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ARTHUR ROBERTSON CUSHNY AND PHARMACOLOGY

ON the evening of February twenty-fifth Arthur Robertson Cushny, apparently in robust health, was stricken down at the comparatively early age of sixty by a rapidly fatal cerebral hemorrhage. He was the fourth son of the late Reverend John Cushny, of Speymouth, Morayshire, Scotland, and was educated at Aberdeen University where he graduated M.A. in 1886 and bachelor of medicine and master of surgery in 1889. In the autumn of that year, having won the Thompson fellowship, he entered at Berne the laboratory of the physiologist, Hugo Kronecker, a former assistant of the great physiologist, Carl Ludwig, of Leipzig, for a year's further training in the methods of physiological research. I also had gone to Berne, to work in the laboratory of the distinguished biochemist, v. Nencki. The laboratories in which we two worked were far apart, that of Kronecker being distant from the medical quarter, and so we became barely acquainted in that year. Little did either of us foresee in those days that the future would bind us closely together and that both of us would take up pharmacology as our life work. After his year with Kronecker, Cushny went to Strassburg for a year's work with Oswald Schmiedeberg, at that time the outstanding figure of pharmacology in Europe. After a year's work at Strassburg young Cushny was appointed to an assistantship (1892–93) in the laboratory of Schmiedeberg. This eminent scientist, trained in physiology in the school of Ludwig, as also in the chemical laboratories, had early won the esteem of Ludwig by his masterly analysis in 1870, in the Leipzig laboratory, of the action of muscarine and nicotine on the nervous elements of the amphibian heart. Once on my alluding to Schmiedeberg's newly published "Grundriss der Arzneimittellehre" Ludwig summed up the man in the words, "Ach, der Schmiedeberg, das its ein Genie." It was he more than any other one man, who following in the footsteps of his teacher Buchheim, at Dorpat, turned the age-old materia medica and therapeutics of our medical schools into the modern and fundamental science of pharmacology. The development of this science is intimately connected with that of physiology and chemistry, but here reference can only be made to its connection with the former science. The experiments of Magendie, of Johannes Müller and later of Tiedemann, Gmelin, Bernard and many others, although undertaken to elucidate physiological problems, really laid the foun-

dation of pharmacology. Even as long ago as 1813 Magendie had found that the blood has the power of taking up and carrying metallic poisons, and by the middle of the century the doctrine of the "action of poisons by sympathy" had received its death blow. About the middle of the century, too, the now classic experiments of Claude Bernard and Köllicker, proving that the paralyzing action of curari centers in the end plates of the motor nerves, called attention to the value of toxic substances in physiological analysis. In the sixties and seventies there followed a succession of important discoveries by pharmacologists and physiologists in relation to the physiological action of important alkaloids, such as atropine, pilocarpine and many other substances, on the various organs of the body.

It was such experiments as these that induced Buchheim and others to insist on the insufficiency of the mere bedside study of medicines, and led to the erection of special pharmacological laboratories in which experimenters can build up their science, undisturbed by the intrusive demands of practical utility. Applied pharmacology or practical therapeutics as distinguished from a laboratory science must be the concern of men with bedside training and experience, and in many universities, more especially in England, we find professors of therapeutics on the same faculty with pharmacologists. The first laboratory devoted especially to pharmacology anywhere in the world was that of Buchheim in Dorpat in the early fifties. This graduate of Leipzig (1845), a pupil and assistant of the famous anatomist-physiologist, Wilhelm Weber, at Leipzig, was given the very inclusive chair of materia medica, dietetics, history of medicine and medical literature at Dorpat in 1849.

In the early eighties many young men, who were not consciously planning to become pharmacologists, entered the laboratory of Schmiedeberg not only because he was known to be a sound physiologist in all questions pertaining to the action of chemical substances in the animal economy (pharmacology) and a master of chemical and biochemical technique, but also because of his many notable discoveries in biochemistry. We were filled with admiration over the steady stream of important researches that emanated from him and his pupils. There were the various digitalis and other glucosides, muscarine, and various alkaloids that had been disentangled from unpromising mixtures, there were the researches made by perfusing organs or treating minced tisues with simple well-known chemical substances such as benzoic acid, benzyl alcohol and salicylic aldehyde that were published under the title "Oxidations, Cleavage and Synthesis in the Animal Organism," and many additional papers on these subjects by his pupils. The first clear proof, for example, that oxidations and syntheses in the animal organism are effected by soluble ferments was brought out under Schmiedeberg's leadership. Small wonder, then, that Cushny also sought out this man for inspiration and further training.

