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THE STUDY OF THE PHYSIOLOGICAL ACTION OF DRUGS.

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Some years ago I was present when some young officers were being instructed and examined by the adjutant of their regiment. He finally asked "What, in few words, is the object of the education given a soldier?" The answers were varied :—To increase his intelligence, to make him hardy, to render him fearless, to train him in the art of war. But the adjutant still shook his head. At last some one suggested "To enable him to destroy his enemy." "That is correct," replied the instructor. "The aim of the soldier's training, from the goose-step taught the recruit, to the instruction in the higher mathematics given an artillery officer, is—To enable him to destroy his enemy."

Suppose the question put to a number of medical students about to graduate—what is the object of medical education? How should it be answered? Some might reply, "To enable the doctor to earn a living;" some, "To give him a knowledge of life and living things;" some, "To fit him to increase scientific knowledge of disease;" but overwhelming and drowning all such answers would surely come the chorus "To fit him to practice;" "To enable him to destroy his enemy—*disease*." The practice of medicine, the prevention and cure of disease is the aim of medical education, from learning the bones to the study of the science of disease, as expounded by a Virchow, a Pasteur, a Cohnheim or a Koch.

When we consider the simple training of the soldier of olden times, and contrast it with the education which enabled a young officer, by observing the stars, to guide Wolseley's army on a moonless night for seven miles, through the winding depressions of a pathless desert, and bring them, before dawn, straight to the enemy's entrenchments at Tel el Kebir, we realize how complex the art of war has become, and how dependent on many sciences.

As modern warfare differs from ancient, so does modern medicine from that of the Egyptians or Greeks. The fundamental qualities necessary to success in overcoming the enemy—energy, courage, quickness of perception, fertility of resource—remain the same as ever, but the amount of scientific knowledge (and consequently the fighting power) at the disposal of those who contend, either in our ranks or those of a great military organization, are far greater.

As professors of physics and chemistry, and great laboratories for the scientific study of explosive compounds are maintained by the military nations of Europe, in order that the soldier who goes to the front, rifle in hand, shall be better equipped for the conflict—so dissecting rooms and laboratories of physiology, of pathology, of therapeutics exist, that the physician may be aided in his daily struggle against disease.

The main ends sought by those who devote their lives to medical work, I have already described as the *prevention* and the *cure* of disease. If I have chosen for this occasion a topic rather connected with cure than prevention, it is not that I think the latter less important; it is surely the goal which our profession must strive to reach—and it is one concerning which the general public is strangely apathetic, unless during periods of panic when an epidemic threatens. Our profession has done its duty in this matter; it remains for the public to perform its share.

When I consider the vast amount of unselfish effort made by physicians to prevent disease—that the medical men in every community are the leaders in sanitary work—that nevertheless such charges are brought against them by the ignorant as that they advocate vaccination because they are paid for performing it, and think it will increase disease—when I read of the physicians of Marseilles and Naples assaulted by the mob because they were believed to have introduced cholera—yet going steadfastly on their way to help the sufferers, and risking their lives in experiments to discover the cause as well as the means of preventing this plague—then, indeed, I feel (and who amongst you does not?) proud of my profession.

You have asked me to address you, as one concerned rather with the theory than the practice of the medical arts—as one whose relations to our holy warfare is rather that of him who makes cartridges in the arsenal, than of the soldier who handles the gun at the outposts. A chief object of such annual gatherings as this of the Medical and Chirurgical Faculty, is to consider in what directions the sciences and the arts of medicine and surgery have advanced. What the practical value of such advance may be at present—with what hope it cheers us for the future—what department, if any, is lagging behind and should be fostered.

I have selected as my topic *Pharmacology*—that branch of science which is concerned with the investigation of the action of drugs on the healthy body—because I believe that it is destined in the near future, to acquire an importance in regard to therapeutics, which is not yet properly appreciated.

Pharmacology can hardly be said to have existed in ancient medicine, nor indeed until the present century. The first persons to study experimentally the action of drugs appear to have been those who desired to discover a sure poison for their enemies, or a certain antidote for themselves.

The etymology for the word shows that, among the Greeks, medicines were regarded as mysterious things; as substances possessing some magical power, either inherent, or imparted by sorcery. φαρμακος meant to the Greek the use of drugs, potions, or spells. The word φαρμακεια indicated alike a physician, a sorcerer, or a poisoner. To-day we find, even in civilized nations, something of this old notion remaining. Medicine is, to a large extent, still regarded by the laity as a mystic art. Seventh sons of seventh sons advertise in the newspapers (no doubt with profit to themselves), that they are prepared, in return for a few dollars, to exercise their magical power for the cure of disease; and many otherwise intelligent persons are gulled by the jargon of those who describe the supernatural virtues of an infinitesimal dose of some drug, raised to almost omnipotent power by a seventeenth or a seventieth trituration.

