SCIENCE

FRIDAY, AUGUST 6, 1915

CONTENTS

MSS. intended for publication and books, etc., intended for review should be sent to Professor J. McKeen Cattell, Garrison-on-Hudson, N. Y.

EXPERIMENTAL AND CHEMICAL STUDIES OF THE BLOOD WITH AN APPEAL FOR MORE EXTENDED CHEMICAL TRAINING FOR THE BIOLOGICAL AND MEDICAL INVESTIGATOR. II

THE BLOOD AND THE SPECIFIC SECRETORY PRODUCTS OF THE ORGANS OF INTERNAL SECRETION

In this field we touch on the one hand upon knowledge which is deeply rooted in the earliest practical experience of mankind, and on the other on the results of epoch-making clinical observations and of experimentation in scientific laboratories up to the present moment. Man has long made practical use of the fact that the removal of the sex glands at a certain age will give us the docile ox in place of the unruly bull, the easily fattened and tender-fleshed capon for the muscular and stringy cock; and human society in its various stages of development has also practised this mutilation on its individuals for various reasons, religious, economic or penal. The sale of eunuchs in Bagirmi and other parts of North Central Africa still continues, we are told, and it was only on the accession of Pope Leo XIII. in 1878 that the practise of castrating boys in order to furnish the Sistine Choir its famous adult soprano voices was discontinued.

From remote antiquity, therefore, man has known that the gonads, or sex glands, exert a marked influence on the development and structure of the body, but until recent times there has existed no valid explanation, no correct theory of their relationship to the rest of the body. It is true, there were not wanting acute minds whose attempted explanation came close to the truth, but experimental proof was lacking. We gather from Æsop's fable that it will not do for the various members of the body to fall out with one another, and the medicine of an older time has long used the expression *consensus partium* as indicating the interrelationship of the various organs. Even in quite modern times this *consensus* of the various organs was supposed to be entirely effected through the intermediation of the nervous system, a view tersely expressed by Cuvier when he said,

> Le système nerveux est, au fond, tout l'animal, les autres systèmes ne sont là que pour le servir.

Side by side with this view of the preponderating rôle of the nervous system we find the old humoral doctrine, having obtained new support in Harvey's discovery of the circulation, struggling to prove the importance of the blood stream for the interrelationship of the organs. In 1775, Théophile de Bordeu[22] of Montpellier and later Paris, a fashionable practitioner with considerable knowledge of anatomy, propounded the doctrine that every organ lives its own life and is the source of specific chemical substances (humeurs particulières) which are yielded up to the blood and which are necessary to the integrity of the body. The idea that every organ has its own special life is repeated again and again in Bordeu's writings:

> It must be remembered that each organic part of the living organism has its own manner of existence, of acting, of feeling and of moving: each has its own particular savor, structure, external and internal make up, odor, weight, manner of growth, of expanding and contracting; each competes after its own manner and for its share in the ensemble of all the functions, in the general life; each organ, in brief, has its own life and its own functions quite distinct from all others.[23]

From the organs the blood derives a multitude of humors and "emanations" (nuées d'émanations qui composent et animent le sang).

> Comparable at bottom to fecundated white of egg, the blood (a fluid tissue which fills the vessels of the body) is animated by the semen, that is to say, it contains a certain quantity of *seminal emanations* which vivify it; it contains in the same way a portion of the bile, and also a portion of the milky juices, especially in infancy and in women at the time of pregnancy; it contains a colored part which is elaborated in the entrails; it has serosity in abundance; it contains an extract of each glandular organ which contributes its share to the emanations in which all the solid parts (of the blood) swim; a certain quantity of air; a portion of mucous substance. . . .[24]

Bordeu's theories in respect to the diseases that are consequent to a superabundance or wrong admixture of these various special principles or emanations, his various cachexias (cachexie bileuse, albumineuse, etc.) can not be considered here.

Three quarters of a century after Bordeu, in 1849, we find a German professor of physiology, in Göttingen, A. A. Berthold, giving the first experimental proof of the correctness of this theory. This experimenter, in a beautifully concise monograph of only four pages, describes his experiments upon young cockerels. By removing the sex glands from their normal position and transplanting them to another part of the body (to the outer surfaces of the intestine in the peritoneal cavity) where it was impossible for them to expel a secretion or to play any external rôle as sex glands, he was able to prove that these glands have two functions: (*a*) the well-known reproductive function, and (*b*) an important function in maintaining, as he says, the "*consensus partium.*" Such cockerels did not show the changes that were seen in the castrated bird; on the contrary, they developed into the usual type, remaining male birds in respect to their vocal capacity,

[22] See his "Recherches anatomiques sur la position des glandes et sur leur action," Paris, 1752; and his "Analyse médicinale du sang," 1776.

[23] P. 942, "Analyse médicinale du sang," Vol. 2, "Œuvres complètes de Bordeu," edited by Richerand, Paris, 1818.

[24] P. 1,006, *ibid.*

their desire for battle, the growth of comb and wattles and the sexual instinct. Berthold draws the conclusion from his experiments that the generative organs influence the *consensus partium* by acting upon the blood and through this upon the organism as a whole.

The observations of Berthold were forgotten and even discredited (Rudolf Wagner) and they had no influence apparently on the development of work in this field during the following half century.