The next step in Cushny's career takes us to Ann Arbor. In the spring of 1893 I accepted the chair of pharmacology in the Johns Hopkins Medical School and in June when I left Ann Arbor to spend the summer in work at Berne, Dr. V. C. Vaughan, then the dean of the school at Ann Arbor, with the sanction of his medical faculty, commissioned me to find in Europe a pharmacologist to take the full-time post at Ann Arbor which I had just resigned. My thoughts at once turned to young Cushny. On arriving at Strassburg and after consulting with the old master discussion and persuasion began. Cushny had planned to return to England for a medical career of combined research, consultation and hospital work, something like that of the late Sir Lauder Brunton, then at the height of his fame. Schmiedeberg and Brunton had known each other in their early days, with Ludwig, I think, but the former always deplored the loss to pharmacology when Brunton was forced by circumstances to devote himself to practice. He remarked once, waving his hand in characteristic fashion, "Der Brunton hätte schöne Sachen machen können."

In urging Cushny to try a full-time post in pharmacology I pointed out to him that he could return to England in a year or two in case a life devoted entirely to teaching and research failed to satisfy him. It was with keen pleasure that I was able to cable Dr. Vaughan on the evening of my second day at Strassburg that Cushny would go to Ann Arbor. And so the young Aberdonian of twenty-seven, who was later to attain an almost unrivalled position in physiological pharmacology, came to this country and gave it twelve fruitful years full of inspiration to others. It was at the University of Michigan that he brought out in 1899 the first edition of his masterly and comprehensive treatise on pharmacology with the subtitle, "The Action of Drugs in Health and Disease." The treatise was built on the general plan of Schmiedeberg's "Grundriss," but with more detail and with more attention to the therapeutic neeeds of the physician and with such alterations in the Buchheim-Schmiedeberg classification of drugs as are inevitably induced by the personal equation. It was dedicated: "Dem Meister, vom Schülergewidmet." It was the first severely critical, rigorously scientific and hence really authoritative general text-book to be written in English by an experimental pharmacologist. In a critical review of the fourth edition of this work in 1906, I wrote:

> To undertake the task of writing a comprehensive treatise on pharmacology calls for courage; actually to

complete the enterprise requires also sound judgment, industry and learning. No teacher can read the articles on the action of alcohol, ether and chloroform, to cite only a few examples, without a feeling of gratitude toward Professor Cushny for presenting to medical students so good a digest of these topics. There is every evidence throughout the book that its presentations are based on first-hand knowledge of original papers and monographs of importance. More than this, Cushny's activity as an investigator has qualified him in an eminent degree to sift the wheat from the chaff.

The work is now in its eighth edition and it is not too much to say that it has had an enormous influence on the development of pharmacology in the English-speaking world.

Cushny, however, was not content with writing a notable text-book. To him was also given the power of being able to bring out from the darkness of the unknown new facts of great importance and correlating them with existing knowledge. While thoroughly appreciating the importance of the chemical side of pharmacology and familiar with its achievements he elected, in consequence, no doubt, of his early training at Aberdeen and Berne, and wisely, as the future showed, to devote himself to the physiological and clinical aspects of the science. Succinctly stated, his discoveries lie in the domain of the action of drugs and other chemical substances on the organs of the body, and they have become, almost without exception, of prime importance for the physiological and medical sciences. Already at Strassburg, stimulated by Schmiedeberg, he had begun his studies on the action of digitalis and other glucosides, that so profoundly affect the entire circulatory apparatus and certain of the nervous structures that control the action of its individual parts. Admittedly, the action on the heart and its inhibitory mechanism is the most significant of all the effects of this very important class of therapeutic agents. It was natural for a man of Cushny's insight into what is worth while to attack this central problem with vigor and pertinacity. In a series of papers which must always remain models of their kind, he first clearly enunciated the main issues and first correctly classified the various stages involved in the action of digitalis on the mammalian heart.

It was at Ann Arbor that his most important discoveries in this field were made. His early observations are described in a paper entitled "Action of the Digitalis Series on the Circulation,"[1] appearing in 1897, and from this time up to the appearance of his valuable monograph in 1925 entitled, "The Action and Uses in Medicine of Digitalis and Its Allies," he published many papers dealing with every phase of the subject, and there is scarcely any feature of the action of digitalis which he has not illuminated.