The discovery of useful remedies was, in former times, a matter of accident. There was no organized search for them; nor any rational attempt to reach some hypothesis as to the mode of action of drugs, which might give a clue to their usefulness in various pathological conditions.

By multiplied experience the list of medicines was slowly increased. According to Strabo, the Egyptians exposed in the streets persons who were dangerously ill, that passers-by, who had seen some similar case recover, might advise treatment. When we consider how, nowadays, everyone has a sure cure for dyspepsia, which he or she recommends as infallible to each sufferer from that multiform disease, we can picture to ourselves the unhappy condition of those Egyptian patients, that is, if they tried to act in accordance with all the advice given them.

However, after repeated trial some remedies, no doubt, proved useful in certain diseases; and handed down by tradition or recorded by priests, made the beginning of a materia medica. Somewhat later in the world's story, in Greece and Rome, the votive tablets describing their disease and its treatment, placed by grateful patients in certain temples, added to the list of medicines which had been tested and found valuable.

In the centuries of mediæval darkness the Arabs did something to advance pharmacology; the Europeans almost nothing. The Egyptians, the Greeks and the Romans, had been sound in their method, so far as it went. It was empirical. What they had found to do good before they gave again in a similar disease, as we to-day order quinine in intermittent fever, not because of any knowledge or theory as to its mode of action, but because we have found it more often useful than any other medicine in the treatment of this disease.

In the middle ages, this sound, if narrow Hippocratic method was replaced by pseudo-sciences of the most absurd kind. All sorts of fanciful doctrines as to drugs were allowed to determine their administration, quite regardless of observation or experiment as to their effect. Of such doctrine, that of "signatures" may serve as an example. It originated with Paracelsus in the sixteenth century, and had great vogue. According to it, natural objects, especially plants, were given medicinal virtues by the stars; and each bore some mark or signature from which its proper use might be learned. The duty of the physician was to decipher these signatures. Thus the houseleek resembles the gums in the texture of its leaves, hence is a valuable remedy for scurvy; the root of the hedgeturnip is like a swollen foot; a sure sign that it is a cure for dropsy; the eyes on a peacock's tail, resembling the nipple of the female surrounded by its areola, are clearly indicated for diseases of the breast. How wide spread this doctrine was is indicated by the many European plants which owe to it their names, both common and scientific. The lungwort, still known to botanists as *Pulmonaria*, owes its same to the belief that the grayish mottled appearance of its petals (somewhat resembling a tuberculous lung) indicated it as a specific for phthisis; the liverworts or *Hepaticæ* have a peculiarly marked epidermis, which suggests the outlines of the liver lobules, hence were used in liver disease. A species of Aristolochia is still known in England as "*birthwort*." It has a corolla, whose opening suggests the form of the female pudendum when dilated. Infusions or decoctions of it were given with great faith in their efficacy in all cases of labor. To those who objected that experience had proven these plants and animals not to have the virtues attributed them, the advocates of the doctrine of signatures replied that to deny it was to call God a liar—a mode of argument not yet entirely given up by those who would have us read the book of Nature through the spectacles of some preconception, rather than by patient, unbiased, and reverential observation and experiment.

Even at the end of the seventeenth century we find in the London Pharmacopœia, issued by the Royal College of Physicians, such drugs as crab's eyes, pearls, oyster shell, and coral. All of these are of course nothing but somewhat impure calcium carbonate, such action on the body as they may exert being the same as that of chalk. But each one, on account of fantastic notions concerning the animal it was derived from, and the nature of disease, was imagined to have very different therapeutic properties. The doctor who should prescribe crab's eyes when tradition ordered oyster shell, would surely have been held guilty of malpraxis.

Other drugs found in this pharmacopœia are the excrement of mice, of the dog, and of the goose; calculi; moss which had grown on the human skull—clearly a most precious remedy, for even in the edition of 1721, edited by Sir Hans Sloane, and a great improvement on its predecessors, this moss is retained, as also dog's excrement and earthworms.

