The nature of fever : being the Gulstonian lectures delivered at the Royal College of Physicians of London in March 1887 / by Donald MacAlister.

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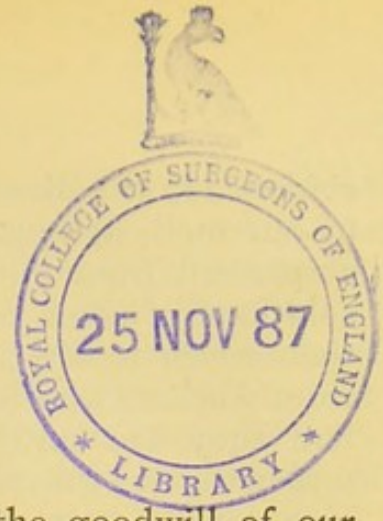
D. M.



LECTURE I.

I HAVE at the outset to acknowledge the goodwill of our much-esteemed President, which led him to invite me, one of the four junior Fellows of the College, to assume the exacting office of Gulstonian Lecturer. The distinction of the audience to be addressed, and the high standard of excellence upheld by previous lecturers, make the office exacting indeed. Had I not understood that the invitation to undertake it had in it something royal, and was almost a command, I would have shrunk from inflicting my crude reflexions and my profound inexperience on your practised ears. But when I considered that you would probably not look for maturity or experience from one who is literally the junior Fellow, when I was assured that your tolerance of youthful effort was large and kindly, I took heart and ventured to announce this course of lectures. Fortunately for me, a wide latitude in the choice of a subject and in the manner of treating it has hitherto been permitted. My term of practice has been far too short to enable me to offer you any generalisation based on extensive clinical work or on ripe knowledge of human nature, such as has in late years delighted and instructed you from this desk. My aim must perforce be humbler. I must be content with attempting to coördinate certain recent advances in our knowledge concerning a department of pure pathology, and with suggesting to you certain lines along which it is possible that further advances may be made.

My subject is the Nature of Fever, and though I did not choose it light-heartedly, it was only when I came to set down my ideas upon it that I fully appreciated all its difficulty. Still, inasmuch as for the last five or six years it has never been long absent from my thoughts, and as its problems physical and physiological have constantly exercised me, I may be pardoned if I venture to discourse on a subject in one aspect so familiar and fundamental, in another aspect so little understood. Our knowledge of the clinical aspect of fever is now singularly full. I can add little or nothing on this side. But that the intimate nature of the febrile process—its morbid physiology, so to speak—is not understood, we have sufficient

evidence in the diverse and contradictory explanations offered in our medical text-books. From time to time, and chiefly at present from the continent, we are receiving fragmentary solutions of some of the outstanding questions that present themselves to the investigator of fever. These often come from workers who have no thought of the pathological problem they are unwittingly helping to solve. They appear under various guises and in many journals. The busy physician cannot hope to notice them all, or to recognise their bearing on his needs. He may therefore welcome an attempt to bring together their results, which are apt to be buried under a mass of experimental detail, and to appraise their value as contributions to the general subject. My literary work for some years has obliged me to survey much of recent pathological literature, and it is on that ground only that I can hope to offer you certain matters for consideration that are perhaps not known to all. That much of what I have to say is already familiar to some of my audience is certain. If I say it notwithstanding, it is because I wish to be clear and complete rather than original.

In the first place it is necessary to state what I mean by *fever*. I need hardly say that I do not refer exclusively to the specific infective diseases grouped together as the "eruptive" or "continued" fevers. I speak of the condition of feverishness or pyrexia which is common to these diseases and to many others—the disordered inward condition of the body-heat, whose frequent and most manifest outward sign is high temperature. It is of course true that the term fever conveys to our mind a more complex notion—it implies, in general, disorder of the circulation and the respiration, of secretion and digestion, of the nervous system and the muscular system, as well as of the body-heat. But without saying, as some have said, that all the other disorders of function which we describe as febrile are merely consequences of the disorder of temperature, I shall not be going too far if I state at the outset that the *essential* fact in fever—the condition which is always present whether other of its symptoms are present or absent—is disorder of the body-heat. In using the word "essential" rather than "primary," I wish to avoid the pre-judgment suggested by the latter. Other conditions may precede in time or in causation the essential symptom of disordered heat, and according to the confidence or the refinement of our analysis we may term one or another of them primary, but not until the essential symptom is present have we to do with fever. We have a like state of things in

the case of *inflammation*. The single word covers a whole series of processes; each process is a complex of many elements. It implies changes textural and changes vascular, changes nervous and changes mechanical. And in the gradual development of pathological knowledge now one and now another of these has been regarded as *primary*. But to-day we are justified in holding, for the reasons so admirably set forth by your Lumleian lecturer in 1882, that alteration or damage of the minuter blood vessels is the *essential* condition, without which there is no inflammation.