I can not leave this part of my subject without mentioning the work of the great Frenchman, Claude Bernard, whose discovery of glycogen in the liver and elsewhere must always rank as one of the great discoveries of physiology. With perfect justice Bernard declared that the conversion of glycogen into sugar and the passage of the latter into the blood constitutes the internal secretion of the liver, while the bile constitutes its external secretion.

One other investigator, the modern pioneer in this field, a restless spirit, a man of enthusiasms, possessing an original mind of a high order, one who is of especial interest to Americans, can not be passed by without mention. Charles Edward Brown-Séquard was born at Port Louis, Mauritius, on April 8, 1817. His father was an American, his mother a French woman, but he himself, it is stated, always wished to be regarded as a British subject. After a varied career in four countries (England, France, Mauritius and the United States) having held the chair of physiology in Harvard from 1864 to 1867, he finally, in 1878, succeeded Claude Bernard as professor of experimental medicine in the Collège de France, where he remained until his death in 1894.

As far back as 1869 Brown-Séquard took the position in his lectures in Paris that all glandular organs, irrespective of whether they possess external excretory ducts or not, give off to the blood substances which are useful and necessary for the body as a whole, an opinion, as we have seen, that had already been stated by Théophile de Bordeu in 1775. He even made experiments on himself with a testicular extract, and the meeting of the Paris Societé de Biologie, June 1, 1889, at which Brown-Séquard, then 72 years old, made his report on these experiments, Biedl calls "the true birthday of the doctrine of internal secretion."

From this time an ever-increasing army of experimental laboratory workers have been engaged in this field. Their names even can not here be given, neither can I go into detail with regard to the great and fundamental contributions that have been made by medical clinicians, surgeons and anatomists, as Basedow, Graves, Addison, Marie, Gull, Ord, Kocher, Reverdin, Minkowski, Von Mering, Sandström and others, to name only some of the leaders of the immediate past, not to speak of the excellent contributions that have been made in recent years by our own surgeons and internists.

And so there has gradually come into existence an enormous store of facts, physiological, pathological, chemical and clinical, in regard to a number of structures that are classed as endocrinous glands or organs of internal secretion.

What is meant to-day by this term, products of internal secretion, and what organs furnish principles that can be classed as internal secretions?

For the present we shall follow custom and apply the term *to definite and specifically acting indispensable chemical products of certain organs* (*organs that may or may not have an external secretion*), *which are poured into the blood and modify the development and growth of other organs,* *more especially during embryonic and early life, and which also greatly affect the entire metabolism, that of the nervous system included, during adult life.* I regard it as not unlikely that with the growth of knowledge of the chemistry of the animal organism we shall drop the term entirely. We have already seen that the liver, according to Claude Bernard's view, has an internal secretion, yet this gland is not usually classed with the endocrinous organs. In a sense, too, as has been frequently pointed out, every cell of the body furnishes in the carbon dioxide which it eliminates a hormone or product of internal secretion, since under normal conditions the carbon dioxide of the blood is one of the chief regulators of the respiratory center, influencing this center by virtue of its acidic properties. These and other instances that could be given show that the term internal secretion could be greatly extended in its scope, but in the present state of our knowledge it is convenient to limit it to the products of a certain number of glands.

The generally accepted list of the organs of internal secretion is as follows, though even at this moment a foreign investigator[25] is asking us to accept certain newly discovered small structures located in the neck as belonging to our list: the thyroid, parathyroid, thymus, hypophysis cerebri, epiphysis cerebri, pancreas, mucosa of the duodenum, the two adrenal systems (the chromaphil tissue and the interrenal bodies) and the gonads, or sex glands.

Permit me to give you a few illustrations of the derangement of health and bodily structure that follow upon the removal or disease of these glands. Many of you have doubtless seen these illustrations, but I am giving them here for the benefit of those who have never been given proof of the great significance of these glands in order that they may have a background of fact for the better apprehension of certain chemical questions which I wish presently to bring to your notice.

The figure[26] is an illustration from a well-known paper of the Viennese surgeon, A. v. Eiselsberg, in which he describes the effects of removing the thyroid gland from young goats. The two animals here shown are of the same age and parentage. On the twenty-first day after birth v. Eiselsberg removed the thyroid gland from one of them. The incision healed by primary intention. After three weeks the control animal began to outgrow the one operated upon and when four months old the animals presented the appearance here shown. The goat with thyroid removed has shortened extremities, a shortened skull and an altered pelvis due to a delayed ossification at the epiphyseal line. The wool of this animal is longer and easily torn out by the handful, the sex glands are atrophied, the hypophysis is enlarged, the intelligence is lowered; in brief, a chronic pathological condition is produced in this experiment which finds an analogy in human beings and is known as *cachexia thyreopriva.* We can not enter into further details, but I may remark that the results obtained in such removal experiments vary greatly with the age and with the species of animal used.

In this figure we have the results of a similar experiment which nature herself has performed for us. The child here shown is a thirteen-year-old idiotic myxedematous dwarf whose general symptoms point to a congenital absence of the thyroid gland. Investigators have proved this to be the true cause by anatomical studies of the

25 "Ueber eine neue Drüse mit innerer Sekretion (Glandula insularis cervicalis)," N. Pende, *Arch. f. mikroscop. Anat.*, Vol. 86, p. 193, 1914.

