The fever of over-exertion / by J.F. Knott.

THE

FEVER OF OVER-EXERTION.

BY

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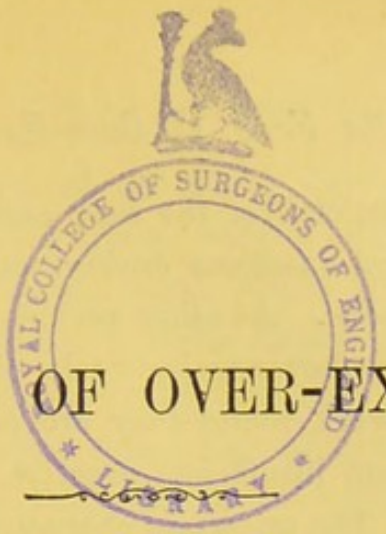
Reprinted from the Transactions of the Royal Academy of Medicine in Ireland.

DUBLIN:

PRINTED FOR THE AUTHOR

BY JOHN FALCONER, 53 UPPER SACKVILLE-STREET.

1888.



THE FEVER OF OVER-EXERTION.[a]

An attempt made at the present date to concentrate, even for a short time, the attention of the professional public on an unrecognised, or but partially-recognised, form of disease, should, perhaps, be prefaced by a sufficient apology. To the still unlicensed student of medicine I offer my cordial and apologetic sympathy, conscious, as I am, of the strain upon his memory produced by enforced familiarity with an already overstocked literature. In my turn, I ask for some sympathetic consideration on the part of the qualified students of the healing art, who are now about to become my critics.

The late Dr. Murchison, in his classical work on "The Continued Fevers of Great Britain," describes the non-specific form included by him in this category (*synochus simplex* of Riverius, or *febris continua simplex* of Lieutaud) as "a sporadic, non-contagious disease, arising from exposure to the sun, fatigue, surfeit, inebriety, &c." The typical symptoms of the febrile state are present, but no specific lesion is discoverable. But a few paragraphs of the goodly-sized volume are devoted to a consideration of the condition. The author refers in a few brief words to a severe tropical form; the native variety he seems to regard as a comparatively trivial complaint, although he hints that it may be sometimes fatal. He does not, however, indicate how the fatal tendency may be manifested. Disregarding the tropical form of the disease, however, I now proceed to inquire into the nature of the unfavourable course which a variety of what may perhaps be still regarded as simple continued fever sometimes takes at home.

Agricultural labourers and the holders of very small farms in

[a] Read in the Medical Section, November 18, 1887.

the "congested districts" of the west and south of Ireland often make great physical exertions during some weeks in the spring and harvesting seasons. At other periods of the year their efforts are less continuous; they usually "take the world easy." When the time for hard work comes they are consequently in very bad training, partly from insufficient exercise, partly from insufficient or ill-chosen diet. The uncertain character of our climate necessitates immediate readiness on the part of those concerned to take advantage of a fair hour, and the wisdom of the homely proverb, "make hay while the sun shines" receives more frequent practical illustration in those places than in most other parts of the world. Accordingly, violent muscular exertion is often performed for several successive days, and this is frequently followed by a chill from careless exposure. With (or without) the latter factor, the exertion referred to is not infrequently followed, especially in the hotter months, by marked febrile symptoms. The patient's temperature runs up rapidly, even to 103° F. or 104° F. within a few hours, and this change is accompanied by the general symptoms of malaise, congested face, thirst, loss of appetite, &c. He sometimes takes a day or two of rest, when, feeling a little better, and being extremely anxious to finish his farm labours, he makes a desperate effort to go back to work, although still suffering from the same symptoms in a slighter degree. His efforts are now necessarily less vigorous, but he does enough to feed the slow fire of febrile combustion which has been already kindled in his muscles. The temperature maintains a standard of about 101° or so; pulse is permanently quickened; thirst, constipation, loss of appetite, and loaded urine continue. In such cases, when the pernicious attempts at manual exertion are continued for a number of days, the unhappy individual afterwards fails to recover. Gradual wasting goes on; the pulse maintains its frequency and becomes weaker, the strength by degrees fails, the patient is obliged to take permanently to bed, the fever tends, after some months, to assume a hectic type. If the lungs have any hereditary weakness, phthisical symptoms may appear, but hardly otherwise. Such is the usual progress of the case I attempt to depict. Beginning, as it oftenest

does, in the hot exertion of the warm days of harvesting, the patient spends the following winter months in bed; with the freshness of the succeeding spring, when nature is putting on all her revivifying powers, he makes a feeble attempt to rally; hopes for returning strength, which, however, fails to come. With the heat of summer he again droops; emaciation progresses; a hectic flush appears on the cheeks, and he sinks as the winter cold approaches. All the wise women in the neighbourhood tell you that he will "go with the fall of the leaf," and they are rarely mistaken. Such cases are well known in the country districts to which I have referred. I have a vivid recollection of a farm labourer who worked with me when I lived in the country, and who fell a victim to this train of symptoms. When I did duty a couple of years ago, during a short time, for a dispensary doctor with a large country district, I took full notes of three cases with such a history. The wise women, whose authority I have already quoted, tell you of such a case that he has got "the plurrisy." But no pleural symptoms, as medical men understand them, are traceable. When staying for a few weeks in the country last autumn, I saw other similar cases. The three cases to which I have just referred all sank with the fall of the leaf—two in October and one in November. One had survived two years from the initial symptoms; each of the others lived through but one winter.

Such cases are not so often seen in town as in the country, and this fact I am disposed to attribute to the more uniform rate of work which is maintained by the urban artisan. Still they sometimes do appear, and are then, I think, either misunderstood or (comparatively) neglected. If not greatly mistaken, I have seen such a case exhibited to a class of medical students as a specimen of "that rare new disease, pernicious progressive anæmia."

The continued physical over-exertion, which is the starting-point of the phenomena with which we are now concerned, has necessarily the effect of throwing into the circulation a greatly disproportionate quantity of the products of muscular waste. These undoubtedly act, in the first instance, as stimulants to the vaso-motor centres, general and local. But the continued applica-

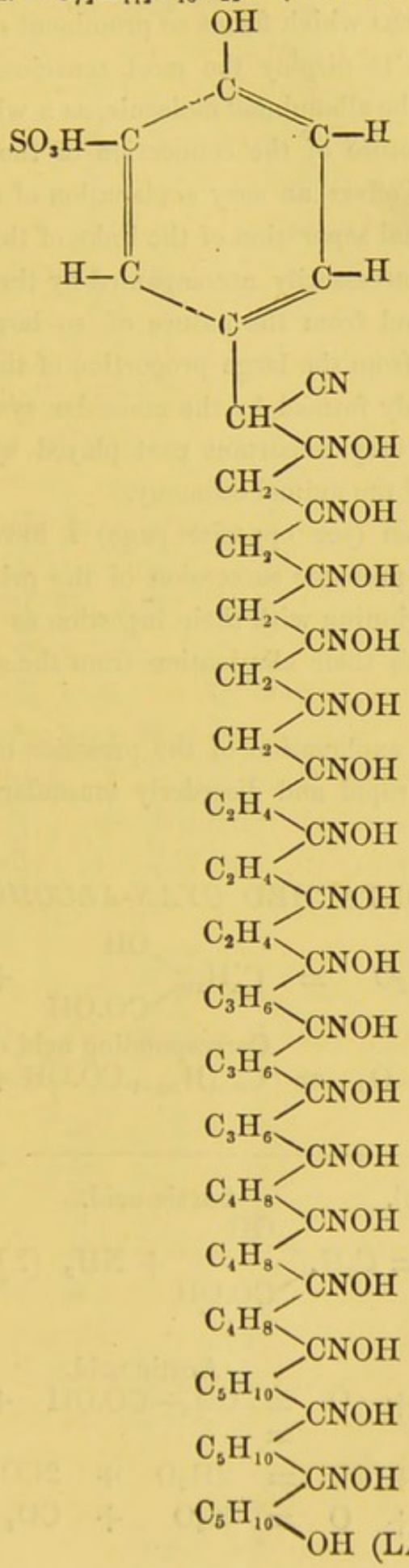
tion of an increasing quantity of the stimulant must soon be followed by exhaustion. Stimulation of vaso-motor centres or nerves, when already partially exhausted, is followed, not by constriction of the vessels of the corresponding area, but by dilatation, which increases with increased strength of the stimulus, till a condition of complete relaxation is attained. Such, as I take it, is the history of the vaso-motor phenomena connected with excessive muscular exertion.

