THE CROONIAN LECTURES ON SOME POINTS IN THE PATHOLOGY OF RHEUMATISM, GOUT, AND DIABETES.

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LECTURE I.

MR. PRESIDENT AND GENTLEMEN,—In rheumatism, gout, and diabetes, we have three disorders about the pathology of which there is still much that is obscure and unsettled. On this ground alone, therefore, they present a very attractive and interesting field for investigation and study; and the interest is intensified by the conviction that a clearer insight, as regards the changes which take place in either of these disorders, would furnish the clue by which to unravel many of the most important phenomena which are associated with other diseases.

I class these three disorders together, because they seem to possess a certain relationship with each other. Cases occur, in which it is difficult to decide whether the disease must be regarded as rheumatic or as gouty; not unfrequently, transient diabetes appears as the harbinger of a gouty attack; and on the other hand, gouty, rheumatic, or neuralgic pains are very common accompaniments of diabetes. In all we have changes, differing however in character, showing themselves in the blood; the result of abnormal metabolism, either in the muscular or in the glandular tissues.

What are the changes which take place in the tissues, or in the blood? In attempting to answer these inquiries, we meet at the very outset of our investigation with a most serious difficulty. Before we can attempt to unravel the changes which will occur in any particular tissue or fluid, either in health or in disease, we must know what is the constitution of the particular substance we are about to investigate. I do not mean its ultimate chemical composition—that is easily arrived at—but its proximate constituents, its structural formula. It seems almost superfluous to make such a statement. But the difficulty which presents itself is, that we do not know what are the proximate elements which make up living tissue; nor what are the chemical changes which take place as it performs its function; nor the alteration in the arrangement of its molecules, as it passes from an active to an effete state. By chemical investigation, it has been shown that various complex bodies which did not exist as such in the living tissue can be extracted from the different tissues after death; in the process of dying, a molecular change of some kind takes place; the ultimate atoms are no longer arranged as they were in the living state, and new substances are formed. The chemical features of dead and living tissues are strikingly different from each other. Blood, for instance, when shed from the vessels of a living body, is perfectly fluid; the moment it is shed it undergoes changes; in a short time coagulation takes place, and a certain substance, fibrin, appears in the blood plasma, the coagulation being the result of a chemical process between certain factors in the blood and the conversion of living *plasmine*, or some part of *plasmine* (fibrinogen) into fibrin.

A living muscle possesses "irritability," which it loses in dying, and is succeeded by what is termed "rigor mortis," during the onset of which, chemical change takes place, and the muscle, being previously neutral or faintly alkaline, acquires a distinctly acid reaction; and this change is accompanied by a large and sudden development of carbonic acid. From dead muscle, by a certain process, we can obtain myosin, one of the proteids, which does not exist, however, in that form in living muscle. From living muscle we can obtain a slightly opalescent substance, termed *muscle-plasma*, which at first is quite fluid, but when exposed, at the ordinary temperature, becomes a solid jelly, splitting up afterwards into clot and acid serum. The loose, granular, and flocculent clot is myosin, which has been produced by some chemical change in the living plasma. The serum contains other proteid substances, serum-albumin, etc., closely resembling myosin and fibrin in their properties, and more especially in their chemical composition.

[1318]

Now, notwithstanding numerous researches, no definite agreement has been arrived at as to the constitution of dead proteid or albumenoid substance, or as to the manner in which the various substances, leucine, tyrosine, etc., are contained in it. The formula by which, according to Lieberkühn, a proteid or albumenoid may be approximately represented, is

and this, according to Hlasiwetz and Habermann, by hydration, may be split up into aspartic acid, glutamic acid, leucine, tyrosine, and ammonia. Schützenberger obtained other products of decomposition, but none of the attempts hitherto made to assign a molecular structure to the substance have been considered successful. If such is the case as regards dead tissue, it may appear somewhat presumptuous and rash on my part, to endeavour to assign a molecular structure, chemically, to living tissue. But, if this problem could be solved, if we were acquainted with the normal chemical changes which take place in the proximate constituents of a tissue in health, and which, when modified, produced disease, what a flood of light would be thrown upon many points in pathology and therapeutics, which at present are very dimly comprehended; and here I need only refer to the action of so-called alterative remedies, such as iodine, bromine, mercury, and arsenic. Even at the imminent risk of failure, then, I think it is worth while to make some attempt to solve the problem, and to bring forward some of the points which have been suggested to me by the action of remedies in disease. I may at least advance a theory which to myself appears to explain many changes in the tissues; and I shall be content if, whilst endeavouring to arrive at the truth, what I say may direct attention to the subject, and be useful to others more competent than myself to work out its solution.

