Ordinarily the hemoglobin carries oxygen in loose combination. When a toxic substance, for example, carbon monoxide, which has a greater affinity for hemoglobin, enters the blood, there is formed the firmer combination known as carbon monoxide-hemoglobin. Oxygen transportation is thus interfered with to an extent which may or may not be compatible with the continuation of life. This will depend upon the percentage of carbon monoxide in the inspired air, and the consequent concentration in the blood. The minimal lethal concentration is, of course, less in rarefied atmospheres where there is less oxygen with which the poisonous gas has to compete.

ANTIPYRETIC DRUGS

The variety in the nature of the chemical bearings of pharmacology may be illustrated further by examples from a single field, that of the action of antipyretic drugs. The term "antipyretic action" was introduced to describe the reduction of fever temperature, but drugs having this capacity, of which we have mentioned the salicylates, atophan and phenacetine, all exhibit to a greater or less extent the property of relieving pain. This analgesic action constitutes their widest field of usefulness today.

To the need of improvement upon most, if not all, of our present synthetics reference has already been made. Among the antipyretics salicylates and atophan in their use in rheumatic fever require doses which sometimes approach the point of toxicity. The ethyl ester of methyl atophan, known as tolysin, appears to remove this objection, for we have found that it is far less toxic. Dr. Lozinsky and I have shown in experiments on dogs as well as in human rheumatic fever that the reason for the comparative safety of this drug is its slow rate of absorption from the intestine. Given over a considerable period of time it is just as efficient as salicylates, and is completely absorbed in therapeutic doses, but when larger amounts are introduced the excess above the therapeutic dose can be largely recovered chemically in the excreta, never having been absorbed by the body at all. This coincidence of therapeutic dosage with the limits of intestinal absorption is a fortunate peculiarity in pharmacological action.

The structure of tolysin is based on the so-called salol principle, the esterification protecting the stomach from the irritating action of carboxylic acid. The dog's stomach is unharmed by doses the aspirin equivalent of which produces serious erosion and ulceration.

FEVER

The mechanism of antipyretic drug action involves a number of problems in our second group. The behavior of living things includes an understanding of the physiology of temperature regulation and the pathology of fever. What are the chemical and other differences between the fevered and the normal organism?

In fever there is an increase in the production of bodily heat; this is paralleled by an increase in the oxidations which, in fact, are usually taken as a measure of the heat production in the body. Increased heat production is not, however, the cause of fever, for far greater increases fail to raise the temperature of a healthy subject. DuBois has recently shown in a variety of clinical fevers that the increase of bodily oxidations corresponds quantitatively to Van't Hoff's law that the velocity of chemical processes increases from two to three times for every 10°C. increase in temperature. The poisons which produce human fevers, whether of bacteriological origin or chemically known substances such as cocaine, do not then accomplish this by increasing the production of heat, but rather by interfering with the mechanism by which heat is eliminated from the body.

This heat-dissipating mechanism has hitherto been considered to depend chiefly upon the shifting of blood from the protected regions of the body to the surface. But in the reaction against a hot environment the blood becomes not merely shifted but diluted, thus affording both a larger surface flow for radiation and more "free" water for evaporation from the lungs and for sweating.

Now in the production of fever these heat-dissipating processes become disturbed, and we are all familiar with the blanching of the skin

due to peripheral vaso-constriction, and the chilly feeling which accompanies a sharp rise in body temperature. These indications of a poor surface flow are associated with a loss of water from the blood, as I have shown particularly in the case of "coli fever" with Dr. Howard, and of cocaine fever with Dr. Moise. The loss of water from the blood may be variously measured, for instance by colorimetric determination of the hemoglobin content, by red blood cell counts, or by weighing blood samples before and after drying to determine the total solids. Certain poorly diffusible dyes may also be injected for the purpose of measuring changes in the water content of the blood. Among other accompaniments of water loss is noted increased blood viscosity.

A further change in the chemistry of the blood in experimental fever has recently been noted by Sansum, who found that the alkali reserve or titration alkalinity of the blood becomes diminished as the temperature rises. One is therefore bound to speculate upon the possibility of water shifting being influenced by the formation of acids in the tissues in connection with the "chill" phenomenon. This and questions relating to the permeability of the cells, and to the rôle of other physical or chemical changes produced by fever poisons afford an untilled field for investigation.

MECHANISM OF ANTIPYRETIC ACTION

To return to the action of antipyretic drugs in fever—this has been investigated both from the point of view of the effects of these drugs upon heat production, and upon heat dissipation. In numerous tests upon fever patients I have found that drug antipyresis is accompanied by only a slight decrease in heat production. The decrease corresponds to the demands of Van't Hoff's law and seems therefore an effect rather than a cause of the temperature fall. Diminished heat production does not then suffice to account for the phenomenon.

Elimination of heat on the other hand was found greatly increased, for example, in the case of aspirin antipyresis. In my experiments the elimination of heat was increased by nearly 40 per cent., its production reduced by less than 4 per cent. The process of dissipation, therefore, is the one which is most affected, and this mechanism is approached, as said, through studies of the circulation.