While physicians believed on mere *a priori* grounds, apart from all serious study of facts or any attempts at experimental investigation, that such drugs had a special and mysterious efficacy in certain diseases; while the therapeutical value of a vegetable preparation was believed to depend largely on whether the leaves had been gathered during the conjunction of Venus and Jupiter; while tradition, not observation, was the basis of medical practice, pharmacology could not be born. Even after Sydenham, the father of modern English and American medicine, had led the way back to Hippocratic methods, pharmacology had still to wait—to wait until chemistry could supply pure drugs, and experimental physiology had taught us how to set about examining their action on various organs and tissues.

Bichat, when he pointed out, early in the present century, that all organs were composed of several tissues, and that some of these might be diseased and others healthy, seems to have also noted that the action of drugs on different tissues and organs needed study. His early death prevented him from undertaking such investigations. The first real pharmacological research was made by his great pupil, Magendie. Its subject was strychnia, and since his work is an excellent example of the investigation of the physiological action of a drug, and as our reasons for prescribing this remedy in certain diseased states and avoiding it in others are based on Magendie's work, I shall give an account of his investigation in some detail. What Magendie actually used was upas, a poison known to cause convulsions and death, and suspected to act on the spinal cord. It was shortly afterwards proved that the active principle of upas was strychnia. To avoid confusion I shall speak as if Magendie had worked with that alkaloid. Magendie's research was undertaken to discover whether this substance could be proved experimentally to have a special affinity for and a specific action on some one organ.

It is almost incredible to us now, that but sixty years ago this had not been proved for a single medicine. That Epsom salts purged and squills caused diuresis was well known, but there had been made no attempt to ascertain the method of action of either. The knowledge now at the physician's disposal, which enables him to select a purgative or a diuretic according to the pathological state of his patient, was entirely wanting. The reasons which to-day guide us to choose digitalis as a diuretic in some cases of dropsy, and squills or nitrous ether in others, did not exist.

Magendie's plan* was very simple. It was not exactly the method which we would now employ as regards details, but it was the same in principle. The symptoms of upas poisoning indicated that the drug acted primarily on the spinal cord. This he tested by administering it under conditions which allowed it to reach quickly all organs of the body except the spinal cord. The result was that convulsions did not occur until sufficient time had elapsed for the poison to be carried by the blood to the cord, but then they appeared. Next he applied the poison to the spinal cord alone; this caused

*Lauder Brunton, Pharmacology and Therapeutics, page 74.

convulsions almost at once, but first of all in the regions of the body supplied by nerves arising from the segment of the spinal cord on which the upas was placed. Next he gave the poison after destroying the spinal cord, and found that no convulsions resulted. Finally, he administered it and, after convulsions had commenced, gradually destroyed the spinal marrow from above down. As this was done the tetanus disappeared, first in the fore limbs and anterior regions of the trunk, then in the belly muscles, finally in those of the hind legs and tail. When the whole cord was destroyed all the convulsions ceased. Magendie concluded that upas was a spinal excitant, a conclusion which subsequent investigation has abundantly confirmed.

His next idea was that practical medicine might be aided by a drug which was a specific stimulant of the spinal cord, for, as he points out, many serious diseases are due to defective activity of that organ. But unfortunately upas was not an article of commerce, and should it be found a valuable therapeutic agent there still remained the problem, How to get it?

This problem Magendie tried to answer by investigating the physiological action of extract of *nux vomica*, a plant belonging to the same natural order as the upas tree, and readily purchasable.

He found this extract to act exactly like the upas, and it consequently came to be used in certain cases of paralysis, especially in cases of what we would now name defective reflex excitability.

Fonguier, incited by Magendie's discovery, appears to have been the first to use the new medicine in such diseases. Magendie afterwards prescribed it with benefit to his own patients; and it is now recognized as one of our most valuable therapeutic agents.

To-day we order strychnia, the active principle, rather than the crude drug, but our knowledge of its activity and our ability to select the cases in which its administration is advisable, are due to Magendie's research.

From strychnia, the most potent exaltant of reflex excitability, let us pass on to consider briefly *chloral*, a powerful depressant.

In this valuable, though in the hands of the laity often abused, medicine we have a remedy which we owe entirely to scientific research. It is no "simple," no plant or mineral which any one might gather, and test as to its effects on human diseases. It is an artificial product created by the chemist, and its introduction to the pharmacopœia was not due to any random attempts to discover whether it might have some physiological activity, but to knowledge of its chemical reactions.