Disorder of the body-heat, then, is the essential condition of fever. To understand the nature of fever we must examine the nature of this disorder. But first it is necessary to consider the natural ordering of the body-heat, the healthy function of which pyrexia is a disturbance. The constancy of the temperature of the body in health, under widely varying internal and external conditions, is a fact so familiar that we have ceased to wonder at it. Yet it rests on a perpetual balance of opposing tendencies which is as mysterious and as beautiful as anything in our frame. As a mere question of physics, the maintenance of a constant temperature by a body plunged in a cooler and variable medium like the air involves three coöperant factors. There must be a source whence heat is produced, whether at a uniform or variable rate. There must be processes by which heat is discharged from the body or transformed within it. There must be a mechanism by which the heat-production and the heat-loss are balanced at the normal height. This mechanism must be in relation on the one hand with the processes of heat-production, and on the other hand with those of heat-loss. And its relations with these must be so intimate that within limits the balance it maintains shall be not only steady, but *stable*. In other words, small deviations from the normal temperature in either direction must call into play thermal tendencies whose resultant is back towards the normal. Increased loss must be promptly compensated by increased production, and increased production met by increased loss. This *stability* is to be distinguished from the property of mere steadiness or constancy, though, of course, the two are connected. In health, as we all know, there are daily fluctuations of a regular kind, and these must be borne in mind when we speak of the temperature of the body as constant. The constancy, so far, is imperfect. But in health the stability of the temperature is nearly perfect. A very short time suffices to overcome the disturbance produced by change in the external thermal

conditions. And in like manner the consumption of a large amount of physiological fuel (*i.e.* food), and the internal production of heat thereby originated, has only a transient influence on the surface temperature. If we use Greek terms, we might say that man, with other "warm-blooded" animals, is not only *homœothermic*, but *thermostatic*. We shall have occasion to refer to this distinction when we come to consider a theory of fever which has found some acceptance among us.

The mechanism which regulates the body-temperature and gives it stability, as the governor of a steam-engine regulates the speed, we speak of briefly as the thermotaxic mechanism. When we reflect on the promptness of its action, on its sensitiveness, on the amount and variety of the substance whose thermal variations it has to control and adjust, we cannot resist the conviction that the mechanism is nervous. And as we go on we shall find numerous reasons in support of this conviction. It is when we come to consider the exact nature of this thermotaxic nervous mechanism that difficulties arise. Where is the seat of the coördinating power? Is its action direct or indirect? Does it control temperature chiefly by varying heat-production, as when we raise or lower the flame of a gas stove or the damper of a furnace flue? or by varying the heat-loss, as when we open or close the window of a heated room? These are questions of physiology, but their solution is in a sense the solution of the problems of fever; and no fruitful discussion of *its* pathology can take place if they are not carefully dealt with, and their scope at least understood.

It is clear that, given a steady and fairly uniform production of heat, regulation might to some extent be effected by a mechanism controlling only the loss of heat from the body. It is as clear that, given a steady rate of heat-loss, a mechanism controlling the production of heat would also suffice to regulate the temperature. But we have abundant reason for believing that neither the production of heat nor the loss of it is even approximately steady in healthy active life, and therefore for believing that both these controlling mechanisms are necessary and in fact exist. The thermotaxic mechanism is, in Dr Hughlings Jackson's sense, "higher" than either of them. It governs them both; it adjusts their mutual relations. It is later in attaining its full development, and it is more liable to fail under injury or disease. We shall see that the mechanism controlling heat-production comes next in functional order, while that controlling heat-loss is lowest of the three. Now, it happens not unnaturally that

our knowledge of these mechanisms is least as regards the highest and greatest as regards the lowest; and as each has its special bearings on the process of fever, I shall subdivide my discourse into three parts having reference (1) to heat-loss, (2) to heat-production, and (3) to the thermotaxic nervous mechanism. I shall thus proceed from the better known to the less, in the hope that in passing from the certain to the probable and thence to the possible I may not wholly fail in carrying you with me.