26 The illustrations were shown in the lecture, but can not here be reproduced.

bodies of other congenital myxedematous children of this class.

Further illustrations were then given by means of lantern slides of endemic cretinism and goiter and it was shown by statistics and by a map of Europe that these abnormalities have very great economic significance, on account of their great prevalence in certain parts of central and western Europe and to a less degree in our own and other countries. For instance, in Switzerland one sixth of the male population is unfitted for military service by cretinism in some degree.[27]

After even these few illustrations of abnormalities that follow on removal or disease of these glands, I think you will agree with me that my colleague, Professor Barker, has not exaggerated their importance when he says,

More and more we are forced to realize that the general form and the external appearance of the human body depend to a large extent upon the functioning, during the early developmental period (and later), of the endocrine glands. Our stature, the kinds of faces we have, the length of our arms and legs, and the shape of the pelvis, the color and consistency of our integument, the quantity and regional location of our subcutaneous fat, the amount and distribution of hair on our bodies, the tonicity of our muscles, the sound of the voice and the size of the larynx, the emotions to which our *exterieur* gives expression—all are to a certain extent conditioned by the productivity of our hormonopoietic glands. We are simultaneously, in a sense, the beneficiaries and the victims of the chemical correlations of our endocrine organs.[28]

I can not here take up questions of therapeutics in this interesting field. I can only say that *aside* from surgical intervention and the brilliant results of thyroid treatment in cases once utterly hopeless, we have little to offer that has been *positively* established. Nor shall I attempt to discuss the interrelationship of these glands. It has become increasingly evident that to touch one of them is to touch all. Various writers have endeavored to express this interrelationship in a series of charts or diagrams. Of these diagrams D. Noël Paton has well said:[29]

They may well be a grotesque parody of what will ultimately be found to be the relationship of the activities of these organs. They are probably as near the truth as those quaint ancient maps of the Indies with their "here be gold" scrawled across them which served as the charts of our forefathers, and if, like them, they merely indicate the direction which further investigation should take and suggest lines of attack, they will have served their purpose.

Notable and well established, apparently, is the relationship existing between the gonads, the thyroid and thymus glands, the hypophysis and suprarenal glands. Very difficult is it also to unravel the relationship of the internal secretions as a whole to the nervous system, both central and peripheral.

In view of the fact that we so little understand the chemical principles elaborated in these organs and discharged by them into the blood, whereby the remarkable changes described above are effected, it is evident that further progress now waits on chemical discoveries.

[27] "Der Kretinismus," H. Vogt, in *Handbuch der Neurologie* (Lewandowsky), Vol. IV., Spezielle Neurologie, III., p. 139. Here also it is stated that the three Italian provinces, Piedmont, Lombardy and Venice had 120,000 cases of goiter and 13,000 cretins in 1883, the total population of these provinces at that time being 9,400,000. In 1908, according to Biedl, Austria had on the average 64 cretins to every 100,000 of the population. In 1873 France had 120,000 cretins in Savoy, the Maritime Alps and the Pyrenees. It will be seen that the thyreopathies constitute a heavy drain on the resources of European people.

Pictures of persons suffering from other disorders, as exophthalmic goiter, acromegaly or giantism and parathyroid tetany, were also given with a brief statement of the glandular and general nutritive changes involved. Animals such as the monkey, the dog, the rat and others are likewise subject to disease of this gland.

[28] "On Abnormalities of the Endocrine Functions of the Gonads of the Male," *Am. Jour. Med. Sciences*, Vol. 149, p. 1, 1915.

[29] "Regulators of Metabolism," p. 183. Macmillan & Co., London, 1913.

The only fairly complete chemical work yet done on any of these organs is that on the suprarenal glands. These organs are two flattened, ductless, yellow-brown glands, each of which is loosely attached to the anterior and inner part of the summit of the corresponding kidney. The normal gland of a healthy man weighs, according to Elliott,[30] between four and five grams, and contains four or five milligrams of the characteristic principle concerning which I shall speak in a moment. These organs are essential to life; their destruction in man by tubercular and more rarely by other processes leads to a chronic condition characterized by gastro-intestinal symptoms, great muscular weakness and a bronzing of the skin and mucous membranes, this whole symptom complex being known as Addison's disease (1855). In man and the higher animals generally this organ is a double structure in which two parts which are quite separate and totally different in lower forms, as in the elasmobranch and teleostean fishes, are united in such a manner that one constitutes the medulla and the other the cortex of the gland, the latter completely enclosing the former.

The cortical part of the gland is called by histologists the inter-renal tissue. Biedl has shown that when this tissue is removed from selachians (where, as just stated, it constitutes a separate organ) the animal gradually weakens, no longer takes food and dies in fourteen to eighteen days. Still other experiments demonstrate that this cortical part of the gland exerts great influence on bodily growth and sexual development. Numerous researches of a chemical character have been carried out on this part of the gland, especially in respect to its lipoid content. Last year Voegtlin and Macht[31] isolated from it and also from blood serum a new crystalline substance which has a vaso-constricting action on the blood vessels and a digitalis-like action on the heart. This has been decided to be a lipoid closely related to cholesterin. As we are entirely ignorant of the means by which the adrenal cortex exerts its profound influence on the body, the isolation of this substance is of especial interest. For the present we can not state whether it represents one or all of the products of the internal secretion of the cortex, or whether, indeed, it has any connection at all with the function of the gland.