A certain number of substances which can be obtained from albuminous material, or which are developed in the animal economy, can be produced in more or less diverse ways in the laboratory—lactic acid, leucine, glycocine, etc.

In examining and investigating the various methods by which these bodies may be prepared artificially in the laboratory, we come upon the remarkable fact that a large number of them can be obtained from a particular series of cyanogen compounds, the so-called cyan-alcohols or cyanhydrins—bodies which may be obtained by oxidising the various alcohols, and so forming the aldehyde, and then combining this with hydrocyanic acid. For instance,

Now these cyan-alcohols are very unstable bodies, readily undergoing change. Treated with ammonia, they form a series of cyan-amides, which also are very unstable, and easily undergo condensation, being converted into imido-nitriles with elimination of ammonia. These facts at once suggest the inquiry: Have we not in these cyanogen compounds substances possessing some properties that belong to living tissue, namely, those of undergoing intramolecular change, and also condensation? And, further, if from these substances we can obtain the various products which result from the disintegration of albumen, may not albumen itself be simply a compound made up of these elements?

Let me indicate some of the animal products which may be obtained from these cyan-alcohols, and show how these various substances are formed.

Leucine is very largely diffused in the animal organism, and may be obtained by various processes from albumen, flesh, gelatine, casein, etc.²

By oxidising amylic alcohol with potassium chromate and sulphuric acid, and distilling, we obtain amylic or valerianic aldehyde³—

Mixed with aqueous ammonia, the aldehyde is converted into valeral ammonia, and this, digested with hydrocyanic acid and hydrochloric acid, is converted into leucine—

This is the usual way of obtaining leucine artificially; but Tiemann

¹ Miller's *Elements of Chemistry*, Part III 1880, p. 733.

² Watt's *Dictionary*, vol. iii, p. 574.

³ *Ib.*, vol. v, p. 973.

⁴ *Ib.*, vol. v, p. 974.

⁵ Fownes, *Manual of Org. Chem.*, 1877, p. 335.

has shown⁶ that the amido-acids, both of the fatty and aromatic series, may be obtained by converting the aldehydes and ketones into cyan-alcohols, and then into amido-nitriles or cyanamides. We may consequently also have the following changes:

Leucine prepared in this way is not quite identical with animal leucine. The explanation I venture to suggest is, that just as sarcosolactic acid is a compound of ethidene and ethene lactic acids, so leucine is a compound of several amido-acids, the molecule C_5H_{10} being made up in different ways

or it may be prepared in the following manner:—

By the oxidation of the pentyl alcohol, diethyl carbinol, we obtain diethyl ketone:⁷

Tiemann⁸ has shown that this, with hydrocyanic acid, is converted into a cyanhydrin, which, acted upon by ammonia and then by an acid, produces leucine—

Butene cyan-alcohol $\text{C}_4\text{H}_9 \cdot \text{CH} \begin{Bmatrix} \text{OH} \\ \text{CN} \end{Bmatrix}$ —may in like manner be prepared from the butyric aldehydes, from aldol or butene glycol, and from one form of this we obtain Amido-isovaleric acid, which occurs in the pancreas of the ox.⁹

Amido-valeric acid or butalanine was also obtained by Schützenberger from albumen.¹⁰

Similarly by the oxidation of propyl alcohol, propionic aldehyde is obtained, which may be converted into propene cyan-alcohol¹¹—

⁶ *Berichte der deutsch. chem. Gesell.*, xiv, s. 1885. "The amido-acids of the fatty series are easily obtained by the familiar reactions which take place on treating aldehyde ammonia with hydrochloric and hydrocyanic acids, and which led Strecker to the discovery of alanine. . . . The reactions indicated by Strecker take place unquestionably according to the following general formulae:

and

The question arises, whether the cyanamide

could not be obtained more readily from the cyanhydrines of the aldehydes

by digesting them with ammonia, expecting the ultimate change to be as follows:

The truth of this supposition has been confirmed by experiment.—*Berichte*, xiii, s. 382.

⁷ Fownes, *Manual of Org. Chem.*, 1877, p. 163.