The vascular changes which initiate the symptoms of gout and rheumatism have recently been traced by Dr. Latham, with admirable ingenuity and clearness, to the action of uric acid on the vaso-motor system. The uric acid, set free by excessive or perverted tissue-change, acts, in the first instance, as a stimulant; afterwards paralysing completely the vaso-motor centres, when it has exhausted all the available power of the latter. I would gladly add my arguments to those of so distinguished an authority, and hope, as I proceed, to establish important indications of parallelism between some of the principal phenomena of the fever of over-exertion and those of the well-known fevers just named, and which are usually associated with pronounced arthritic change.

When I sat at the feet of our President, to receive my first lessons in the theory of medicine, I learned an interesting fact, which happened to be soon afterwards emphatically impressed on my memory by an experience occurring in my own person. I have often wondered that greater prominence has not been given it by the writers of our text-books. I allude to the supervention of the symptoms of subacute rheumatism upon those of ordinary simple-continued fever, when the latter has been neglected or injudiciously treated. I hope, before the conclusion of the present paper, to be able to offer an intelligible explanation of the intimate connection between these two, apparently, very dissimilar conditions.

With the view of throwing some light on these clinico-pathological facts, let us now inquire, as closely as we can, into the nature of the products of muscular waste. To facilitate the inquiry, I have placed on the diagram the empirical formula for albumin deduced by Lieberkühn, and following it is the structural formula which has been elaborated by Dr. Latham.

ALBUMEN = $C_{72}H_{112}F_{18}O_{22}S$ (LIEBERKÜHN); or



(LATHAM).

The benzene nucleus which forms so prominent a feature in the latter, is well known to display the most tenacious resistance to chemical change. The albuminoid molecule, as a whole, is notably unstable, and the nature of the connection of the long chain of cyan-alcohol groups, offers an easy explanation of this fact. The detachment and mutual separation of the links of this long chain of molecular groups is necessarily accompanied by the evolution of a quantity of heat; and from the nature of so large a molecular structure, as well as from the large proportion of the total mass of the tissues of the body formed by the muscular system, we can at once understand the very important part played by the latter in producing the heat of the animal economy.

In another diagram (see opposite page) I have arranged, in schematic form, the probable succession of the principal products of proteid waste, beginning with their ingestion as albuminoids of food, and ending with their elimination from the system as effete matter.

We have now an explanation of the presence of an excess of uric acid during the rapid and disorderly muscular metabolism of the febrile state.

FATE OF THE DETACHED *CYAN-ALCOHOL GROUPS.*

$$C_nH_{2n}\begin{matrix}OH\\CN\end{matrix} + 2H_2O = C_nH_{2n}\begin{matrix}OH\\CO.OH\end{matrix} + NH_3$$

$$C_nH_{2n}\begin{matrix}OH\\CO.OH\end{matrix} + O_2 = \underset{\text{Corresponding acid of Acetic Series.}}{C_{n-1}H_{2n-1}.CO.OH} + CO_2 + H_2O.$$

Ethedene cyan-alcohol. Lactic acid.

$$C_2H_4\begin{matrix}OH\\CN\end{matrix} + 2H_2O = C_2H_4\begin{matrix}OH\\CO.OH\end{matrix} + NH_3 \quad [?\ \underline{\text{RHEUMATISM}}].$$

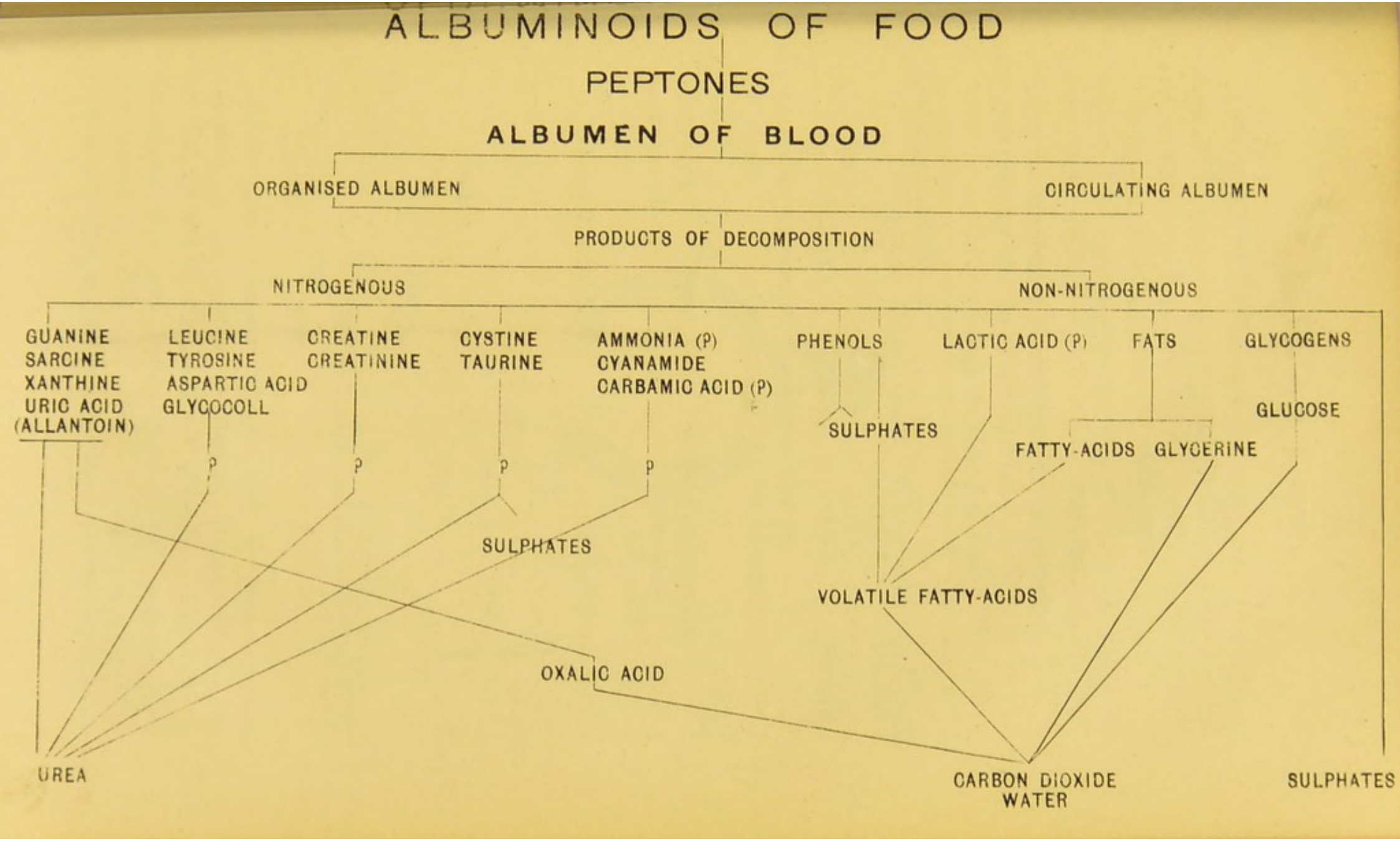
Lactic acid. Acetic acid. Formic acid.