The medullary portion consists of cell groups which assume a brown color when treated with chromic acid or dichromates, in consequence of the reduction of these compounds to brownish or reddish-brown basic chromates. For this reason it has been designated the chromaphil tissue. Now such chromaphilic cell groups are not confined to the medulla of the suprarenal gland, but are also found lying alongside the abdominal aorta, in the carotid gland and in the sympathetic system.

It was known to earlier experimenters that aqueous extracts of the entire capsules were highly toxic to animals when injected directly into the circulation, but it remained for Oliver and Schäfer in 1894 to demonstrate that extracts of the medullary part, in the most minute quantity, cause a marked rise in blood pressure and greatly stimulate the heart. In 1897 I showed that the substance responsible for these actions could be isolated from the glands in the form of a benzoyl compound.[32] Salts of a

[30] "Death and the Adrenal Gland," *Quar. Jour. of Medicine,* Vol. 8, p. 47, 1914. An interesting paper by E. R. Weidlein, a fellow of the Mellon Institute, on the adrenal glands of the whale will be found in the *Jour. of Industrial and Engineering Chemistry,* Vol. 4, No. 9, September, 1912.

[31] "Isolation of a New Vasoconstrictor Substance from the Blood and the Adrenal Cortex," *Jour. Amer. Med. Assoc.,* Vol. 61, p. 2,136, 1913.

[32] For literature see Abel and Macht, *Jour. of*

base obtained by saponifying this benzoyl derivative were shown by me (1898) to possess the characteristic chemical and physiological properties of the gland itself. To the principle thus isolated I gave the name epinephrin. Very soon after this v. Fürth (1899–1900) isolated the principle under discussion in the form of an amorphous indigo-colored iron compound, and in 1901, Takamine and Aldrich succeeded independently in precipitating the native substance with the help of ammonia, and without first subjecting it to the more complicated processes which had been used by myself some years before.

These results were soon followed by the brilliant researches of a number of organic chemists, Dakin, Jowett, Pauly and Friedmann, which culminated in the synthetic production, first, of the racemic form by Stolz in 1906, and later of the levorotatory form by Flächer in 1908, the form in which the substance exists in the gland itself. The chemical history of this remarkable blood-pressure-raising constituent which is found wherever chromaphil tissue is encountered is therefore now a closed chapter. We are no longer dependent upon the glands of the ox or the sheep for its preparation for the many uses to which it is put by the medical specialist, the surgeon and the general practitioner, but shall always be able to produce it in our laboratories as long as coal-tar remains at our disposal. In chemical language it is described as a di-hydroxymethyl-aminoethylol benzene, or more concisely and simply, it is an aromatic amino alcohol. It is as noteworthy for its instability in solution as it is remarkable for its physiological properties. It is a true product of internal secretion and can apparently be detected in the venous blood of the adrenal glands.[33] I shall not further describe its chemical properties, but would call your attention to the fact that in at least one animal, a tropical toad, *Bufo agua,* this principle occurs also as a constituent of an external secretion.

The toad, I may say here, has a very interesting history.[34] It has been regarded from the earliest times as a poisonous animal and various races, including our own, have long made medicinal use of its skin. The Chinese to this day use as a cure for dropsy a preparation derived from toad skin, called *senso.* Among western nations it has always been a folk's remedy, and almost up to the time of the introduction of digitalis (1775) as a medical agent our very best medical authorities used these skins in cases of dropsy. Dr. Langworthy, Department of Agriculture, Washington, has given me the following recipe for making a toad ointment which was in use among our early New England colonists for the treatment of sprains and rheumatism. Toad ointment: good-sized live toads, 4 in number; put into boiling water and cook very soft; then take them out and boil the water down to one half pint, and add fresh churned, unsalted butter 1 pound and simmer together; at the last add tincture of arnica 2 ounces.

The particular toad, *Bufo agua,* to which I have referred, is of further interest because the aborigines of the Upper Amazon make an arrow poison from the creamy secretion that exudes from its skin glands when it is irritated or overheated, a poison

Pharmacol. and Exp. Therapeutics, Vol. 3, p. 327, 1912.

33 It has not been conclusively shown that the blood-pressure-raising constituent of this blood is really epinephrin (adrenalin) and not an alteration product.

34 Abel and Macht, "The Poisons of the Tropical Toad, *Bufo agua,*" *Jour. Amer. Med. Assoc.,* Vol. 56, p. 1,531, 1911, and "Two Crystalline Pharmacological Agents obtained from the Tropical Toad, *Bufo agua,*" *Jour. Pharmacol. and Exp. Therapeutics,* Vol. 3, p. 1,319, 1912.

so powerful that it kills in a few moments large game, such as the stag or the jaguar.

Two years ago I was examining a specimen of this giant among toads when I noticed that this creamy secretion made on a scalpel a peculiar, greenish-blue discoloration. I at once remembered where I had seen this color years before on a scalpel used in cutting into the medulla of a suprarenal gland. Working from this hint, I was soon able to isolate the now familiar substance, adrenalin or epinephrin, from this toad's glands. Scientists have been not a little surprised to learn that this substance is present in very large amounts in the skin of this tropical toad. It is not found in the skin of the common American toad.