⁸ *Berichte*, xiv, s. 1975.

⁹ Fownes, p. 335.

¹⁰ *Comptes Rendus*, t. lxxxi, p. 1,110.

¹¹ Fownes, *Manual of Org. Chem.*, 1877, p. 329.

propionic aldehyde propene cyan-alcohol

By oxidation of isopropyl alcohol, dimethyl ketone or acetone may be produced and then converted into dimethyl-ketone-cyan-alcohol¹²—

acetone dimethyl-ketone-cyan-alcohol

Propene cyan-alcohol may also be obtained, by converting propene glycol into chlor-alcohol¹³ and acting upon this with potassium cyanide—

Each of these cyan-alcohols, treated with ammonia and then with acids, will yield the corresponding amido-butyric acid, a substance also obtained by Schützenberger from albumen—

If the cyan-alcohols are treated directly with acids we obtain the corresponding oxybutyric acid—

By oxidation oxy-isobutyric acid is resolved into carbonic acid and acetone, a substance which sometimes appears in diabetic urine—

Ethidene and ethene cyan-alcohols may be prepared (i) by oxidising ethylic alcohol, and treating the aldehyde so obtained with hydrocyanic acid—

aldehyde ethidene cyan-alcohol

(ii) By converting ethene alcohol or glycol into a cyan-alcohol—

And from these cyan-alcohols the corresponding amido-acids or alanines may be obtained, namely—

Alanine or amido-propionic acid was also among the products which Schützenberger obtained from albumen.

Lactic acid, again, is an important product of the animal organism. It is developed when a living muscle contracts, and it is produced when a muscle dies. The variety of this acid, which is obtained by the disintegration of albuminous compounds, and is formed during the contraction of tetanus of muscular fibres, and hence called sarco-lactic acid, may be regarded as a mixture of two kinds of lactic acid¹⁵ the more abundant being paralactic acid or

ethidene lactic acid $\text{CH}_3 \cdot \text{CH} \begin{Bmatrix} \text{OH} \\ \text{COOH} \end{Bmatrix}$ the other ethene lactic

¹² Fownes, *Manual of Org. Chem.*, 1877, p. 329.

¹³ *Ibid.*, p. 176.

¹⁴ Fownes, *Manual*, p. 319.

¹⁵ Watt, *Dictionary of Chemistry*, vol. vii, p. 1100.

acid $\text{CH}_2 \cdot \text{C}_n\text{H}_2 \left\{ \begin{array}{l} \text{OH} \\ \text{COOH} \end{array} \right.$. Now (i) by treating ethidene cyan-alcohol, with acids or alkalies, paralactic or ethidene lactic acid is obtained

(ii) By treating ethene cyan-alcohol in the same way, ethene lactic acid is obtained.

Methene cyan-alcohol, $\text{CH}_2 \left\{ \begin{array}{l} \text{OH} \\ \text{CN} \end{array} \right.$. Though methylic aldehyde has not yet been isolated, but only obtained in solution in methylic alcohol¹⁷, we may infer from the reactions of the other members of the alcoholic series, that similar changes will be produced here. That by oxidising methylic alcohol the aldehyde will be obtained, which, combined with hydrocyanic acid, will form methene cyan-alcohol.

methylic aldehyde methene cyan-alcohol
and from this we should obtain amido-acetic acid, or glycocine—

Again, by acting on albumenoids with certain oxidising agents, such as a mixture of potassic dichromate or manganic dioxide with sulphuric acid, (Guckelberger¹⁸ obtained the following products:

Now, all these acids can be obtained from the bodies under discussion, namely, the cyan-alcohols. By treating them with acids, we have, first of all, the corresponding oxyacid formed.

and the oxyacids of the form

when oxidised are converted into CO_2 , the corresponding acid of the acetic series and water,

ethidene cyan-alcohol $\text{CH}_3 \cdot \text{CH} \left\{ \begin{array}{l} \text{OH} \\ \text{CN} \end{array} \right.$, for instance, may be converted into lactic acid $\text{CH}_3 \cdot \text{CH} \left\{ \begin{array}{l} \text{OH} \\ \text{COOH} \end{array} \right.$, which, treated with chromic acid mixture, is oxidised to formic and acetic acids¹⁹—

lactic acid acetic acid formic acid
and the formic acid may be further oxidised into carbonic acid and water.