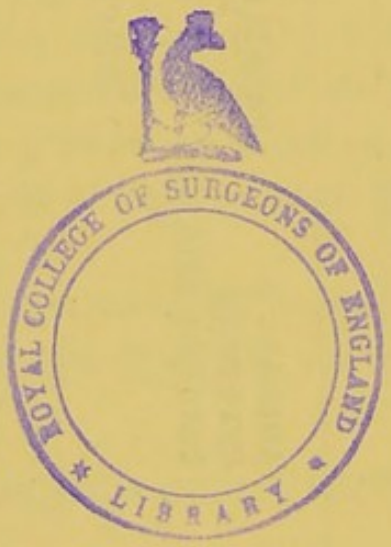
$$CH_3.CH\begin{matrix}OH\\CO.OH\end{matrix} + O = CH_3—CO.OH + H.CO.OH.$$

$$=$$

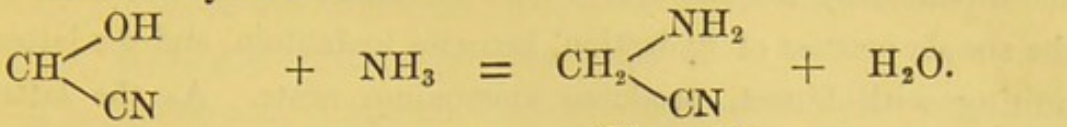
$$CH_3.CO.OH + 4O = 2H_2O + 2CO_2$$

$$H.CO.OH + O = H_2O + CO_2$$

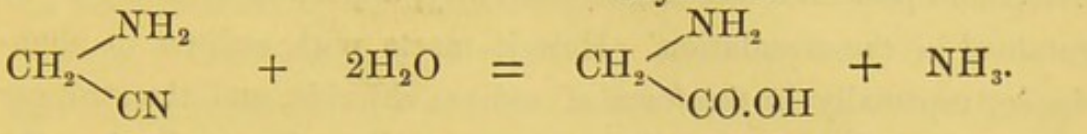

ALBUMINOIDS OF FOOD
PEPTONES
ALBUMEN OF BLOOD
ORGANISED ALBUMEN
CIRCULATING ALBUMEN
PRODUCTS OF DECOMPOSITION
NITROGENOUS
NON-NITROGENOUS
GUANINE
SARCINE
XANTHINE
URIC ACID
(ALLANTOIN)
LEUCINE
TYROSINE
ASPARTIC ACID
GLYCOCOLL
CREATINE
CREATININE
CYSTINE
TAURINE
AMMONIA (P)
CYANAMIDE
CARBAMIC ACID (P)
PHENOLS
LACTIC ACID (P)
FATS
GLYCOGENS
GLUCOSE
SULPHATES
FATTY-ACIDS
GLYCERINE
P
P
P
P
SULPHATES
VOLATILE FATTY-ACIDS
OXALIC ACID
UREA
CARBON DIOXIDE
WATER
SULPHATES


ROYAL COLLEGE OF SURGEONS OF ENGLAND
LIBRARY

Methene cyan-alcohol.



Glycocine.



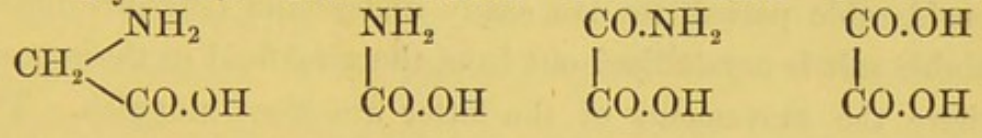
FATE OF *GLYCOCINE* IN THE HUMAN ECONOMY.

(A.) THE WAY IN WHICH IT *SHOULD* GO.

—— Through the kidney as urea.

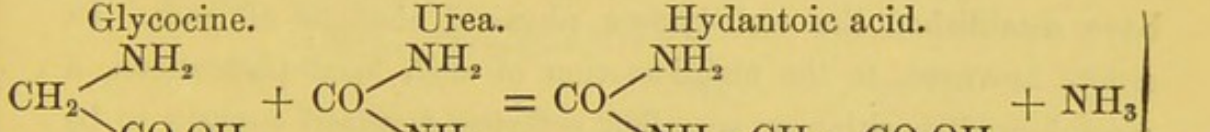
Products of oxidation of—

Glycocine. Carbamic acid. Oxamic acid. Oxalic acid.

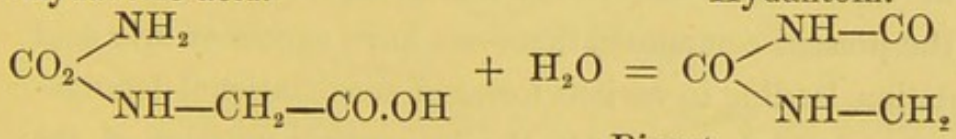


(B.) THE WAY IN WHICH IT SHOULD *NOT* GO.

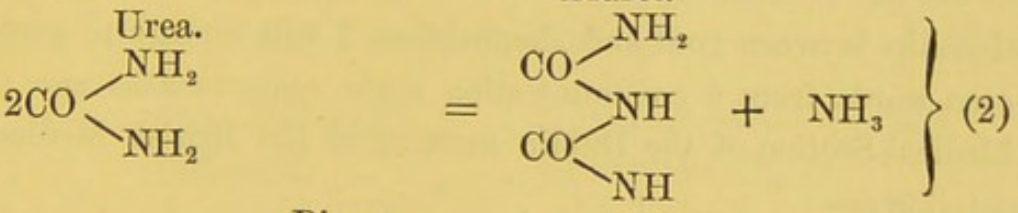
Glycocine. Urea. Hydantoic acid.



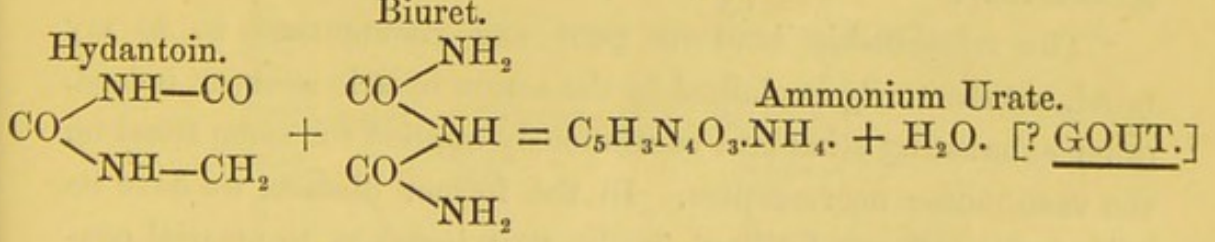
Hydantoic acid. Hydantoin.