When Liebig, in 1830, prepared the first chloral, he was engaged on a purely chemical research, and had no thought of producing a useful medicine. The hydrate of chloral was soon after discovered, but like chloral itself remained for years merely a chemical curiosity. The sole interest and importance of chloral depended on the fact that it was an aldehyde in which three atoms of hydrogen were replaced by three atoms of chlorine; and on the light thus thrown on the chemical architecture of ethylic alcohol and its derivatives and allies.

As the chemists continued their work on chloral, seeking to unravel its molecular structure, it was discovered that when treated with alkalies it broke up into formic acid and chloroform. Physiological research having already proved that the circulating blood is feebly alkaline, it occurred to Liebreich thirty years after the discovery of chloral, that this substance might be of therapeutic value: that by slowly giving off chloroform in the blood, it might act as a safe anæsthetic; and in cases where thorough anæsthetism was not desired, might be useful in producing sleep. This was first tested on the lower animals and the efficacy and safety of the drug being demonstrated on them, it was next administered to human beings, with what success you know.

Although it has now been ascertained that chloral hydrate does not split up in the blood as Liebreich supposed it might do, but circulates and acts as chloral, yet the fact remains that we owe our knowledge of its therapeutic value to scientific experiment.

What that value is may be stated in the words of Koehler: "Like opium, chloral hydrate is, and will continue, an indispensable agent for therapeutists of all future time."

Interesting as is the history of strychnine and chloral, still more so is that of *amyl nitrite*, a drug not yet officinal, but now being born, if I may use such a metaphor. The chemist has discovered it; the physiologist and pharmacologist have experimented with it; and now the practising physician is testing it clinically. Whatever his ultimate decision be as to its greater or less value, its story serves well to illustrate how a new remedy is discovered, and how many sciences cooperate to add to the physician's armament.

More than forty years ago certain proprietors of vineyards in the south of France found that the brandy distilled from the "*marc*," the crushed residue of grapes whose juice had been expressed for wine making, had sometimes an unpleasant taste, which greatly diminished its market value. This taste was found to be due to a greasy liquid, named *oil of marc.* They collected some of this oil and sent it to Balard, then professor of chemistry in the Faculty of Sciences of Paris, asking him to study it, with the hope of learning how it might be separated from the brandy. The substance was already known to chemists but was difficult to obtain. Hence Balard eagerly agreed to the request; to quote his words, "I assented very readily to this proposition because it offered, for myself, an opportunity to obtain materials for a purely scientific research, and for those who asked my advice, some chance to improve the quality of a product which was the principal source of wealth in these districts."

On examining the "oil of marc" Balard found that its chief constituent was a substance already described by Dumas as *potato oil.* He soon arrived at the conclusion that it was an alcohol; but before his results where published this fact was discovered and announced by Cahours, who named the substance *amylic alcohol.* Cahours however did not go farther with its study, and so Balard took it up again: he examined the compounds which it might form and, to still further elucidate its nature, the action upon it of oxidising agents; among these nitric acid naturally found a place. The combined action of nitric acid and heat gave rise to an ether, entirely analogous to the well known nitrous ether produced in like way from common alcohol, but with amyl instead of ethyl as its radicle. This substance was what we now name nitrite of amyl, and its discovery was announced by Balard in 1844. It remained for years something that merely interested chemists as throwing light on the nature and constitution of alcohols, as no one thought of testing it as a therapeutic agent.

In 1852 Claude Bernard discovered that section of the cervical sympathetic was followed by rise of temparature and dilatation of the blood vessels on the same side of the head, and, following up this discovery, Brown-Sequard demonstrated that irritation of the sympathetic caused vascular constriction. Thus the vascular nerves were discovered; an advance in our knowledge of the physiology of the circulation second only to Harvey's great work.

Bit by bit the functions of the vaso-motor system were ascertained. Its main nerve centre was located in the *medulla oblongata*, and it was found that in a variety of ways this centre could be aroused to abnormal activity; that if irritated it might so excite the nerves of the vessels as to cause extreme contraction of the muscular coats of the arterioles, and thus oppose great resistance to the flow of blood through them: in this way enormously raising aortic pressure and putting a great strain on the left ventricle of the heart. It was also demonstrated that destruction of the vaso-motor centre or section of the spinal cord (which put most vascular areas in the body beyond its control) was followed by dilatation of the arteries and a great fall in blood pressure. Thus we came to know that the nervous system and the muscular coats of the arteries played an active part in controlling the blood supply to various regions of the body; and that congestion or anæmia of any organ not only might be, but in most cases is due rather to abnormal activity of nerves or blood vessels, than to changes in the work done by the heart. This fruitful idea was, of course, soon seized by pathologists and applied in many cases with good results, to clearing our conceptions of diseases dependent on local vascular spasm or paralysis.