In the same way, butene cyan-alcohol is converted into oxy-valeric acid $\text{C}_3\text{H}_7 \cdot \text{CH} \left\{ \begin{array}{l} \text{OH} \\ \text{COOH} \end{array} \right.$ which oxidised, is transformed into carbonic dioxide and butyric acid.²⁰

Oxy-iso-valeric acid iso-butyric acid

From these cyan-alcohols, then, we can obtain the corresponding amido-acids, glycocine leucine, etc., and all the acids of the acetic series, as well as those of the lactic acid series. This being the case, we come to the question; Can we reverse the process, as we know can be done chemically in many similar cases? Can the amido-acids be converted into the cyan-alcohols, and can we then theoretically build up albumen from such constituents?

The first step towards this is, I think, indicated in what follows when amylaceous matter or sugar is introduced into the alimentary canal. A certain accumulation of glycogen takes place in the liver, and, further, a considerable quantity of sugar can be slowly injected into the portal vein without any appearing in the urine. The sugar, therefore, as it passes into the liver, loses a molecule of H_2O , and glycogen is formed. We cannot as yet tell how glucose in a living plant is converted into starch, nor can we tell in what way the liver transforms the glucose into glycogen; all we know is that, in some way, in the tissue glucose is dehydrated and glycogen is formed.²¹

Now, in order to obtain the various amido-acids from albuminous tissue, the reverse process must be adopted; the tissue must be hydrated, that is, a certain amount of water must enter into combination with it.²² Some of these amido bodies are found in the alimentary canal; glycocine and taurine appear as the result of the decomposition in the duodenum of the biliary acids, glyco- and taurocholic acids, these two acids by hydration splitting up into cholic acid and glycocine, and cholic acid and taurine respectively.

the cholic acid passing off by the intestine, the glycocine and taurine being reabsorbed.

are also among the substances produced when proteid substances are digested in the alimentary canal. What becomes of them?

"One result of the action of the pancreatic juice is the formation of considerable quantities of leucine and tyrosine. In dealing with the statistics of nutrition, our attention will be drawn to the fact that the introduction of proteid matter into the alimentary canal is followed by a large and rapid excretion of urea, suggesting the idea that a certain part of the total quantity of the urea normally secreted comes from a direct metabolism of the proteids of the food, without these really forming a part of the tissues of the body. We do not know to what extent normal pancreatic digestion has for its product leucine, and its companion tyrosine; but if, especially when a meal rich in proteids has been taken, a considerable quantity of leucine is formed, we can perceive an easy and direct source of urea, provided that the metabolism of the body is capable of converting leucine into urea. That the body can affect this change is shown by the fact that leucine, when introduced into the alimentary canal in even large quantities, does reappear in the urine as urea; that is, the urine contains no leucine, but its urea is proportionately increased; and the same is probably the case with tyrosine. Now the leucine formed in the alimentary canal is carried by the portal blood straight to the liver; and the liver, unlike other glandular organs, does, even in a perfectly normal state of things, contain urea. We are thus led to the view that among the numerous metabolic events which occur in the hepatic cells, the formation of urea out of leucine, or out of other antecedents, may be ranked as one.....Probable, therefore, as this view may seem, it has not as yet been established as a fact."

"The view that leucine is transformed into urea lands us, however, in very considerable difficulties. Leucine, as we know, is amido-caproic acid; and, with our present chemical knowledge, we can conceive of no other way in which leucine can be converted into urea than by the complete reduction of the former to the ammonia condition (the caproic acid residue being either elaborated into a fat or oxidised into carbonic acid), and by a reconstruction of the latter out of the ammonia so formed. We have a somewhat parallel case in glycin. This, which is amido-acetic acid, when introduced into the alimentary canal, also reappears as urea; here, too, a reconstruction of urea out of an ammonia-phase must take place."²³

Again, "To ascertain the influence of the liver in the formation of urea, Solnikoff has established a direct connection between the portal and jugular veins by means of an India-rubber tube, an operation which, if carefully performed, is borne with impunity. Vascular pressure at first lowered soon returns to the normal. The urinary

¹⁶ Fownes, *Manual*, p. 319.

¹⁷ Miller's *Elements of Chemistry*, part iii, 1880, p. 728.

¹⁸ Liebig's *Annal*, lxiv, 39.

¹⁹ Fownes, p. 325.

²⁰ *Ibid.*, p. 330.