Urea. Biuret.



Hydantoin. Biuret. Ammonium Urate.



By the chemical changes here indicated we have glycocine, formed from the methene cyan-alcohol groups, detached by the disintegration of the albuminoid molecules. This body, by conjugating with urea, forms hydantoic acid, ammonia being at the same time separated. Biuret is formed by condensation of urea molecules, as here represented—a process which is also

accompanied by the elimination of ammonia. Hydantoic acid, by the simple process of hydration, becomes hydantoin, and the latter, uniting with biuret, produces ammonium urate. As the latter compound possesses but slight solubility, a portion is likely to be retained in the circulation. Here it meets with sodium in abundance, especially in the form of sodium chloride, and the stronger chemical affinities of the alkali element easily suffice to displace the ammonium from its position in the molecule. The ensuing double decomposition results in the formation of sodium urate. The existence of the latter in quantity must produce vaso-motor disturbances, even from the beginning; when its presence is prolonged for any considerable period, we can easily understand how this difficultly-soluble salt is crystallised out from the vital fluid in those positions where the movements of the latter are most sluggish. This is exactly in the central areas of the articular cartilages, and thus we have established the well-known physical changes of gout. In order, however, to the manifestation of such local phenomena, a special predisposition or so-called arthritic diathesis appears to be essential; in other cases—including the group which forms the subject of the present communication—we have excess of uric acid in the circulation, leading to various forms of constitutional derangement, but not to local deposit. On the interesting question of the relationship between gout and rheumatism, I will venture to quote my own words from a communication made some months ago to the Medical Section of the Dublin meeting of the British Medical Association:—

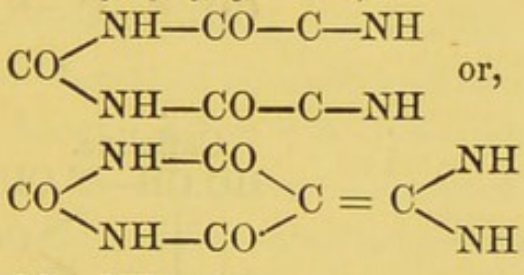
"The relationship between gout and rheumatism is, to my mind, satisfactorily explained by the action of uric acid (or, indeed, other exhausting stimulant continuously applied for some time) on the vaso-motor nerve-centre. In the former disease, we have its stimulating effects, leading, in the first instance, to arterial contraction and constructive metabolism; and these phenomena are followed (when exhaustion of the centres supervenes) by dilatation and destructive metabolism. In the latter affection, we have only the results due to the stimulating action of uric acid on an already exhausted centre. In gout the primary area of disordered nutrition is in the liver, in rheumatism it is situated in the muscles.

The lactic acid, which is necessarily produced in increased quantity from the increased muscular metabolism, has further secondary effects, especially on the cutaneous area."

The presence of a special diathesis appears to be necessary for the manifestation of the characteristic local lesion in each of these diseases. The existence of the fever in either case, as well as in that of the fever of over-exertion (with which we are now more especially concerned), can be fully explained by the action on the nerve-centres of the impurities derived from the *debris* of muscle tissue.

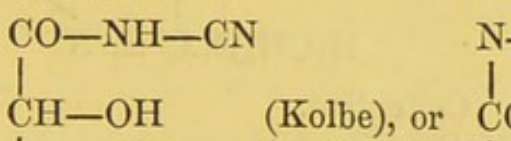
To facilitate the understanding of the chemical relations of uric acid, I here subjoin the principal constitutional formulæ which have been supposed by various chemical authorities to represent its atomic structure. That suggested by Medicus is now generally accepted.

URIC ACID—$C_5H_4N_9O_3$ or,



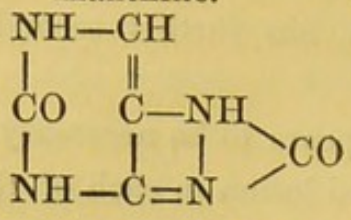
or,

or,

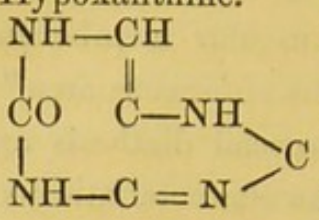


The interesting constitutional relations between uric acid and some of its congeners are indicated in the formulæ arranged on the following page.

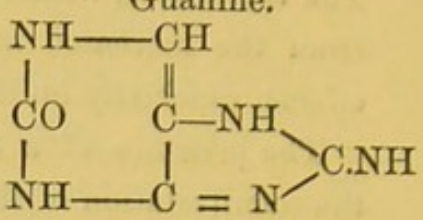
Xanthine.



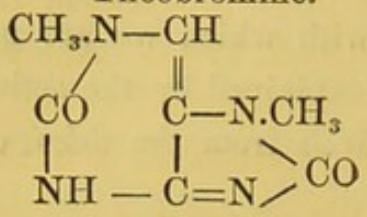
Hypoxanthine.



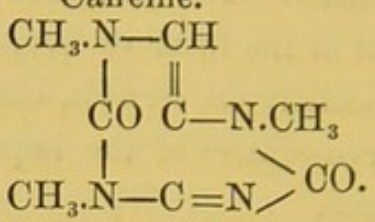
Guanine.



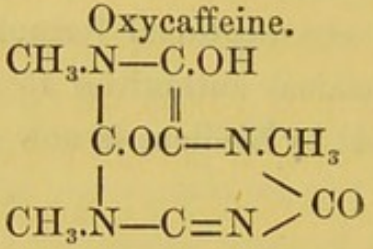
Theobromine.



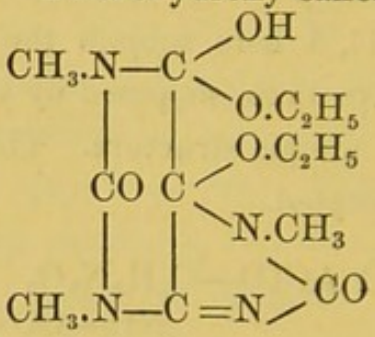
Caffeine.



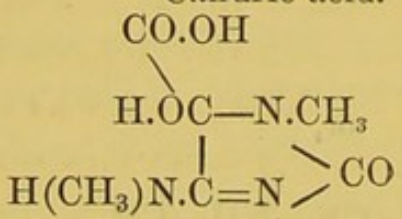
Oxycaffeine.



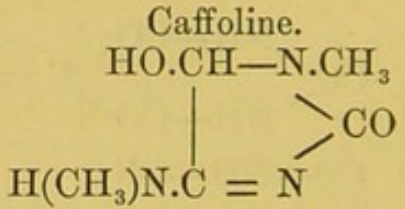
Diethohydroxy caffeine.



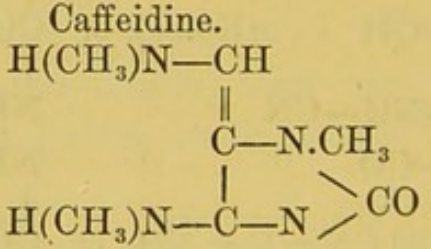
Caffuric acid.