Years passed by and no one suggested that there might be a disease whose essential symptom was a convulsive activity, an epileptic fit, of the muscles of the arterioles in general.

In 1859, Guthrie* observed that amyl nitrite, when inhaled, caused flushing of the face, throbbing of the carotids, and a quickened heart-beat. Some years later (1865) Richardson called attention to this substance, as an agent which might be useful, from its power of causing dilatation of the smaller arteries and capillaries.

Next Gamgee discovered by experiment on animals, that nitrite of amyl reduced arterial pressure to a remarkable extent, and Lauder Brunton, assisting at some of Gamgee's experiments, had this fact impressed on his mind.

So far we have chemistry, physiology, and pharmacology cooperating; but to give us a therapeutic result pathology was needed.

Brunton lived day and night with a victim of *angina pectoris:* baffled and irritated by his ignorance of the nature of the disease, he strove in every way to get a knowledge of the proximate cause of its frightful symptoms. Marey had invented the sphygmograph for the purely physological end of ascertaining the mode in which the blood flowed through the arteries but it had been learned that this instrument could also afford information regarding intra-arterial pressure.

*Journ. Chem. Society. 1859.

Brunton, making use of the sphygmograph found that during a spasm of breast pang the intra-arterial tension was greatly increased; increased so much that the anguish of his patient might well be due to the resistance opposed to the systole of the left ventricle of the heart. Pondering on this fact it occurred to him that the agony should, then, be relieved if the smaller arteries could be dilated. Brandy, ether, chloroform, ammonia, and other remedies had been used over and over again in similar cases and with little benefit. He thought of Gamgee's experiments with amyl nitrite, and his chief in the Edinburgh Infirmary, Dr. Hughes Bennett, gave him permission to try it; the result stated in his own words was,* "my hopes were completely fulfilled. On pouring from five to ten drops of the nitrite on a cloth and giving it to the patient to inhale, the physiological action took place in from thirty to sixty seconds, and simultaneously with the flushing of the face the pain entirely disappeared. * * * Occasionally it began to return about five minutes after its first disappearance; but on giving a few drops more it again disappeared and did not return."

The subsequent pharmacological researches of Brunton, of Wood, of Amez Dioz have justified the therapeutic conception which led to the first administration of amyl nitrite; and have suggested its use, with good results, in other diseases whose prominent symptom is vaso-motor convulsions.

Although it may and does fail in certain cases, there still remains the fact that many men and women who lived in terror, never knowing when a spasm of angina pectoris might agonize them, now go about their daily duties in peace, because they carry with them a tiny phial of amyl nitrite. To quote the words of Wood, "it seems useless to speculate how the nitrite acts in many cases; but there is now abundant evidence of its value in relieving, almost instantly, agony which has resisted all other treatment."

I should only weary you were I to repeat the story of other valuable additions to the materia medica due to pharmacological and physiological research; it would be to most of you but an old tale. It is, moreover, hardly necessary to point out that the story of the past, thoughtfully read, is the safest guide for the future. When, bearing this story in mind, we think also of the activity of modern chemistry, especially on its synthetic side, and realize that almost daily there are created in the chemical laboratories of the world new compounds, whose action on the animal body may be as potent, and,

*Lancet, 1867. Vol. II. p. 98.

in disease, as beneficial as that of chloral or strychnia; and that not one in a hundred of such compounds is now tested as to its possible therapeutic value; when we bear, I say, all these facts in mind, can there be any among us who does not feel eager to encourage and promote pharmacological research?

There are at present a small number of laboratories devoted entirely to such work on the continent of Europe; not one, I think, in the United States. Such investigations are of course often made here in physiological laboratories, but usually as a secondary matter and for purposes with no direct therapeutic end in view. I believe that as regards the advancement of medical art, there is nothing at present more desirable than an increase of well-equipped workshops, in which men already trained in chemistry, in physiology, in pathology, shall investigate the action of substances, with a view to discover whether they may be useful as medicines, and in what pathological conditions they may be rationally expected to prove of benefit.

Pharmacology depends on experiments on living animals. The whole history of the materia medica teaches that until such experiments were systematically made, drugs were selected and prescribed in accordance with erroneous and often fanciful notions. Its history also teaches that the action of no substance can be discovered by *a priori* reasoning. The attempt to do so leads only to such absurdities as the doctrine of signatures. The art of medicine advances by observation and experiment, rarely by accident.