²¹ See Foster's *Physiology*, 4th ed., pp. 418-422.

²² See Schützenberger's experiments, *Comptes Rendus*, ts. lxxx, lxxxi, lxxxiv.

²³ Foster's *Physiology*, 4th ed., pp. 438, 439.

secretion was, however, completely arrested, and was not re-established until urea had been injected into the veins of the animal. The only effect of these injections was to raise the vascular pressure; the results were in no way modified by the preceding section of the splanchnic nerves. If, on the other hand, instead of the portal, the crural vein is placed in communication with the jugular vein, the urinary secretion is unchanged. It is thus clear that the urea which passes out of the system by the kidneys, enters the circulation with the blood which issues from the liver.²¹

No much for the physiological side; let us turn to the pathological. Frerichs²² pointed out that, in acute atrophy of the liver, the urine contains a large quantity of leucine and tyrosine, and that urea almost or entirely disappears.

It is evident from these statements that these amido-acids, when introduced into the alimentary canal of a healthy animal, are carried by the portal blood into the liver, and there undergo some change, urea being one of the products. It is hardly intelligible, however, that the nitrogen in the fresh nutritive material should immediately be transformed into urea, and as such at once pass out of the system; and I shall endeavour presently to show that this is not the case, and subsequently to show that some of the glycocine, at least, is not concerned in the formation of urea.

These amido-bodies or glycines are capable of uniting with each other (Hofmeister), and it is probable that their molecular weights are at least double as great as their formulæ would indicate.²³ They may be represented by the formula

Now, as the function of the liver in the formation of glycogen seems to be the dehydration of glucose, the question naturally suggests itself: What compounds would result from the liver acting in the same way on these duplex or triple glycines; what substances would be produced by their dehydration? Can they in any way be converted into a series of cyan-alcohols?

From two molecules of glycocine dehydrated²⁷ we should have

A very interesting point arises here. In 1828, Wöhler showed that urea $\text{CO} \left\{ \begin{array}{l} \text{NH}_2 \\ \text{NH}_2 \end{array} \right\}$ can be produced by molecular transformation of ammonium cyanate $\text{CNO} \cdot \text{NH}_4$, this change taking place simply by heating a solution of the latter. Pflüger,²⁴ in calling attention to the great molecular energy of the cyanogen compounds, suggested that the functional metabolism of protoplasm by which energy is set free, may be compared to the conversion of the energetic unstable cyanogen compounds into the less energetic and more stable amides. In other words, that ammonium cyanate is a type of living, and urea of dead nitrogen, and the conversion of the former into the latter is an image of the essential change which takes place when a living proteid dies.²⁵ In accordance with this view then, $\text{CO} \cdot \text{NH}$ in the above formula for the dehydration of glycocine would represent dead nitrogen, and as the substance becomes part of a living tissue, it would be transformed into CNOH .

The two molecules of glycocine, therefore, on passing through the liver would be transferred as follows:

Similarly

and in the same way these compound molecules may be connected together by combining the COOH in one with the NH_2 in the other, with elimination of H_2O .

By dehydration of the glycines, then we should have generally

and in this way we arrive at an atomic combination of the cyan-

alcohols $\text{C}_n\text{H}_{2n} \left\{ \begin{array}{l} \text{OH} \\ \text{CN} \end{array} \right\}$ united to a cyanamide, $\text{C}_n\text{H}_{2n} \left\{ \begin{array}{l} \text{NH}_2 \\ \text{CN} \end{array} \right\}$

and an acid $\text{C}_n\text{H}_{2n} \left\{ \begin{array}{l} \text{OH} \\ \text{COOH} \end{array} \right\}$

Another of the glycines; namely, tyrosine $\text{C}_6\text{H}_4 \left\{ \begin{array}{l} \text{OH} \\ \text{C}_2\text{H}_4(\text{NH}_2)\text{COOH} \end{array} \right\}$ or para-oxyphenyl-amido-propionic acid, which is obtained from albumen and other proteid substances, may be thus represented

²¹ *Lancet*, December 3rd, 1881, p. 971.

²² *Klinik der Leberkrankheiten*, 1858, s. 206.

²³ *Miller's Chemistry*, 1880, part iii, p. 866.