Caffoline.



Caffeidine.



Among the immediate congeners of uric acid is the body caffein, whose more ready solubility makes its introduction into the circulation in experimental researches much easier than that of uric acid. The intimate structural relationship between uric acid and caffein is shown at a glance when we compare their structural formulæ. The latter body, or vegetable uric acid, as it has been called, is known to stimulate the cardiac and vaso-motor centres, as its introduction into the circulation is rapidly followed by increased

rate of the heart's action, and marked rise of the arterial tension. We know that the application of such ganglionic stimulants, when applied to centres already overstrained, is to overpower them completely, and cause immediate vascular relaxation. There is every probability in the belief that the introduction into the circulation of uric acid, and, indeed, of many other products of rapid and perverted muscular metabolism is followed by the display of these phenomena in consecutive order.

It is well known that the muscular system, as a whole, forms, even in health, the main factor in the production of heat within the animal system. It is the great furnace of the body; and, according to careful calculations, furnishes, during health, fully four-fifths of the total quantity of heat generated by the vital mechanism. The known relations between chemical transformation and liberation of heat offers a satisfactory explanation of the dependence of the latter on the complex molecular changes that are constantly taking place in the unstable constituents of muscular structures. Increased muscular activity means, of course, increased chemical change; and, as it is always accompanied by elevation of temperature, the very natural assumption has usually been made—almost without question—that the production of heat was a simple function of the production of work, the former always varying directly as the latter quantity. More recent researches went to show that the connection was somewhat more complex, but attempts were made, with apparent success, to define it in terms of a small number of variables. It was, however, reserved for my distinguished friend, Dr. Donald Macalister, of Cambridge, to successfully differentiate the thermogenic from the motor function. Starting with the very simple fact that heat is produced by a resting muscle, and asking himself the obvious question, "If heat is produced without contraction, may not contraction take place without heat?" Macalister has shown by a series of ingenious experiments that fatigue from over-stimulation and exhaustion from long abstinence, each differentiated the thermogenic from the motor function. The muscle was always fatigued as a heat-producer before it was exhausted as a work-producer. Further investigation showed, on the

other hand, that cold has the effect of greatly depressing or even abolishing the thermogenic function, while it leaves the motor function unaffected.

Further investigations on this subject have been carried out by Drs. Meade Smith and Lukjanow, from the results of which they conclude that "the effect of stimulating a muscle through its nerve is to start in it two processes—one, as it were, explosive, and manifested by change of form and performance of mechanical work; the other more continuous, and manifested by the increased development of heat. Each process has its own laws." These results justify the conclusion that "the heat developed in the second or thermogenic process is not simply a thermo-dynamic waste product—an excretion of no greater dignity than urea or carbonic acid."

Let us see what light the modern concepts of molecular physics may be made to throw on the thermal phenomena connected with excessive muscular disintegration. Matter, from whatever source, is made up of individual molecules, to each of which is allowed in the ordinary quiescent state a certain limited range of vibration. The effect of heat is to increase the range and velocity of vibration of each molecule, thereby causing the phenomenon of expansion. The action of heat on a given substance is represented on an exaggerated scale by the annexed diagram. When cold it is represented by A, A′; when heated, by B, B′ (Figs. 1 and 2).

The molecular movements of the various constituent tissues of the living organism are undoubtedly under the direct control of the nervous system. The principles of government will be understood when we examine our next diagram. At B (Fig. 3, p. 15), is represented a nervous arc, formed by a ganglionic nerve cell, connected in one direction with a sensory surface, and on the other with a motor end-organ.

The former connection is made by an afferent, the latter by an efferent, nerve-fibre. A further advance in the evolution of such nervous mechanisms is shown at C where two central ganglionic nerve-cells are connected by an internuncial nerve-fibre. Such peripheral sensory organs in all parts of the body are thus connected with corresponding centres in the spinal cord, while groups

FIG. 1

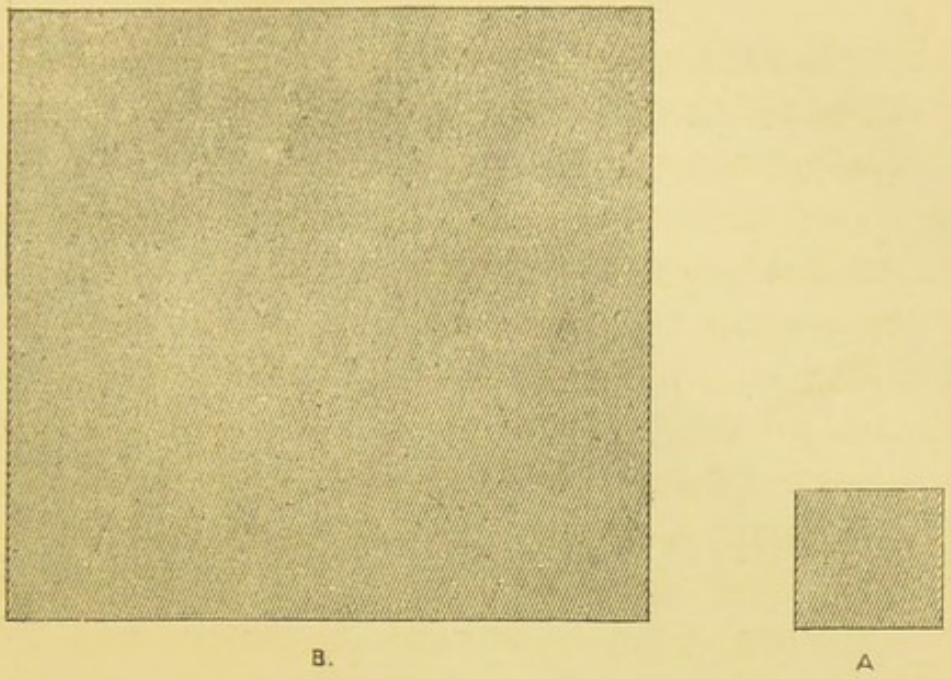
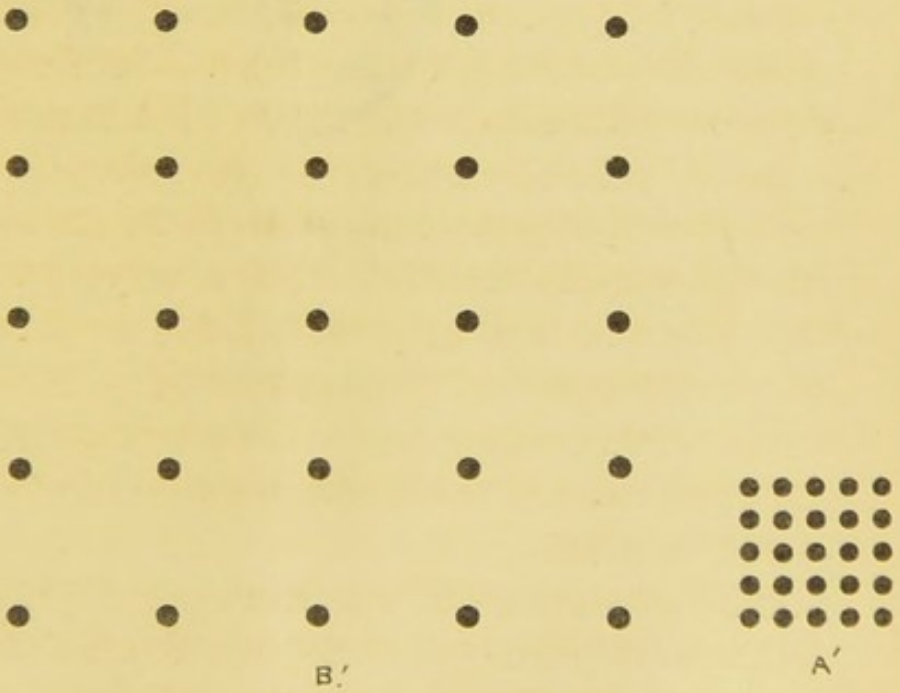


FIG. 2.