I also succeeded in isolating the principle to which the toad skin owes its curative power for dropsy, a very different principle from epinephrin. It has been obtained in the form of beautiful crystals and has the composition represented by the formula, $C_{18}H_{24}O_4$, and has been named bufagin.

Just as in the case of bleeding, we have here another instance of the every-day observation of mankind justified by science. That powdered toad skin could cure dropsy has been ridiculed by the learned for a century, and now we possess in bufagin and in the slightly different bufotalin, which has only recently been obtained in crystalline form from the skin of the common European toad, the actual proof of the correctness of the old belief.

We are now studying the chemical constitution of bufagin in my laboratory, and although this problem is one of great difficulty, we hope, nevertheless, that our work will throw some light on the fundamental chemical properties of cardiac stimulants. We now also understand why the secretion of the skin of *Bufo agua* may be used as an arrow poison, since it contains these two powerful drugs, epinephrin and bufagin, which in overdose act fatally on the heart and blood vessels.

We can not leave the consideration of this subject without noting the influence that the study of the pharmacological properties of epinephrin has exerted on certain departments of medical science.

Chromaphilic cells of the body, whether located in the medullary portion of the suprarenal gland, or elsewhere, all yield epinephrin, and modern studies have shown that these chromaphilic cells are intimately related to the sympathetic nervous system in their origin, and have differentiated themselves from it. We are not surprised, therefore, to find that epinephrin, the secretory product of these cells, has an elective affinity for the sympathetic nervous system, the thoracico-abdominal part of the autonomic system. The well-known symptoms that follow upon the administration of epinephrin, extreme vaso-constriction, tachycardia, dilatation of the pupil, inhibition of peristaltic movement in the alimentary canal, contraction of the pyloric and ileo-cecal sphincters, increased motility of the pregnant uterus and glycosuria have all been shown to be due to the fact that this hormone stimulates and sensitizes the sympathetic myoneural and adenoneural junctions or terminations of the sympathetic nervous system. Numerous experiments have shown that the changes induced by epinephrin in the activity of various organs which are innervated by the sympathetic nervous system are in all respects like those that are brought about by electrical stimulation of this system, and it is apparent that such experiments have already assisted in elucidating many obscure points in the functional activity of this part of the nervous system.

Other interesting observations which deal with the action of this principle upon the metabolism of the body or with the pathological changes induced by toxic doses can not be taken up here.

The discovery of the chemical structure and pharmacological properties of epinephrin has greatly encouraged investigators to take up the isolation of other active principles. Thus Abelous[35] and his coworkers showed that the intravenous injection of extracts from putrid meat caused a rise of an animal's blood pressure. Barger and Walpole[36] then proved that this effect was due to the presence of isoamylamine, phenyl-ethylamine and para-hydroxyphenylethylamine.

These amines are produced by putrefactive bacteria from proteids, and they exhibit pressor or blood-pressure-raising effects that in general are very similar to those produced by epinephrin. A close similarity in chemical structure of two of these amines, phenyl-ethyl-amine and para-hydroxyphenylethylamine, to epinephrin is shown in the graphic chemical formulæ which will presently be given. The last-named base is of special interest to us, since Barger has discovered that it is also present in ergot and is in some degree responsible for the characteristic activities of this drug. It is also present to a small extent in Emmenthaler cheese. More remarkable still is the discovery of Henze that this amine is the effective principle of a highly active poison produced by the posterior, so-called salivary glands of a certain cephalapod found in the Bay of Naples. It has long been known that this mollusc renders its prey, as the crab, quickly helpless by means of this poison and until Henze's discovery it was believed to be a toxalbumin.

We find, therefore, that p-hydroxyethylamine is produced by putrefactive bacteria, that it is present in ergot (the permanent mycelium of the fungus, *Claviceps purpurea*), and that it is the product of the metabolism of a glandular tissue. In each case it may be assumed that it is obtained by chemical reactions from the protein molecule, its immediate precursor being the innocuous tyrosin.

By merely splitting off a molecule of CO_2 from tyrosin, as was demonstrated by Barger, we at once secure this amine, as shown by the accompanying formulæ. As a recent writer has remarked, "Our poisons and our drugs are in many instances the close relatives of harmful compounds that represent the intermediary steps in the daily routine of metabolism."[37]

The fact that putrefactive microorganisms can produce poisonous amines by decarboxylating the harmless amino-acids has become of the highest importance to medicine. It would appear that we have at last got onto the right road for the chemical investigation of alimentary toxemia and its alleged consequences, such as arteriosclerosis and chronic renal disease. Phenylalanine, tyrosine, tryptophane and histidine, the harmless precursors of toxic amines, are always present in the intestine, and when they are acted upon by an excessive number of certain microorganisms the resulting toxic bases will surely be formed in excess. If they are then taken up into the blood in quantities too large for transformation by the liver, or other defensive organs, into less harmful derivatives they must inevitably manifest their pharmacological and toxicological properties. Let me give but one further example of recent advances in this field. It has been shown by Barger and Dale[38] that the highly poi-

35 *Compt. rend. Soc. de Biol.*, Vol. 58, I., pp. 463 and 530 (1906), Vol. 64, p. 907, 1908.