In 1899 appeared the paper[2] in which he first called attention to the similarity of the disordered mechanism of the auricles of the dog induced by faradic stimulation to certain disturbances of the heart seen at the bedside—later to be named by him auricular fibrillation. It may be of interest to recall the gradual evolution of our conceptions of clinical auricular fibrillation, a condition which will always be linked with Cushny's name. Though fibrillation of the ventricle in experimental animals had been known since 1850[3] it was not until the appearance of MacWilliam's paper[4] in 1887 that a similar condition of fibrillary contraction of the auricles following faradic stimulation was first briefly described. Cushny discovered (1897) that the digitalis bodies in the last or toxic stage of their action also not infrequently produced auricular delirium or fibrillation of the auricles exactly as does faradic stimulation. In the paper of 1899 just referred to dealing with the "interpretation of pulse tracings" Cushny states:

> A few words may be added in regard to the extreme irregularity of the heart known clinically as delirium cordis. It is necessary to explain that in physiology this term is used to indicate fibrillary contractions of the heart, which arrest the circulation and prove immediately fatal. The clinical sphygmogram in these cases resembles exactly that obtained from dogs when the auricle is undergoing fibrillary contraction, which may be continued for a long time without proving fatal. I do not wish to assert that the clinical delirium cordis is identical with the physiological delirium auriclae, but the resemblance is certainly striking.

Seven years later, in a paper with Edmunds,[5] entitled, "Paroxysmal Irregularity of the Heart and Auricular Fibrillation," he again emphasized the inferences of his earlier paper and stated his belief that the irregularity observed at the bedside is definitely an auricular fibrillation. This paper was the first to appear with the words "auricular fibrillation" as an integral part of its title, and it is interesting to note the constant and ever-increasing frequency of the use of this description in the subsequent literature of heart disease.

The diagnosis of Cushny and Edmunds, as Cushny has stated in his monograph on "Digitalis and Its Allies," was received with doubt by the various schools of investigators of disease of the heart, and efforts to

[1] *Journal of Experimental Medicine*, ii, 233–239.

[2] *Journal of Experimental Medicine*, iv, 327.

[3] Hoffa and Ludwig, *Zeitschrift für rationelle Medizin*, ix, 107.

[4] *Journal of Physiology*, viii, 296.

[5] *American Journal of the Medical Sciences*, 1907, n.s. cxxxiii, 66–67.

arouse interest in it were fruitless up to 1909, when the new electrocardiographic methods in the hands of Rothberger and Winterberg, Lewis and others demonstrated the correctness of his contention and showed that fibrillation of the auricles is indeed of frequent occurrence in cardiac disease. The late Sir James Mackenzie, a leading English authority, who held "that clinical observers are obsessed by laboratory discoveries," says, in his "Diseases of the Heart":

> When the full significance of the discovery of this condition [auricular fibrillation, earlier called "delirium cordis, paralysis of the auricle and nodal rhythm," at a time when its true nature was not understood][6] comes to be recognized, it will be looked upon as one of the most important discoveries not only in cardiology but in medicine; while its important pursuit continues to throw new light upon many clinical and physiological problems.

Throughout the succeeding years many other papers appeared from his pen dealing with the subject of cardiac irregularities but more especially with the problems involved in the pharmacologic study and therapeutic control of the fibrillating heart. For a period of thirty years the study of the effects of digitalis and other cardiac glucosides continued to occupy his attention, and his studies have made clear many obscure and confused ideas in relation to the pharmacological action of these important drugs and have greatly assisted in giving us a sound and rational conception of their therapeutic action. That the specific effect of digitalis in cases of auricular fibrillation in man depends entirely upon the direct action of the drug on the myocardium, without vagal effect, a view supported by Cushny, is however still a matter of uncertainty in the opinion of cardiologists of experience.

The study of the nature of the action of diuretics has necessarily occupied the attention of pharmacologists and very naturally they have been equally interested with physiologists in theories that have been advanced to explain the secretory activity of the kidney. At a time when most physiologists appeared to be inclined to accept the Bowman-Heidenhain view of vital secretion, Cushny published three papers presenting results which could be more easily interpreted on the reabsorption theory of Ludwig. He found that if sodium chloride and sodium sulphate are injected into the blood stream in such amounts that an equal number of anions are present, the excretion of the two bodies in the urine follows different curves and varies independently of the concentration of the salts in the plasma. He interprets this as due to a variation in the permeability of the tubules to sulphate and chloride, the latter being reabsorbed and the former not. On retarding the flow through the tubules by partial obstruction of the one ureter, results were obtained which appeared to confirm those mentioned above. Both the percentage and the absolute amount of water and chlorides secreted by the kidney on the obstructed side were found to be lower than on the normal side, while sulphates appeared on the obstructed side in greater percentage but in smaller absolute amount, decreased urinary volume being taken into consideration. This divergence in the percentile and absolute excretion of two simple inorganic constituents was attributed by Cushny to their differential absorption by the epithelial cells of the urinary tubules. The kidneys were also found to deal with both sodium phosphate and urea in exactly the same manner as the sulphate. After investigating also the changes in reaction of the urine during saline diuresis, he came to the conclusion that the formation of an acid urine from an alkaline plasma could be explained in accordance with the filtration-reabsorption view of Ludwig. "The presence of salts in the glomerular fluid which are capable of extensive hydrolysis and of which the cations can permeate the tubule, while the anion fails to do so in equal measure, and sufficient reabsorption in the real tubules" are the essential factors of acid secretion. Many years later, at University College, London, and at Edinburgh, he again took up urinary studies and published in 1917 and 1921 two papers dealing with other phases of the subject, which may be summarized as follows:

Many years before (1874) Heidenhain had shown that after the injection of indigo carmine into the blood stream of rabbits, following cervical section of the spinal cord, in order to annul urinary secretion, this dye accumulated in the epithelial cells of the convoluted tubule of the kidney, and he drew the inference from his experiments that this dyestuff is eliminated into the tubules by the "vital activity" of their cells. By analogy he inferred that urea, the main nitrogenous waste product of the body, is also excreted not by filtration through the glomeruli, as Ludwig had maintained, but by the "vital secretory action" of the tubular cells. Cushny proposed to himself to test Heidenhain's theory of urea secretion, employing the same experimental procedure with rabbits, but examining the tissues of the kidney in respect to their content of urea in place of their content of indigo carmine. Heidenhain had estimated the tubular content of indigo carmine by means of the microscope, while in Cushny's experiments the urea content of the kidney was quantitatively estimated by reliable chemical methods. After section of the spinal cord one kidney was removed immediately, and two hours later the other kidney was excised, ground up and its urea content determined. The kidney removed immediately after the section

[6] Insertion in brackets is mine.

of the cord contained rather more urea than the one removed two hours later. It was thus shown that no accumulation of urea occurs after the kidneys ceased to eliminate water, "and that the cells of the tubules are unable to accumulate urea either in their interior or in the lumen in the absence of a flow of urine."

Whether or not future experimenters succeed in substantiating Heidenhain's idea that indigo carmine is excreted by the tubular cells (in addition to the now accepted elimination through the glomeruli) it is nevertheless true that Cushny's experiments prove that the kidney deals in a different manner, under similar experimental conditions, with urea than with indigo carmine. Here, as elsewhere in science, analogy is found to be a dangerous guide. The determination by Cushny of the amounts of glucose present in the kidney after injection of phloridzin in experiments similar to those described above, led to the same results as were obtained with urea.

Cushny's next and last work on urinary secretion deals with that fundamental problem which has always intrigued pharmacologists, namely, to what extent the action of diuretics is localized in the kidney itself (in other words, in its own vascular, cellular and nervous elements) and how far it is brought about through alterations in the composition of the blood and functional alterations in the blood flow. In a paper with Lambie he studied the action of such diuretics as caffeine, strophanthin, the salines, urea and pituitary extract, estimating directly the renal blood flow by a modification of Barcroft and Brodie's method which avoids employment of the older and misleading oncometer. These experiments led him to conclude that pituitary extract is the only one of the many diuretics examined that appeared to act directly by increasing the blood flow through the kidney.

Cushny's original contributions on urinary secretion and on the action of diuretics are of less outstanding importance than those made in the other two main fields of his life work—the study of the effects on man and animals of the cardiac glucosides and of the pharmacological action of optical isomers. Fortunately for us, however, he was induced by Starling in 1917 to undertake the writing of a comprehensive monograph on the secretion of the urine. After the completion of the book, he wrote to Starling a letter in place of the usual author's preface, from which I may cite the following paragraph:

> The growth in the literature on the kidney has been extraordinary since the time when you and I began to work on it, and this increase in bulk has not gone along with an improvement of quality, but rather the reverse. No other organ of the body has suffered so much from poor work as the kidney, and in no other region of physiology does so much base coin pass as legal tender. It was therefore necessary to sift thoroughly this mass of printed matter of about 6,000 pages, and I have read it carefully and, as far as might be, sympathetically, though I must confess that my patience has been sorely tried by some papers in which the depth bore no proportion to the length. It soon became obvious that if each writer were to be dealt with faithfully, this would be, not a monograph, but a series of volumes, and the whole trend of the argument would be lost in a tangle of discussion.

In this monograph Cushny sifts and coordinates the mass of contradictory data that have accumulated since Ludwig's day, and modifies and reshapes the theory of that master into what he modestly calls "the modern theory." The "modern theory" may be briefly stated as follows: The glomeruli filter from the blood all the diffusible bodies of the plasma. This glomerular filtrate contains, therefore, all the non-colloid constituents in about the same concentration as they exist in the plasma. During the passage of this filtrate along the tubule, water and various constituents (threshold bodies) are reabsorbed, while other substances (non-threshold bodies) are concentrated more and more during their course along the tubule. The reabsorbed constituents with the water accompanying them constitute, as he thinks, a fluid of unvarying composition, approximately that of Locke solution. This theory then "accepts the general scheme of filtration and reabsorption of Ludwig, but, appreciating the inadequacy of the known physical forces, supplements them as far as is necessary by the 'vital activity' postulated by Heidenhain."