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of the latter are in their turn connected with a centre of superior grade placed at a higher level. This graduated scale of increasing influence has probably very many degrees among the central ganglia; all the cells for one denomination being placed under the inhibitory influence of the superior centres in the cortex cerebri.

Fig. 3.

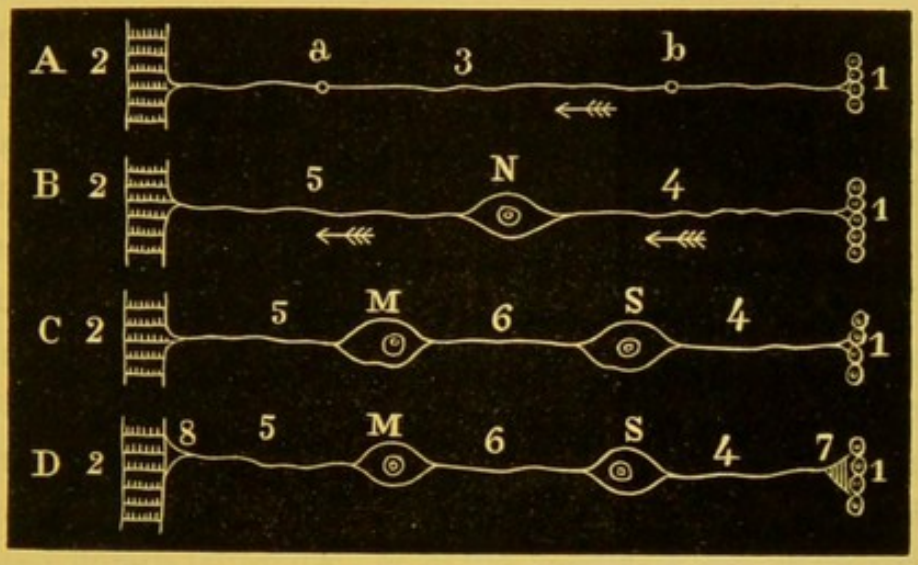
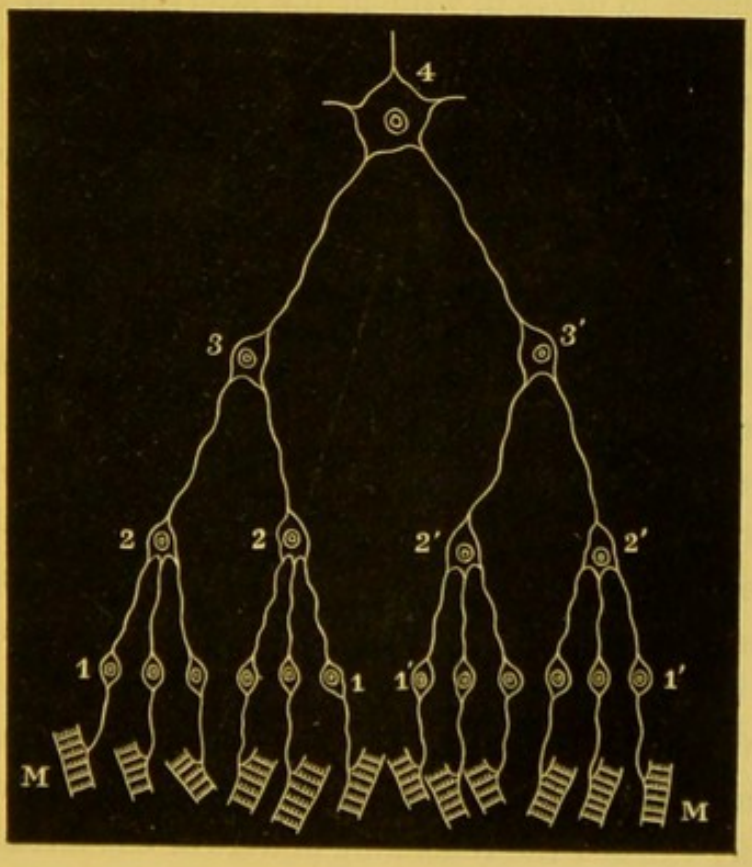


Fig. 4.



I have here (Fig. 4) given a diagrammatic scheme illustrating the super-position of such a series of reflex centres. The first ganglion cell (1) in this lower series regulates the contraction, &c., of a certain muscle. A group of such muscles—three in the present instance—is under the control of a higher centre (2), the stimulation of which would lead to contraction of all three muscles, while the stimulation of an inferior cell would be followed by the contraction of but one. A cell of the third order (3) presides over the movements of two muscular groups. Suppose, now, that the first of these groups is made up of the flexors of the leg, and the second of the flexors of the thigh, the cell which governs the movements of both will have under its control these two movements, which, when occurring simultaneously, constitutes one of the phases of walking; and by so ascending the ganglionic scale, we, by-and-by, arrive at the supreme centre (4) to which is deputed the control of all the co-ordinated movements of pedestrian exercise. A corresponding description applies to all complex groupings of superimposed reflex centres—motor, vaso-motor, secretory, and so on. An initial stimulus, starting from the periphery, and acting on the highest of these governing centres, suffices to develop, without the intervention of the will, all the corresponding reflex movements—molar or molecular, as the case may be—according to the functions of the centre concerned. The resulting series of phenomena follow the initial stimulus, pretty much as the whole complex mechanism of a chronometer is thrown into movement by a touch of the pendulum when the instrument has been just wound up.

On the other hand, when such stimulation is carried to over-fatigue, or applied to a centre already exhausted, it has only the effect of carrying the exhaustion to a still more extreme degree.

Let us now apply the information so far gained to the elucidation of the question more immediately before us. We are particularly concerned with the vaso-motor mechanisms of the muscular system. We have indicated that the uric acid and allied products thrown into the circulation by excessive or by perverted muscular metabolism act as a stimulus to a fresh and vigorous centre, while they rapidly exhaust the remaining powers of one already fatigued.

Even in the former case, the persistent presence of the unhealthy stimulus must necessarily be soon followed by paralytic phenomena. Vaso-motor paralysis of the muscular areas is the inevitable result of muscular overstrain. The vascular dilatation ensuing means, among other things, the presence of an excess of oxygen, the chemical activity of which helps to keep up the fever-heat. Every agency that contributes to the increased molecular agitation which constitutes fever-heat must keep up the unstable molecular equilibrium, and under these conditions the albuminoid molecules of the muscular tissue—whose constitution we have already depicted—being labile in structure, crumble down in rapid succession.