Are we to experiment in the first case on men and women, or on the lower animals? It is incomprehensible that any one should hesitate as to the answer!

Test the new substance on the frog, on the rabbit, on the dog; and when we have thus gained a knowledge of the organs on which it acts and the mode in which it affects them, then, but not till then, try it on man. Repeated experience has taught us that in the vast majority of cases we may argue with much certainty from the influence of drugs on lower animals to their effect on human beings; therefore, we refuse to test first on man or woman a new remedy, though even the Bishop of Oxford and the editor of the Spectator protest that we have no right to sacrifice frogs or rabbits for the promotion of human welfare. To the physician, the preservation of human life is the most sacred of all duties. It is one to which all sentiments must yield, save those of truth and honor!

There is one great fallacy which invalidates most of the reasoning of the anti-vivisectionists. They assume that physical pain is the greatest of evils. Some of the more extreme among them maintain that we have no right to kill a dog to save a man's life! These need no answer; they belong to the great army of "cranks," and the common sense of mankind will render them harmless. By the remainder, those who dispute our right to make man happier at the expense of lower animals, the question is not stated so plainly. They maintain that we may not hurt an animal in order that we may save man from pain. Were this a fair and full statement of the case, some of us might hesitate before dissenting from their view of the matter. There *are* men in the world whose sufferings I might rather witness than inflict the same on a dog. But physical pain is, after all, a relatively trivial matter; it is disagreeable, and it is one of our greatest rewards to be able in many cases to remove or alleviate it; but it is by no means the worst of ills. Many persons gladly submit to it for some mere gain in personal appearance, as the removal of supernumerary hairs from the face, or the extraction of an unsightly tooth. Not merely do men and women themselves undergo very severe pain for such purposes, but they cause their children to submit to it; thus emphasizing their conviction that there are things much worse than physical suffering.

It is not mere physical suffering that we labor to diminish. We labor to save *life—human life* with all its ties. Were I to see a man tortured with facial neuralgia, and knew that I could relieve him by inflicting equal pain on a dog or horse, I hardly know what my decision would be. I suppose I should decide in favor of the man. But that is not the question which faces our profession in regard to experiments on animals; it is how we may better our knowledge and increase our power to save the life of husband and father—of wife and mother—of the child in whose life the hearts and hopes of its parents are bound.

Certain of our opponents have their sympathies greatly excited by the occasional cry of a dog enduring pain from pharmacological experiment. Have they listened to the wail of the new-made widow? Some of them use their fiercest invective to calumniate those who have kept animals alive a few days after an experiment, that the causation of disease may be better understood and its prevention made possible. Have they realized the years of penury and misery too often the lot of the orphan? They have not felt personal responsibility for the life of the bread-winner, or they would surely say with us, kill a hundred, kill a thousand animals if you have any reasonable hope of thereby preserving to one wife her husband; to one child its mother.

The history of experimental pharmacology teaches us that we have abundant ground for such hope.

No doubt many of you have sat up all night with a patient dying of tetanus—have seen convulsion follow convulsion and feared each one would be the last, yet almost hoped so, that the suffering might end. I shall never forget the night I spent by such a bedside. Harrowed by the agony before me, convinced that abnormal excitability of the gray matter of the spinal cord was its cause; certain that there was some drug, if I only knew it, which could act specifically on the nerve cells of this gray matter, and paralyze them long enough to give the system a chance to overcome the disease: reduced to despair, and suffering perhaps as much as the patient before me, from the torturing consciousness of my ignorant impotence—I felt then and feel now that this man's life should have been spared to his wife and children. We knew what the disease was; more earnest pharmacological research could and would have taught its cure.

As we look around, we see the fields white for the harvest! Is life or death to reap them? Truly the laborers are few, and if we toil not day and night to increase our knowledge and power to prevent and heal disease, the crop will nevertheless be garnered; a ghastly reaper who gathers where he has not strewn will be tirelessly at work; and his name is—premature death.

To those who impede our work we answer: look around you and see the daily suffering due to disease. We are striving, and with greater success each year, to control and to diminish it; you can help us if you will; you can use your influence to ensure that sanitary laws be known and obeyed; that the hungry child has wholesome food; that the laborer shall not arise each morning so enervated by sleeping in an over-crowded room as to be driven to drink.

When through your efforts in such directions, supplemented by our investigations, it comes to pass that human disease no longer exists, and death is known only as the result of accident or old age, *then* we may listen to you if you ask us not to experiment on the lower animals. Until then we close our ears to your protests and, looking neither to the right nor left, press onward!