Nearly every one has witnessed the reddening of the skin and sweating which is associated with antipyretic action, and in this connection Dr. Herrmann and I first showed that antipyretic drugs dilute the blood of the fevered animal coincidently with the reduction in temperature. Evidence of the importance of this increase in the water content of the blood is found in the fact that in healthy subjects equivalent doses of antipyretics will neither reduce the temperature nor dilute the blood.

Having observed some increase in the dextrose content of the blood as a result of antipyretic drug action, and having noted also that dextrose itself may reduce the body temperature, we were led to consider an increase in the osmotic pressure of the blood as possibly responsible for the accumulation of water. This argument was pursued by the injection of dextrose intravenously in normal and in fevered animals. It was found that under the same conditions in which dextrose produced a slight dilution of the blood and no fall in temperature of the normal animal, a marked antipyretic action with rapid and extensive dilution of the blood was seen in the case of fever. Similarly, intravenous injections of acacia were found to reduce the temperature of fevered rabbits and dogs. The question of antipyretic drug action therefore resolves itself into a problem with many chemical bearings, especially that of water shifting and water metabolism in the body.

Before leaving the antipyretic drugs attention may be called to studies which Dr. D. S. Lewis and I made of the mechanism of their analgesic action. Coincident with the relief of headache we have found again a dilution of the blood, which, as stated above, does not occur in normal individuals. Since Cushing, Weed and others have shown that so-called pressure headaches may be relieved by use of concentrated salt solutions, either by mouth or intravenously, apparently withdrawing fluid from the brain in this way, one is led to expect that antipyretic drugs may act in a similar manner.

Sufficient has been said to indicate how superficial our knowledge of drug action still is,

and in how many directions the aid of chemistry must be invoked.

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THE PRESENT SITUATION IN THE RADIUM INDUSTRY[1]

DISCOVERY OF RADIUM

THE discovery of X-ray in 1895 by Roentgen paved the way for the discovery of radioactivity which occurred about a year later. Becquerel, stimulated by the observations of Roentgen, investigated the field of phosphorescent light and found that phosphorescent uranium compounds emitted a type of radiation similar to X-ray in that it traversed material bodies.

This property of uranium salts was later found to be due to the disintegration of the uranium atom and not to phosphorescent light, and this eventually led to the discovery of the entire uranium series consisting of fifteen radioactive elements.

UNITED STATES THE PRINCIPAL PRODUCER IN THE PAST

Although radium has been found in many countries of the world, including Bohemia, Portugal, Australia and England, the United States has been the principal producer.

It has been estimated that 150 grams of radium, costing approximately $20,000,000, have gone into consumption to date in the United States, of which 90 per cent. has come from the carnotite ores of southwestern Colorado and southeastern Utah, which clearly shows the commanding position the American industry has enjoyed. This industry is naturally exceedingly young, not having existed more than fifteen years. During this time about ten domestic companies have engaged in the production and sale of radium. Last year five companies were still operating.

In spite of the youth of the industry, approximately $10,000,000 have been expended by American companies, this capital being entirely represented by mines and plants.

[1] A paper given before a joint meeting of the American Chemical Society, the American Electrochemical Society and the Société de Chimie Industrielle, New York Sections, February 9, 1923.

PROBLEMS OF AMERICAN PRODUCER

American carnotite ore is low grade, running about 2 per cent. uranium oxide content. The deposits, although extensive, are spotty and must be prospected by means of the diamond drill. It is true that the ore occurs near the surface, but after it is mined it has to be hand-sorted, put in canvas bags, packed several miles by mules to a motor truck line, hauled by motor truck to a narrow gauge railroad line, transferred from narrow to standard gauge and transported to Denver. The cost per ton varies between $40 to $70 depending on the location of the ore and on 2 per cent. ore; this means that 98 per cent. of these high freight rates is paid on sandstone.

As ore bodies are widely scattered, and as one pound of acid is required to treat each pound of ore, it would not be profitable either to treat the ore at the mines or to put up a mill for water concentration.

Besides the physical difficulties of prospecting and of transporting the ore to the plant, exceedingly complicated chemical problems are met with in the treatment of the ore, 200 to 400 tons having to be treated to produce one gram of radium. This can be understood when it is remembered that radium is a disintegration product of uranium, there being only one part of radium to 3,200,000 parts of uranium in any ore.

Never a year went by but rumors were circulated of the discovery of rich deposits of radium-bearing ore which would put the American producer out of business and these rumors had to be carefully investigated at heavy expense.

RADIUM IN THE BELGIAN CONGO

Strange to say, during all this time deposits of radium bearing ores, many times as rich as the American carnotite ore, existed in the Belgian Congo.

These ores were discovered in 1913 near Elizabethville in the province of Katanga, in the course of prospecting work which was being done on the Luiswishi copper owned by the Union Miniere de Haut Katanga, a powerful Belgian corporation.

Shortly after the discovery and before any commercial operation of the deposits could be attempted, the war broke out and the Union