Each of the muscles which we employ in our daily avocations being made up of millions of such albuminoid obelisks, we can fancy what vast sources of heat and energy we carry concealed within us, and the consideration makes us admire still more the wonderful regulation of the mechanism by which the balance between waste and repair, between heat-production and heat-loss, is, in the healthy state of the system, so exquisitely maintained.

There has been a tendency abroad in the pathological world for a considerable number of years to refer most, if not all, of our febrile disturbances to the presence in the blood and tissues of certain minute parasitic organisms.

When a specimen of the bacterial tribe finds entrance to one of these domains of previously orderly molecules, the necessary results appear to correspond to those following the proverbial visit of a bull to a china-shop. Rapid and disorderly movements, followed by shivering of many constituent individuals into the simpler molecular or even atomic fragments is the inevitable consequence. The modern conception of heat being a mode of motion, an elevation of temperature is merely one of the manifestations of the agitation which ensues. The alarming rate at which the mischievous schizophyte reproduces its own image, necessitates, while other circumstances remain favourable, a progressive increase of such phenomena at a rate of compound interest.

As the scientific—and, indeed, the lay public as well—have heard a good deal of the vices of the bacterial brotherhood—which

were repeated even to some degree of monotony—many felt rather refreshed on hearing of the probability that a new scapegoat was to be furnished.

The activity of the minute vegetable parasites in the animal body appears to lead to the formation of—or, at least, to be accompanied by—the presence of *ptomaines*—perhaps excrementitious products. Still, bacteriologists have not been able to satisfy themselves that the occurrence of such bodies is constant, although the hypothesis has been confidently advanced by some that all the unpleasant constitutional symptoms are due to their presence.

Still more recently a new group of claimants to the conspicuous position of sole disease-producers has been brought to light by advancing chemical research. These junior pretenders have been baptised with the generic name of *leucomaines*, and their powers are referred solely to their chemical properties. The full admission of their claims, as placed in this manner before the scientific public, would involve complete exclusion of the microbes from the rights and privileges which have for some years been so freely conceded to them. On this very comprehensive question I could not even venture to express an opinion. To those who wish to come to any conclusion respecting the life and labours of the *bacterium*, the *micrococcus*, the *spirillum*, and the *vibrio*, the nature and scope of their operations in the past, and their probable achievements in the future, I would merely say, Are they not all written in the Book of the Chronicles of the Surgical Section of the Academy of Medicine in Ireland?

Of the precise pathological significance of the presence of any of these minute parasitic growths I know simply nothing, and I can only console myself for my ignorance by reflecting that many practitioners who have attained to high eminence in the public esteem know a great deal less than even that, if their written and spoken communications can be accepted as a reliable index of the state of their opinions.

And here I may notice how extremely modified are the circumstances and conditions of chemical changes within the animal body, as contrasted with the corresponding processes when artificially

produced outside the system. It is well known to the physiological chemist that rapid conjugation of benzoic acid with glycocine takes place in the human body at the ordinary temperature, when the former substance has been introduced into the alimentary canal. In the chemical laboratory a temperature of 160° C. (320° F.), with the expenditure of a good deal of manipulative skill and trouble, are necessary to bring about the corresponding result. The influence of the chemico-vital forces—and I venture to express my belief in such, although it is the fashion with the advanced scientist of the present day to ignore them—will perhaps account for this, and for many other mysterious phenomena of physiological chemistry. May they not inhibit the formation of fibrin within the healthy living blood-vessels? May they not inhibit the coagulation of albumins at paradoxically high temperatures, of which our President, had, I believe, some years ago a very remarkable example under his care, and whose existence has been, to my mind, very unsatisfactorily explained by attributing ingenious powers of physical experimentation, or rather of physical conjuring, to utterly uneducated patients?

These considerations, however, involve a digression from the subject more immediately before me, so I will return to an examination of the nervous influences concerned in the development of fever-heat.

The experiments of Aronsohn and Sachs have demonstrated that stimulation of a limited area within the medial portion of the corpus striatum—situated near the *nodus cursorius* of Nothnagel—causes an immediate rise of temperature in the muscles; with a corresponding elevation in the rectum, and also upon the surface. This artificial fever was accompanied by increased consumption of oxygen, and increased elimination of carbonic acid and of urea; the respective amount of the quantities being about equal to what would have been produced by ordinary fever of corresponding intensity. No motor, and, apparently, no vaso-motor phenomena accompanied these remarkable results; and the obvious deduction was made that in this region we have a veritable *thermogenic* centre.

Again, section of the spinal cord high up in the neck has been

followed by various, and not always very intelligible, effects on the temperature of the organism. But when the section is made at the junction of pons with medulla, we have the constant result of increased evolution of heat. Stimulation in the same situation is found to be followed by a decided diminution of heat-production. These experimental facts point clearly to the existence of inhibitory fibres in that situation, and a regulating or *thermotaxic* centre, from which they are derived.

Sixteen years ago Liebermeister explained the heat-regulation of the animal body by the existence of two such reflex centres—an *excitor* and a *moderator*—both located in the intracranial portion of the cerebro-spinal axis, and whose influences, during the healthy state of the body, accurately balanced one another. In the present year Dr. Macalister formulates the state of our hypothetical knowledge of the subject as follows:—"The thermogenic tonus of a resting muscle is dependent on a balance between the nervous impulses subserving anabolism and those subserving catabolism of thermogen." "*Thermogenic tonus*" here expresses the healthy equilibrium between heat-production and heat-loss; "*anabolism*" and "*catabolism*," in Cambridge nomenclature, signify upbuilding and unbuilding (or construction and destruction) respectively; thermogen is the convenient term coined by the writer to denote the heat-producing (thermogenic) stuff of a muscle as distinguished from the contractile, and whose existence as a separate entity he has demonstrated by the experiments above referred to. This author comes to the conclusion that the thermal nervous system includes three parts: a *thermogenic*, or producing; a *thermotaxic*, or adjusting; and a *thermolytic*, or discharging mechanism. More extended experimental investigation is necessary before a final opinion can be arrived at, but the balance of evidence at present before us entirely favours Dr. Macalister's views.

In the ascending scale of evolution, our thermotaxic centre is the last to be developed. In cold-blooded animals it is non-existent. In the young mammal (in the human infant, for instance) it is unable to assert its influence; and, accordingly, the instability of temperature is its main characteristic at this period of our

existence. Its action is certainly reflex, and, accordingly, its position and connections would be accurately represented in schematic form by the diagram before us (p. 15.) Besides being latest of our thermal centres in growth, its influence is more easily disturbed than is that of the others. Its functions are early thrown into complete abeyance by the vaso-motor and nutritional changes we have been considering; and we have thus explained one of the most prominent features of febrile temperature—the readiness by which it is affected by slight disturbing causes.

Let us now return to the nutritional disturbances first set a-going by the passage into the circulation of the products of excessive muscular disintegration. We have seen how these products first stimulate and afterwards paralyse the vaso-motor centre.