²⁷ In dealing with the formation of uric acid later on, I shall show that dehydration of glycocine does take place in the formation of hydantoin in the living system.

the nascent ammonia may, however, combine with the hydroxyl of the next molecule in the chain to form a cyanamide which, hydrated, would form the amido-acid, ammonia being again liberated, and forming a cyanamide with the next molecule higher up; and so on all through the different series. The changes then may be thus represented

Two different conditions now present themselves; (i) the molecule $CH_2 \begin{Bmatrix} NH_2 \\ CN \end{Bmatrix}$ may become detached, or (ii) the larger molecule $CH_2 \begin{Bmatrix} OH \\ CN \end{Bmatrix} \cdot NH_2$ may be separated from the chain. In case (i) we should have by hydration

and so on, the remaining two molecules by hydration being converted into $CH_2 \begin{Bmatrix} NH_2 \\ COOH \end{Bmatrix}$ glycocine, $C_2H_4 \begin{Bmatrix} NH_2 \\ COOH \end{Bmatrix}$ alanine, and NH_3 , which last passes on to form another cyanamide in the chain.

and

If the larger molecule $CH_2 \begin{Bmatrix} OH \\ CN \end{Bmatrix} \cdot NH_2$ is detached from the

chain, we have then the elements of creatinine $C_4N_3H_7O$, and the transposition of the atoms may be supposed to take place as follows: if the $CN \cdot NH_2$ is detached, and takes the form

$C \begin{Bmatrix} NH \\ NH \end{Bmatrix}$ we should have

But, as I have previously pointed out, $CN \cdot OH$ represents living, $CO \cdot NH$ dead nitrogen; the formula therefore becomes

The ordinary formula for creatinine.³¹

The change is, perhaps, more intelligible if we consider the formation of creatine. If before the separation of the molecule $CN \cdot NH_2$, we hydrate the compound, we have

The ordinary formula for creatine.

A third mode in which the molecules may become detached is the following. The ammonia, when liberated by hydration of one of the bodies, may, instead of combining with the hydroxyl of a cyan-alcohol higher up in the chain to form a cyanamide, combine with the molecule $CNOH$ to form $CNO \cdot NH_4$, which, if detached, would in the blood, as out of the body, be converted into urea.

Thus we should have

and there is formed the next cyan-alcohol in the series

In this way, we pass from the lower cyan-alcohols to the higher, with the formation of urea; the two molecules of CH_2 combining to form C_2H_4 . Similarly,

and

Here we have not only an explanation of the formation of urea in the tissues, but the reason why the amido-acids obtained from the tissues possess different properties from those made in the laboratory. It may easily be shown that the last cyan-alcohol $C_5H_{10} \begin{Bmatrix} OH \\ CN \end{Bmatrix}$, from which leucine may be prepared, will contain six

different forms of $C_6H_{10} \begin{Bmatrix} OH \\ CN \end{Bmatrix}$.

There is another mode, in which the molecules may split up, which is interesting from two points of view. It appears to explain the formation of lactic acid and carbonic acid, when a muscle contracts, or when it dies, and it seems to throw some light on the formation of tyrosine.

³⁰ We have an example of such a transposition of atoms in the formation of crotonic acid $CH_3-CH=CH-COOH$ from allyl iodide $CH_2=CH-CH_2I$ by its conversion into a cyanide, and thence into the acid. See Fownes, p. 307.

³¹ Fownes, p. 614.

³² Fownes' *Chemistry*, p. 96.

a substance whose composition is $C_{72}H_{118}N_{18}O_{22}S$, differing from Lieberkühn's formula $C_{72}H_{112}N_{18}O_{22}S$ only by six atoms of hydrogen.

I have thus endeavoured to show that albumen is a compound of cyan-alcohols united to a benzene nucleus, these being derived from the various aldehydes, glycols, and ketones, or that they may be formed in the living body by the dehydration of the amido acids; that, from a body so constituted, all the different substances may be obtained which have been extracted from albumenoid tissues; that lactic acid is obtained in two ways, either from

with the simultaneous development of CO_2 , a result which is brought about when a muscle contracts or when it dies; and that urea may be obtained from one series of cyan-alcohols with the production of a cyan-alcohol higher in the series.

Such a compound of cyan-alcohols, therefore, presenting so much resemblance in its properties to albumen cannot, I think, differ very widely (though, perhaps, not absolutely correct) from the molecular constitution of albumen.

Taking this view, then, of the constitution of albumen, the following may be given as a summary of the nutritive changes.