36 *Jour. of Physiol.*, Vol. 38, p. 343, 1909.

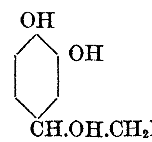
37 *Jour. Amer. Med. Assoc.*, editorial comment, Vol. 62, January 3, 1914.

38 *Jour. of Physiol.*, Vol. 40, p. 1,910; Vol. 41, p. 499, 1910–11. Consult also the work of Ackermann, who first demonstrated that when pure his-

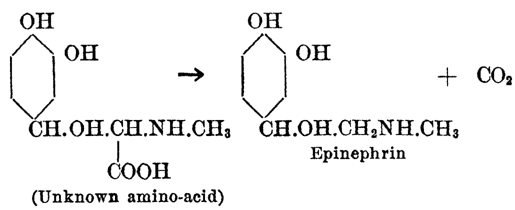
sonous depressor base, β-imino-azolylethylamine may be isolated from the intestinal mucosa, and Berthelot and Bertrand[39] have demonstrated that it is in all probability formed in the intestinal canal from histidine by the decarboxylating action of a bacillus newly discovered by them which they have named *Bacillus aminophilus intestinalis.* These investigators have shown that their bacillus produces the base from histidine even in the presence of 0.3 per cent. lactic acid, unless, indeed, an excess of glucose be present, in which case only this is attacked, and they have also made the interesting observation that rats, fed on a milk diet, are not affected by either *Proteus vulgaris* or *Bacillus aminophilus intestinalis* when these organisms are given separately, but that when they are given simultaneously the rats succumb to a diarrhea in from four to eight days.

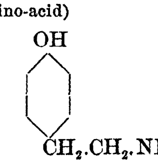
Investigations on the pharmacological behavior of β-imino-azolylethylamine have shown that it acts very powerfully on plain muscle, stimulating the isolated uterus, for example, to contraction in the almost unbelievable dilution of 1:250,000,000.[40] The muscular coats of the guinea-pig's bronchioles are so sensitive to its action that large pigs are killed in a few minutes by the intravenous injection of a half a milligram. The death of the animal is due to asphyxia produced by a spasm of the bronchioles. Recently investigators have been much occupied in studying similar features in the symptoms of the poisoning by large doses of the base and those observed in anaphylactic shock (action on the circulation, body temperature, respiration, etc.) and some do not hesitate to affirm that the poisons of anaphylactic shock must be put into the same pharmacological class with the proteinogenous bases that we have been considering.

We may now give the chemical formulæ that illustrate the various relationships that have been discussed.

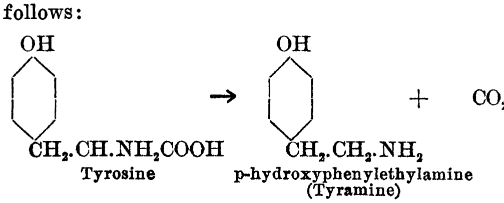
1. 

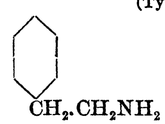
Epinephrin, adrenaline, suprarenin, possibly derived by decarboxylation from a still unknown amino acid, dioxyphenyl-α-methylamino-β-oxypropionic acid, as suggested by M. Guggenheim. *Therap. Monatsh.*, XXVII., p. 508, 1913.



2. 

p-hydroxyphenylethylamine, derived from p-hydroxyphenyl-α-amino-propionic acid, or tyrosine, as follows:



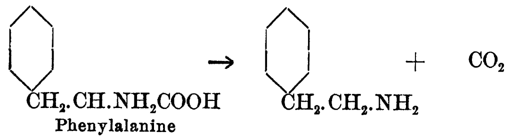
3. 

tidine is submitted to the action of putrefactive bacteria a considerable yield of β-imino-azolylethylamine is produced. *Ztschr. f. physiol. Chem.* Vol. 64, p. 504, 1910.

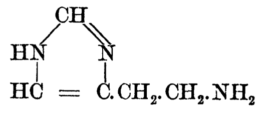
39 *Compt. rend. de l'Acad. des Sciences,* Vol. 154, pp. 1,643 and 1,826. See also Mallenby and Twort, "On the Presence of β-imino-azolylethylamine in the Intestinal Wall, with a Method of Isolating a Bacillus from the Alimentary Canal which Converts Histidine into this Substance," *Jour. of Physiol.*, 45, p. 53.

40 See Fröhlich and Pick, *Arch. f. Exp. Pathol. u. Pharmakol.*, Vol. 71, p. 23, and Sugimoto, *ibid.*, Vol. 74, p. 27.

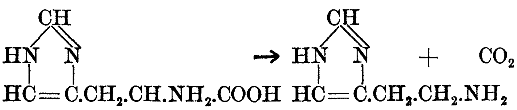
Phenylethylamine, derived by decarboxylation from phenyl-α-amino-propionic acid or phenylalanine, as follows:



4.



β-Imidoazolylethylamine, histamin, obtained by decarboxylation of histidine, as follows:



IV. I come now to the concluding portion of my address. That science in general is a basic fact in the development of commerce and industry seems to be fully appreciated in this city, as shown by the establishment of the Mellon Institute of Industrial Research and School of Specific Industries, through the munificence of two of your public-spirited citizens, the Messrs. Richard B. and Andrew W. Mellon. I believe that no act of their lives will give them more enduring satisfaction than this which marks out your city as one more great center of industry which acknowledges the dependence of all advance in material civilization on the quiet labors of the investigator. This dependence has been forcibly expressed by former ambassador James Bryce in an address to the members of the National Academy of Sciences.