Cushny is quite conscious that any theory of urinary secretion advanced in our day can not claim finality. He himself says of this theory, "It is impossible at present to prove it correct . . . it is sufficient to show that it is in accordance with a large body of observations. Even if it fails to offer a complete explanation of these, it merely requires further development, not abandonment."

At this writing, the second edition of the book has not come to hand, but I have been led to believe that Cushny, like the true scientist he was, has been induced by the discovery of new facts, at the hands of others as well as by his own pupils, to modify his views in some particulars.

This excellent monograph with its coherent theory of urinary secretion has stimulated many younger investigators to attack problems in this field. Men who knew not Ludwig or Heidenhain have found it of great value to have the contributions of an earlier day analyzed and codified, as it were, by a man of

wide experience and sound judgment in the allied fields of pharmacology and physiology.

We come now to an entirely different aspect of Cushny's work, that dealing with the pharmacological behavior of optically active substances. Omitting here all references to the fundamental discoveries of Pasteur in 1845 and thereafter and to studies of a few observers in the early 80's and 90's in regard to the difference in the taste of pairs of isomers, we may pass at once to a brief consideration of certain physiological and pharmacological experiments antedating those of Cushny.

The first physiological experiments on the assimilation of optical isomers by the tissues of the higher animals were those made by Brion in 1898, who attempted to show that *l*-tartrates are oxidized more easily by the dog than the *d*-tartrates. These results were critically examined by Neuberg and Saneyoshi twelve years later, who prove that *l*- and *d*-tartaric acids are assimilated with equal ease in the tissues, which appear to be unable to differentiate between them. The many observations made along these lines since Brion's can not be entered upon here. Suffice it to say that an extensive literature now exists in regard to the preferential utilization by the tissues of higher animals and by lower organisms of isomers among sugars, organic acids, camphors, alkaloids and many other compounds, much of which has been adequately reviewed by Cushny in his Dohme Memorial Lectures of last year, now appearing as a monograph entitled "Biological Relations of Optically Isomeric Substances," published for the Johns Hopkins University by the Williams and Wilkins Company, of Baltimore.

After these earlier experiments there soon followed pharmacological observations by Chabrie (1893), who compared the toxicity of *d*- and *l*-tartaric acid by injecting them into the peritoneal cavity of experimental animals and found a difference between the two isomers, but Cushny holds that death here was not due to the optically active portion of the molecules but to their hydrogen ion and that "the supposed difference in toxicity was purely casual." Cushny criticizes many of the toxicity determinations, effects on serum reaction, blood clotting, etc., with the four tartaric acids that have been done since 1910 as being quite valueless, since the supposedly essential tartrate action is complicated by the vastly more powerful one of the hydrogen ion.

In 1904 Pictet published observations made by Mayor, who states that *l*-nicotine, the natural alkaloid, is twice as poisonous as *dl*-nicotine and that the former also causes greater local pain and more violent convulsions than the latter, but Cushny evidently regards Mayor's work as needing corroboration, as he says of it, "it would be desirable to repeat these experiments." It will thus be seen that the earlier pharmacological experiments with isomers are probably more open to criticism than the earlier and later experiments with fermenting organisms and the earlier and later biochemical studies, since they suffered such grave defects in technique that no conclusions of lasting value can be drawn from them.

The first definite example of distinct and measurable pharmacological differences in the action of two optical isomers falls to the credit of Cushny, who published the results of his earlier studies in 1904. Pure *l*- and *dl*-hyoscyamine (atropine) were at first used and it was found that the two bases are equally poisonous to many organs of the frog, such as the heart, muscle and nerve ends, but that the *dl*-form is more excitant for the central nervous system than the *l*-form and that this action is more persistent. It was found that in mammals many organs were unaffected by even large doses of either isomer, while certain organs, such as the heart and central nervous system, react to the same degree to the two isomers, but in the case of other structures the *l*-hyoscyamine is almost twice as powerful as the *dl*-form. This last ratio held true for all the specific pharmacological actions of the "tropeines" in the dog, as evidenced, for example, in the myoneural junctions of the motor oculi and in the adenoneural junctions of the submaxillary glands. The same ratio also held for the intestines, but it is thought doubtful whether the action of these alkaloids on smooth muscles is exerted solely on their hypothetical myoneural receptors, as is more clearly the case with their action on the receptors of the heart, iris and ciliary body.