The amido-acids, glycocine, leucine, tyrosine, etc., in passing from the alimentary canal to the liver, are dehydrated, forming a series of cyanhydrins, or cyan-alcohols, attached to a benzene nucleus, and then pass into the circulation. In the tissues, these cyan-alcohols, partly by condensation, partly by hydration and oxidation, give rise to the various effete products which are eliminated from the system chiefly in the form of carbonic acid and urea.

There is still one other point that I do not wish to leave

unnoticed. According to Tiemann, the cyanamides $R-C \begin{cases} NH_2 \\ CN \end{cases}$ are very unstable bodies, and, with the elimination of NH_3 , very easily condense into imido-nitriles.³⁶

If, then, the force holding the cyan-alcohols composing living proteid together were suddenly withdrawn, changes would quickly take place in these unstable bodies, there would be the formation of some acid and the different cyanamides, which latter would undergo the condensation above described; the liberated NH_3 combining with other cyan-alcohols to form other cyanamides, and further condensation taking place. Does this not offer some clue to the phenomena of rigor mortis and the coagulation of the blood?

Again, by combining two molecules of $CH_2 \begin{cases} NH_2 \\ CN \end{cases}$ we should have by Tiemann's formula

which, when hydrated with weak acids, would give

a body having the same composition as aspartic acid, but differing in that it is an imido instead of an amido body. Similarly

which hydrated would give $C_3H_6(NH) \begin{cases} COOH \\ COOH \end{cases}$ a body having the same

composition as glutamic acid, differing only in structure. But by strong HCl and high temperature, these "imido-nitriles" seem always to give aldehyde, HCN and an amido acid. It is not improbable therefore that, under certain conditions, we may have

In discussing the pathology of rheumatism, gout, and diabetes, we shall have to deal chiefly with the lowest cyan-alcohol of the series, namely, $CH_2 \begin{cases} OH \\ CN \end{cases}$, and the substances derived from it. What part these play in regard to these disorders I will endeavour to show in the next lectures.

THE GULSTONIAN LECTURES,

ON

SPASM IN CHRONIC NERVE-DISEASE.

*Delivered at the Royal College of Physicians of London,
March, 1886.*

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LECTURE III.

II. SPASM IN CONNECTION WITH SPINAL MOTOR MECHANISMS.

IN my second lecture, I finished the remarks which I had to make on the connection between the cerebral system of fibres and the clinical phenomena of spasm, and I shall now proceed to a short consideration of the spinal system, and the relation between diseases which affect it and spasmodic contraction of muscles.

II. By the spinal system, I mean all those nerve-centres which occur between the central ganglia of the brain and the termination of the spinal cord. Each of these centres consists of afferent and efferent nerves and ganglionic cells; and as my object is to treat the subject from a general point of view, we may divide it into: 1. Spasm produced by diseases of efferent spinal nerves; 2. Spasm produced in a reflex manner by diseases of afferent nerves; and, 3. Spasm produced by diseases of the ganglionic cells.

1. *Spasm produced by Diseases of Efferent Spinal Nerves.*—A very large proportion of the cases in which spasm of muscles produces distortion are not to be explained by supposing that irritation of the diseased nerve gives rise to excessive muscular contraction. On the contrary, the healthy muscles are those actively concerned, while the diseased muscles are for the most part passive. Progressive muscular atrophy is a well known instance of this, where a peculiar claw-like distortion is produced by atrophy of the interossei and the continued activity of other muscles (Fig. 42). Here the neuro-muscular disease

FIG. 42.—"Main en griffe" in a case of progressive muscular atrophy.

appears to owe its origin to an affection of the large cells in the anterior cornua of the spinal cord. But even where no gross disease of nerve or muscle exists, it seems to be a rule that, when the origin and insertion of a muscle remain approximated for a certain time, the muscle contracts and gradually shortens. This frequently occurs in

ERRATUM.—On page 531, four lines from the bottom, for "lenticulo-striate and lenticulo-optic arteries," read "lenticulo-striate artery."

potassic cyanide, can furnish para-derivatives of benzene, namely, terephthalic acid. See Miller's *Org. Chem.*, 1880, part iii, p. 526.

³⁶ Berichte, xiv, s. 1953.

³⁶ We have an example of such a change of an imido into an amido body in the action of boiling hydrochloric acid on hydrazo-benzoic acid. See Fownes, p. 526.