> You men of science are really the rulers of the world. It is in your hands that lies control of the forces of activity; it is you who are going to make the history of the future because all commerce and all industry is to-day far more than ever the child and product of science. . . . It is in your hands that the future lies, far more than in those of military men or politicians.

Let me also in this connection recall the inspiring words of that great investigator and benefactor of mankind, Louis Pasteur, which point out the still wider influence of science. He wrote:

> Laboratories and discoveries are correlative terms; if you suppress laboratories, physical science will be stricken with barrenness and death, it will become mere powerless information instead of a science of progress and futurity; give it back its laboratories, and life, fecundity and power will reappear. . . . Ask that they be multiplied and completed. They are the temples of the future, of riches and of comfort. There humanity grows greater, better, stronger. There she can read the works of nature, works of progress and universal harmony, while humanity's own works are too often those of barbarism, of fanaticism and destruction.

And here I shall permit myself to speak more specifically of the paramount importance of chemistry in biological and medical research. The subjects to which I have been calling your attention to-night, viz., the still unknown chemical properties and molecular structure, with the single exception of epinephrin, of the mysterious, correlating substances stored and formed in the many organs of internal secretion, and the equally unknown character of numerous constituents of the circulating blood, both offer a virgin field to the biologist with a chemist's training.

The practical importance of decisive chemical advances along this line are hardly to be overstated. At present we meet only vast confusion and contradictory theories. A single clean-cut discovery, the separation from another of these glands of a definite chemical individual shown to possess one or more of the specific actions of the gland would clear away the mists at once, and we should see the same rapid progress that has followed the isolation of epinephrin, which is only one, and perhaps not the most important, constituent of the suprarenal gland.

What a flood of light was thrown on the whole question of carbohydrate metabolism in the discovery by Claude Bernard of glycogen in the liver! Innumerable fruitful researches have come from this as a starting-point, and their bearing on our understanding of such diseases as diabetes mellitus has been of the most fundamental nature.

Miescher's discovery of the existence of protamin nucleate in the spermatozoan heads of the Rhine salmon is another case of the far-reaching importance of a definite chemical fact for both biology and medicine. For further discoveries in the field of nucleinic acids, a later worker, Professor Kossel, received the Nobel prize. To name only one practical outcome of these discoveries, our theories of the origin of uric acid in gout and of the purins in general have undergone entire transformation.

The actual finding of definite and specific chemical principles in the organs of internal secretion has in each case an importance in the way of explaining and correlating a large number of disconnected facts, only to be likened to the discovery of the etiological cause of an infectious disease. The bacilli of tuberculosis or of typhoid, or the protozoa of syphilis and sleeping-sickness, are illuminating examples in point. Here, too, simplicity at once took the place of what had been confused and complex, and a multitude of already recorded facts fell into their proper place.

From my insistence on our ignorance of the specific secretory products of the organs of internal secretion, and of numerous constituents of the blood, it is not to be inferred that important chemical facts are lacking with regard to these tissues. On the contrary, a vast number of facts, some of immediate, others of potential significance, have been amassed by an army of workers in the past 30 years; it is their *relation to each other and to an underlying cause* which remains obscure. For example: it has been recently shown by Cramer and Krause[41] that when fresh thyroids are fed to cats or rats kept on a carbohydrate-rich diet, the glycogenic function of the liver is inhibited, and in consequence this organ is soon found to contain only traces of glycogen. And these investigators suspect that the well-known action of thyroid secretion on the metabolism is effected through this change in the carbohydrate metabolism. But this important discovery can not reach its full significance until we know the chemical properties of the special hormone of the thyroid gland which is carried in the blood to the liver and there prevents the formation of glycogen even though the food may contain an abundance of carbohydrate.

Thus, too, one of the facts known about the parathyroids, as shown by MacCallum and Voegtlin,[42] is that their removal from the body is followed by increased excretion of calcium salts. This chemical discovery also can not yet be brought into a causal connection with a definite chemical constituent of the gland.

That I may not be accused of placing too much emphasis upon only one mode of attack in biological and medical research, let me say that I am fully aware of how many-sided are all these problems, and that fundamental discoveries have been made and will continue to be made without the aid of chemistry. This is true especially in the field of morphology. But as soon as we touch the complex processes that go on in a living thing, be it plant or animal, we are at once forced to use the methods of this science. No longer will the microscope, the kymograph, the scalpel avail for the complete solution of the problem. For the further analysis of these phenomena which

[41] *Proc. Roy. Soc. B.*, Vol. 86, p. 550, 1913.

[42] *Jour. Exp. Med.*, Vol. 11, p. 118, 1909.

are in flux and flow, the investigator must associate himself with those who have labored in fields where *molecules and atoms, rather than multicellular tissues or even unicellular organisms, are the units of study.* To-day investigators in biology and medicine are reaching out with eager hands into the more exact branches of science. The great progress in biology and in medicine that has been made during the past century proves that advantages hardly to be imagined must follow upon the further application of physics and chemistry to these sciences. A striking example of the debt which medicine owes to that newer branch of chemistry called physical chemistry is seen in our better understanding in the last twenty years of certain dynamic equilibria of the body, such as the relationship between the hydrogen and the hydroxyl ions of the blood and tissues, of surface tension, osmotic pressure and the colloidal state.