The specific action, then, as Cushny first demonstrated, of *l*-hyoscyamine on many organs is twice as great as that of *dl*-hyoscyamine, and as two molecules of atropine (*dl*-hyoscyamine) contain one molecule of *l*-hyoscyamine and one of *d*-hyoscyamine Cushny stated his results in the following simple form:

$$2\ dl = l + d \text{ chemically}$$
$$2\ dl = l \text{ pharmacologically}$$

Cushny's first conclusion was evidently that the *d*-isomer is practically devoid of action on the myoneural junctions of the autonomic system, but further experiments, in which the pure *d*- and *l*-isomer were compared directly with each other in place of the *l*- and *dl*-forms, led him to modify slightly his statements. Both isomers were now found to act qualitatively in the same manner, but the *l*-form acted in general about twenty times as strongly as the *d*-form except on the central nervous system, in which the *d*-form caused a distinctly greater and longer excitation than the *l*-form.

Similar observations were made with *l*-, *dl*-, and *d*-hyoscine and with the *l*-, *dl*-, and *d*-homatropines on the cardiac inhibitory, oculomotor and secretory peripheral nerve terminations. In experiments in which the *l*- and *d*-hyoscines were compared directly it was found that the *l*-base acted sixteen to eighteen times as strongly as the *d*-base on these organs and this ratio also held for their action as antagonists to pilocarpine on the intestines. Recently, according to Cushny, Moir has shown, while studying the efficacy of *d*- and *l*-hyoscine in "twilight sleep," that *d*-hyoscine has little or no effect on the central nervous system in man, while the *l*-isomer is efficient. In the case of the homatropines it was found that the ratio of the activity of *l*:*d* on the autonomic terminations is about 5:8, that is, the *l*-isomer is approximately only twice as powerful as the *dl*.

After Cushny had shown that natural laevo-rotatory alkaloids, such as hyoscyamine and hyoscine, are distinguished by quantitative differences in their action on the nerve terminations of the autonomic system he next studied the behavior on the animal body of the isomers of the then recently synthesized adrenalin, or epinephrine of our pharmacopoeia. Shortly after the synthesis of *dl*-epinephrine was effected by Stolz in 1904, Biberfeld stated that this isomer is exactly equivalent to the natural *l*-base, as prepared from the medulla of the suprarenal glands, in respect to their action on blood pressure, on the pupil of the enucleated frog's eye, and in causing glycosuria in animals.

Cushny at first, in repeating the work of this investigator, confined himself to an examination of the relative activities of *l*- and *dl*-epinephrine on the myoneural junction in the arterioles, measuring their action by means of blood pressure estimations. He was able to show that Biberfeld was in error and that the natural or *l*-base raises the arterial pressure nearly twice as much as its synthetic *dl*-isomer, and he concluded that the *d*-isomer (then not obtainable) is devoid of action. Later he had the opportunity to compare *l*- and pure *d*-epinephrine (Flächer) directly and found that the *d*-base has an action qualitatively similar to its *l*-isomer but that the latter acts about 12–15 times as strongly as the former on the sympathetic terminations controlling the glycogenic function of the liver, and further "that the relative minimum lethal doses of the two isomers appeared to be of the same order of magnitude but could not be ascertained so accurately." All these results were soon confirmed by Abderhalden and his pupils, by Tiffenau and others.

The fundamental observations of Cushny in respect to the pharmacological action of isomers was soon followed by the studies of other investigators who have examined the pharmacological action of a large number of isomers of the cocaine series, of coniine, tetrahydroquinaldine, camphor, hydroxyhydrindamine, tetrahydro-β-naphthylamine, the canadine methochlorides and other compounds. The findings of these workers are given in concise form by Cushny in the monograph above referred to.

So much for Cushny's fundamental researches on optical isomers, so suggestive and stimulating to others. In conversations with me he has repeatedly expressed his conviction of the ultimate very great importance of continued research in this field, an opinion that will be shared, I believe, by all students of the biological sciences. In an inaugural sessional address delivered before the North British Pharmaceutical Society in 1919, he said.

> This optical activity is, in fact, the most persistent evidence of life which we possess. An optically active alkaloid or acid may be kept for centuries after the plant which formed it and the chemist who isolated it are dead, but it will still possess its optical activity, testifying that it was formed by some living thing either directly or indirectly. When we find an optically active substance in the earth, we may know at once that it arose through the agency of life. The petroleum we burn, for example, must have arisen from living tissues, for it is optically active. Not only is it the most persistent sign of life, but it is the most definite physical characteristic of life. No other can be measured in actual numbers in the same way.