The imperial nervous centre, when thus paralysed, is unable to retain its influence over the local and subsidiary centres which more immediately regulate the chemico-vital processes that are continually going forward in the muscular tissues. The latter centres themselves suffer by a corresponding exhausting influence. The graduated series of bonds which had connected the various molecular groups with the central governing mechanism are broken or rendered temporarily ineffective. Home Rule being thus established among the muscular municipalities, high jinks immediately commence. The individual molecules, previously vibrating within a limited range, and with a moderate *vis viva*, begin to oscillate with increased rapidity; and in endeavouring to extend the range of their movements, they collide against their equally ambitious neighbours with increased momentum—in fact, every rise of temperature above the normal level sets up an agitation for expansion of the territory claimed by each member of the community. The question of eviction or of "landgrabbing" can hardly here be raised, as all the individuals of the commonwealth possess a social and political value exactly equal, and conspiracies and "leaguing" of every kind are unknown, for each individual is equally attracted in all directions by his surrounding neighbours, with the necessary result that he is unable to bind himself to any.

So long as the source of heat is supplied the molecular agitation has no natural tendency to come to rest.

Modern researches on the phenomena of thermo-chemistry, and on the precise relations between energy, heat, and chemical change, have helped to throw additional side-lights on these complicated molecular changes. The initial impetus in these laborious investigations is chiefly due to the enthusiasm of Berthelot, and they have been extended in nearly every available direction by the admirable researches of Thomsen. Berthelot's conclusions on the connection between thermal manifestations and chemical change led him to formulate his celebrated "law of maximum work" in these terms:—"Every chemical change accomplished without the addition of energy from without tends to the formation of that body or system of bodies the production of which is accompanied by the evolution of the maximum quantity of heat." Also in its correlated form as the "theorem of the necessity of reactions," thus:—"Every chemical change which can be accomplished without the aid of a preliminary action or the addition of energy from without the system, necessarily occurs if it is accompanied by disengagement of heat." The law of maximum work has been rather roughly handled by recent critics, yet it is still upheld, in forms more or less modified, by many of the most eminent chemists; and even our most recent English authority, Pattison Muir, although by no means ready to acknowledge the authority of the law in all its necessary consequences, acknowledges that "when the physical conditions of comparable chemical processes are kept as nearly as possible constant, the process which involves the maximum production of heat very frequently occurs in preference to the other possible processes, or occurs to a considerably greater extent than any of those other processes."

The most indefatigable of all workers in the domain of thermo-chemistry—Thomsen—has stated the law of maximum work in the following form:—"Every simple or complex reaction of a purely chemical kind is accompanied by evolution of heat." In explanation of this phraseology, he tells us that by a reaction of a purely chemical kind, he understands one which "proceeds

without the expenditure of external energy, and is accomplished only through the striving of the atoms towards more stable equilibrium." The occurrence and nature of the reaction depend chiefly, according to the writer, on (1) the striving of the atoms of the reacting bodies towards stable equilibrium; (2) the resistance of the molecules to decomposition; and (3) the stability of the possible products at the temperature produced by the reaction. The greater the molecular mobility and the atomic mobility of a given chemical system, the more ready will that system be to undergo change; and the less the molecular and atomic mobilities the more stable the system. In every purely chemical reaction these two will tend towards a minimum. The reduction of molecular and atomic mobility will be attended by evolution of heat. In other words, all the thermal manifestations of purely chemical origin are examples of the degradation of energy which Sir William Thomson tells us is going on throughout the length and breadth of the universe, and which, according to him, must go on progressing till a uniform dead level of temperature has been established in all regions of space.

In summarising my conclusions, then, I would say that if I have read aright the clinical history of the class of cases to which I have now called the attention of the Medical Section, their essential feature is the presence in the circulation of a large excess of the chemical products of muscular waste, rapidly leading to an overthrow of the governing powers of the thermotaxic nerve centre. Under favourable circumstances the elimination of such effete material from the system would be soon followed by restoration of its adjusting function. When the elimination has, however, been long retarded, this centre, which, as we have already seen, always is, in the febrile state, the first to lose, and the last to regain its authority, will be found to have permanently abdicated its claims, and the anarchic condition remains, during which all the physical enemies of life are permitted to go on sapping its powers.

With regard to the treatment of such a febrile condition as the one we have been considering, some further remarks may be found suggestive. Authorities on the subject of ephemeral fevers are

fairly unanimous in telling us that for such conditions no specific treatment is necessary. The early administration of a purge, followed by saline diaphoretics and diuretics, with ordinary remedies for any other troublesome symptoms, such as headache or sleeplessness—are all that we usually hear recommended.

To anyone who has noticed the minor symptoms of simple febrile conditions with the attention which they deserve, but do not always receive, the extreme gratification produced by small quantities of moderately acid drinks will be very familiar. I suppose it is on this account that physicians are so much in the habit of prescribing for administration on a considerable scale dilute solutions of the mineral acids. Grapes, lemons, and some other fruits form convenient vehicles for administration of certain organic acids, and are very acceptable to the patient. They cannot be so conveniently made the basis of an orthodox prescription, and perhaps for that reason, among others, are regarded with more favour by the patient, and perhaps by his nurse, than by the visiting physician. Yet I believe that they are sound therapeutic agents, and that the taste which fever patients so usually display for these things is a truly conservative provision of nature. I have elsewhere within the present year endeavoured to call the attention of the profession to the importance of the use of some organic acids in promoting the elimination from the system of urates and other products of excessive or of perverted tissue-change. The power which certain organic bodies have of retaining in solution compounds otherwise easily precipitable is utilised in several Pharmacopœial preparations, and is indeed often a source of annoyance to the analytical chemist whose manual labour it increases very considerably. The preparation of the Liq. bismuthi et ammonii citratis exemplifies the utilisation of such property possessed by the acid of lemon juice, while the well-known test solution of Fehling shows a corresponding property of the principal acid of the grape. That the introduction of these acids or their soluble salts into the animal economy determines the solution and consequent elimination of the deleterious products above referred to, there can be no doubt whatever, and I would accordingly venture to recommend their systematic administration in cases where the

system is surcharged with waste material. The usefulness of a saline purge is unquestioned. Its efficacy is appreciated by the labouring poor themselves, and it is usually administered in the shape of enormous doses of Epsom, or (still better, because cheaper) of Glauber's salts. Up to half a pound of the latter is often administered to a strong country labourer. The great adjunct to this treatment in former days was to utilise the services of the country bleeder; and the wise woman of the district, whose authority I have so frequently quoted, lays the blame of the death of some of the most promising "boys" in her neighbourhood on the authorities who have made this remedy unattainable, even rather than on the dispensary doctor, who, according to her account, knows nothing about it, or will not employ the treatment she suggests. The adoption of such a remedy now possesses, of course, but a historic interest.

To the use of the mineral acids I would object, that although their administration affords a momentary relief by lessening the thirst from which the patient suffers, their ultimate effect on the tissues and circulation is to aggravate the existing mischief by setting free the uric acid from its compounds. The organic acids, on the other hand, whose uses I advocate, have the effect—with or without chemical change—of determining the solution of the deleterious organic compounds present in the fluids of the body, and so promoting their ready elimination from the system.

With regard to the treatment of the chronic stages of the condition I have described, I would expect the best results from a carefully-regulated diet, with the internal use of quinine and salicylic acid, as antipyretic remedies. Change of air, especially to the seaside, would be very desirable, but in the great majority of the cases I am now dealing with this is quite unattainable.

In drawing to the close of my communication, I wish to thank my audience for the patience with which they have listened to what I have had to say, and to express my hope that the attention of wiser and more experienced heads than mine may soon throw additional light on the somewhat complicated questions which I have thus crudely broached.