I also recognize that all the various aspects of any one problem in our field are intimately bound together, and that progress along the chemical side, for instance, of a question may have to wait on the clearing up of the morphological side. When I have the honor of being consulted by a young man who has not yet found himself intellectually but who is filled with the desire to devote his life to some branch of medicine, be it clinical medicine, pathology, hygiene, bacteriology, physiology or pharmacology, my advice always is, "Study chemistry for at least three years. Try with all your power to master enough of this great science to start you in your career." Why not make this attempt at a time of life when one still takes kindly to a rigid discipline[43] such as this science exacts? To this preparation must be added the special medical training of another four or more years. A long road to travel? But I find that many young men have entered upon it with great enthusiasm.

I do not mean that this long tutelage is to be a cramming process. I have in mind conditions where these students shall be constantly under the influence of teachers who are themselves investigators and daily engaged in the search for new truths. Under the stimulus of such examples our young man is saved from the sterile life of the mere crammer, because he sees the relation of what he learns to living questions. During this period of study and growth he will himself make occasional attempts at the solution of problems. Even with the best preparation, workers in our fields have always to return again and again to the fundamental sciences for assistance.

But to what end is all this preparation for our young man? Is it solely that he may solve problems whose solution is of practical value to mankind? Is his mind to shape itself only to the insistent demands of utility? Even then our method of training will yield the largest profit. But it does vastly more than that. Thus trained our young scholar will be able to see beyond the immediately practical problem, even though it be as great a thing as the discovery of the cause and cure of the plague that decimates a people. *Greater even than the greatest discovery is it to keep open the way to future discoveries.* This can only be done when the investigator freely dares, moved as by an inner propulsion, to attack problems not because they give promise of immediate value to the

[43] The professor of physics in McGill University, Dr. A. S. Eve, has recently expressed himself as follows in a paper describing modern discoveries on the constitution of the atom (*Jour. Franklin Institute,* 1915, p. 269): "It may be noted that the discoveries set forth in this brief summary have been achieved by savants in the western half of Europe, and it may be asked if the education in the New World is at the present time sufficiently thorough, imaginative and philosophical."

human race, but because they make an irresistible appeal by reason of an inner beauty. Some of the greatest investigators indeed have been fascinated by problems of immediate utility as well as by those that deal with abstract conceptions only. Helmholtz invented the ophthalmoscope and thus made modern ophthalmology possible, and at the same time did work of the highest order in theoretical physics and wrote on the nature of the mathematical axioms and the principles of psychology. Lord Kelvin took out patents on great improvements in the compass and on oversea telegraphy, and also made contributions to our knowledge of the ultimate constitution of the atom and the properties of the ether. From this point of view the investigator is a man whose inner life is *free* in the best sense of the word. In short, *there should be in research work a cultural character, an artistic quality, elements that give to painting, music and poetry their high place in the life of man.*

Ladies and gentlemen, I have attempted in this hour to point out some recent advances that have been made in the study of the blood and of the organs of internal secretion, and have cited the beneficent effects of even these small advances—a very few bright stars in a darkened sky—in order to emphasize the great rôle that chemistry is destined to play in biology and medicine. I have strongly urged that those who are to be medical teachers and investigators should not content themselves with a mere smattering, but endeavor to acquire a really sound training in one of the fundamental sciences.

You, my colleagues, working with open-minded and generous trustees, must see to it that the men selected for important posts shall be those that are capable of training and inspiring the young men who in their turn will furnish the leadership of the future.

In our country many agencies combine to foster the higher learning. It is to the lasting honor of men of wealth that they have appreciated the need for institutes of research and in a number of notable instances have placed large sums at the disposal of science. They have responded nobly to that appeal of Pasteur which I have already cited in which he calls laboratories "the temples of the future, of riches and of comfort."

John J. Abel

The Johns Hopkins Medical School

CHARLES WILLIAM PRENTISS

Charles William Prentiss, professor of microscopic anatomy in the Northwestern University Medical School, died at Chicago on the twelfth day of June. Born in Washington, D. C., August 14, 1874, he spent many of his early years at Middlebury, Vermont.

His undergraduate work was done at Middlebury College, where his father, Dr. Charles E. Prentiss, was librarian. He was graduated with honors in 1896 but remained there another year as a graduate student. During the next three years he was at Harvard University in the department of zoology. Here he received the degree of doctor of philosophy in 1900. The following year was spent at the Harvard Medical School as instructor in anatomy. He was then awarded a Parker Traveling Fellowship and studied in Europe for two years. Although the greater part of this time was spent at Freiburg and Naples his work with Bethe at Strassburg had the more important influence on his career.

On his return to America he held appointments successively in the zoological departments of Western Reserve University and the University of Washington, Seattle. While in the latter place he first developed the symptoms of duodenal ulcer from which he suffered for the last eight years. He came to Northwestern University Medical School as assistant professor of anatomy in 1909 and was made professor of microscopic anatomy in 1913.