The specialist will find in Cushny's monograph on optical isomers, in which his unrivalled judgment and wide knowledge are brought to bear on the general aspects of pharmacological action, whether induced by optical isomers and ferments or other principles, an analysis, extending over about thirty pages, of the influence of chemical configuration and constitution on pharmacological action, with illustrations drawn from various older as well as more recent sources. To cite an example, in considering the specific activity of such a drug as hyoscyamine, he points out that three factors have to be taken into account:

> (1) The general structure of the molecule, which is a tropine ester, preferably of an aromatic acid, and which gives a slight activity as a general rule; as a type phenacetyltropine may be taken, (2) the presence of alcoholic hydroxyl in the side chain of the acid, which intensifies the activity to a pronounced extent; for example, atropine, possessing OH, is some 200 to 300 times as powerful as hydratropyltropine which is devoid of it, and (3) the presence of an asymmetric carbon, which gives optical rotation to the molecule, and may vary its activity about 15 to 20 times according to the direction of that rotation.

Space forbids a further elaboration of these factors or to what extent in enzymic or other biological reactions it is "the configuration of the whole molecule,

rather than the presence of individual radicles, that is the determining factor." Cushny concludes that the analysis he has given "of the reactions of enzymes and substrates, of receptors and drugs, far from clarifying the relation of living matter and chemical constitution, indicates that more factors are involved than are generally recognized and that very slight changes in chemical structure may alter enormously the reaction between them. Such investigation discourages such crude rules of the relation of chemistry and therapeutics as have often been laid down and shows how far we have still to travel before we begin to understand the chemistry of life."

In the above account of the relation of optical isomers to biology I have entered into some detail because of the importance of such investigations not only to chemists but to biologists in general, and I have drawn freely in the foregoing statements on Cushny's original papers and on his monograph.

Cushny's work in the field of the isomers of alkaloids and of the cardiac glucosides will remain, I think, in days to come his outstanding contribution to science and medicine.

Numerous other contributions to pharmacology were made by Cushny. Since 1891 papers have appeared that deal with the action of chloroform and ether, the active constituents of gelsemium, of muscarine, cocaine, sparteine, piperidine and some of its compounds, the saline cathartics, ricin, alcohol, calycanthine, oxidizing salts, nutmeg and the senecio alkaloids. He also occupied himself with problems concerning the uterus, the respiration, exhalation of drugs by the lungs, the action of serum, the nature of antagonism, and in addition wrote a valuable pamphlet in defense of vivisection and extensive articles on the nitrites, the members of the atropine group and ergot for Heffter's "Handbuch der experimentellen Pharmakologie."

I shall here refer to one only of the above-mentioned papers, as it involves a matter of great economic importance for animal industry. In the paper on the *Senecio family,* Cushny, working with pure alkaloids, confirms the views of previous investigators who had already demonstrated by feeding experiments that a fatal disease affecting horses and cattle and characterized by hepatic cirrhosis, known in New Zealand as Winton disease, in South Africa as Molteno disease and in Canada as Pictou disease, is really only chronic poisoning with these alkaloids.

In 1905, Cushny, to the lasting regret of his many friends and admirers in this country, resigned the chair of materia medica and therapeutics at the University of Michigan to accept the chair of materia medica and pharmacology at University College, London; here he remained until 1918, when he was elected to the chair vacated at Edinburgh by the death of the distinguished Sir Thomas Fraser. "At University College he had to undertake the creation of a department out of nothing," as his former colleague, Professor Starling, has written, "the quarters of his predecessor consisting simply of one ill lit and badly furnished room—when at last, through a generous gift of Mr. Carnegie, it became possible to provide Cushny with a laboratory adequate to his work, we hoped that we had secured his continued and permanent help in building up the school of our ambitions. But to an Aberdeen man the old reputation of a professorship at Edinburgh University was too strong to be resisted and the succession to the chair of Fraser seemed a fitting crown to his life's work." And at Edinburgh he remained until his untimely death a few weeks ago.

At both British centers of learning he continued to carry on his research work, remodeled the teaching, instilled a new spirit into pharmacology, collected about him a number of able young men, some of whom, influenced by his unusual personality, elected to enter upon a life of combined teaching and research work and now hold important chairs of pharmacology in England and the dominions.

Cushny returned to England at a time when English pharmacology, so long taught and pursued as a separate science on the continent, had not reached its present position. A number of younger men, to be sure, who have since become eminent were then teaching the subject and trying themselves out in it, but the older generation, although men of undoubted ability and with many fine achievements to their credit, were after all too much absorbed with the details of medical practice to do full credit to themselves in an exacting science that calls for a more modern and fundamental training, such as only men of a later day can secure. It is easily understandable that, returning to England at this time, a man of Cushny's type, with his unrivalled experience and already high reputation, his sound judgment of men and matters scientific, his kindly and sympathetic nature, and above all a man devoid of ostentation and one who taught by precept and example, could do more than any of his contemporaries to put English pharmacology in its present high place.

I have written above as one man may write of another's life work in a science to which both have been devoted. But there is a word more to be added. We were friends for thirty-seven years. During this time scores of letters passed between us concerning our own researches or those of others, the affairs of the journal in the editorship of which he assisted me, the work of international committees on which we were serving and many other matters of mutual interest. On his recent visit to this country we were

planning, indeed, a new venture in the interests of our science.

With Cushny's death there was lost to humanity a striking example of a life devoted to high and unselfish purposes. Only those bound to him by ties of blood can mourn his passing more than does the writer.[1]

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THE DEPARTMENT OF TROPICAL RESEARCH OF THE NEW YORK ZOOLOGICAL SOCIETY

FOR nine years the New York Zoological Society has maintained this department, and the year 1925 has been the most successful. Three important undertakings are given in the résumé below:

First, the Arcturus Oceanographic Expedition, which left New York on February 10, 1925, and returned July 30, having carried on work in the Sargasso Sea in the Atlantic and in the waters about Cocos Island and the Galapagos Archipelago in the Pacific. Months of careful preparation were devoted to the selection of the staff and the outfitting of the converted freighter, the *Arcturus,* which was given to the society by Mr. Henry D. Whiton. The greater part of the financial burden was undertaken by Mr. Harrison Williams, and Messrs. Marshall Field, Vincent Astor, George Baker, Jr., and other gentlemen also contributed generously.

While a certain amount of shore work was done at the islands visited, our activities were confined almost exclusively to the fauna of the deep sea and of the shallow waters around the islands. Special attention was given to the study of the habits of littoral fishes, work which was much facilitated by the use of a copper diving helmet; the luminescence of deep sea animals was a vast and intensely interesting field of research, in which some remarkable problems were worked out, while the locomotion and distribution of various forms and the study of larval fish yielded important results.

We were so fortunate as to be present at a volcanic outbreak on Albemarle Island, in the Galapagos, of which splendid moving pictures were obtained, and chanced upon an extraordinary current rip in the Pacific which teemed with fish, birds, mammals and even reptiles, as well as incredible numbers of invertebrates.

We returned to New York with large collections, including many new species of deep sea fish, tremendous quantities of plankton, seven hundred photographic negatives, eleven thousand feet of excellent moving pictures and about four hundred colored plates made from living oceanic creatures. Since that time an elaborate exhibit of specimens, apparatus, photographs and paintings has been held at the American Museum of Natural History, and Miss Cooper has held exhibitions of her paintings in Chicago and Washington. Over fifty lectures have been given by myself and Ruth Rose throughout the country and fifteen articles have been published in the *Zoological Society Bulletin* and other magazines. Many collections have been prepared for technical study, and some are now being worked over by specialists.

A volume, "The Arcturus Adventure," has just appeared, treating of the expedition from the same popular angle as the book published by Putnam's two years ago, "Galapagos: World's End."

A gratifying result of the two expeditions—one on the *Noma* in 1922 and that of the *Arcturus* in 1925—has been the interest which they have awakened in others to carry on work near the Galapagos. I was able to give some assistance to Mr. Harry Payne Bingham for his oceanographic trip in the *Pawnee* to the Caribbean, which aroused his enthusiasm to such an extent that he has now built a ship specially for such work. Mr. William K. Vanderbilt, who has just returned from an oceanographic expedition to the Galapagos on the yacht *Ara,* drew upon our experience in the outfitting of his ship and in methods of collection, and has brought back many interesting specimens for identification and study. Zane Grey consulted with me concerning the big-game fishing trip which he afterward made to the Galapagos on his schooner *Fisherman* and concerning which he has since published an interesting volume.

Four United States cruisers visited the Galapagos on their way home from Australia, and Commander Kalbfuss sent me an account of the volcano, which in late September was still in eruption, together with airplane pictures of the lava pouring into the sea.

The most unexpected result of the *Arcturus* expedition was the great interest which it aroused, not only in this country but abroad. The only direct outside articles about it appeared in the New York *Times,* consisting of wireless accounts, and more detailed stories which were sent by mail as opportunity offered.

The second part of the year's work falls under the head of the zoological work by the department dealing with the fauna of Kartabo, British Guiana. For parts of eight years my staff and myself have engaged in intensive study of a quarter of a square mile of jungle in this rich field. During the past year more has been published concerning it than in

[1] The reader will find a complete bibliography of Dr. Cushny's writings in the April issue of the *Journal of Pharmacology and Experimental Therapeutics.*