First, then, as to heat-loss and its relations to the process of fever. The main channels by which heat passes out of the body to its environment are of course the skin and the lungs. Through the skin in health by evaporation, conduction, and radiation there escapes more than 80 per cent. of all the heat discharged. In warming and moistening the breath less (perhaps much less) than 20 per cent. escapes. The rate of loss is varied, as we know, by alterations in the vascularity of the skin and in the period and amplitude of the respirations. A face flushed with wine feels warm, for it is rapidly discharging heat; a dog, whose skin lets little heat pass through, pants to cool itself. Experiment and observation have established the existence in the brain and spinal cord of vaso-motor "centres" that control the blood-supply of the integuments by varying the calibre of the arteries. The efferent nerves that pass from these centres to the vessel-walls are of two kinds; the one vaso-constrictor, or, as we may say, motor; the other vaso-dilator, or inhibitory. The "centres," whatever meaning be given to the term, must themselves have something corresponding to this twofold differentiation. In like manner the rate of respiration is governed by a nervous mechanism, consisting of centres in the medulla and cord, with a twofold complement of nerves proceeding to the respiratory muscles. There are strong grounds for regarding these nerves also as respectively motor and inhibitory, and the respiratory centre as consisting of two correlated parts, one subserving inspiration, the other checking inspiratory movement and subserving expiration. The channels of heat-dissipation are thus admittedly under the control of nervous mechanisms, twofold or double-acting mechanisms we might say, each having a motor and an inhibitory aspect. Moreover, these mechanisms are known to be susceptible to rise of temperature, reacting thereto in such a way that the resulting vascular and respiratory changes increase the discharge of heat from the body. Attracted by the apparent simplicity of these arrangements for the governance of heat-loss, it is not wonderful that Traube

should have sought to base on them a theory of thermotaxis, and of that derangement of thermotaxis whose manifestation is pyrexia. "In health," he would say, "the temperature of the body is maintained by the vigilant action of the sensitive nerve-centres that control the great systemic functions of circulation and respiration. Fever is due primarily to a disorder of these centres, by which the normal rate of discharge is diminished, heat is thus pent up within the tissues, and their temperature rises by 'retention.' This general rise of temperature then reacts on the organs to their hurt, and the disorders of secretion and nutrition, which we know as febrile, naturally follow." No explanation could well have been more simple, and it was applied with much skill to account in a natural way for many of the clinical features of pyrexia. Irritation of the vaso-motor centres by injury or poison led to prompt and abiding spasm of the arterioles of the skin. When the centres were very irritable or the irritant intense, the resulting rise of temperature was rapid. The sudden difference thus caused between the temperature of the peripheral ischæmic parts and that of the central parts acted as a powerful sensory stimulus, and this by a reflex action set up a powerful motor disturbance —the initial *rigor*. When the spasm of the arterioles suddenly relaxed, a gush of heat took place from the fevered body, and its temperature fell by *crisis;* when the spasm yielded gradually and with intermissions, we had a *lysis*. It is not wonderful, I say, that observers like Traube and Marey, whose labours on the mechanism of circulation and respiration had been so great and so fruitful, should favour this "retention theory." It rested on their own work, it involved only mechanisms with which they were intimately acquainted, it was apparently capable of wide application to clinical facts, and it was partially true. And so long as certain other facts were unknown or ignored, the theory certainly satisfied many acute observers, and even now appears in some of our medical text-books as the last word of physiological pathology.

Let us consider, then, the *retention theory* of Traube, and examine wherein it fails. "Pyrexia is due to a diminished discharge of heat from the surface of the body, and this to a powerful contraction of the arterioles of the skin." It is plain that the structure rests on the one fundamental assumption—namely, that the escape of heat from the body is unduly small. If that assumption is itself unfounded, we have no choice but to conclude that, though retention may be a *vera causa* of fever, it is not the essential cause. Twenty years ago experiments were made to test the assumption. Inasmuch

as the question is one of quantities of heat and not of temperature only, it was clear from the outset that the test must be calorimetrical, not thermometrical. In other words, the heat passing from the fevered body must be measured by the mass of water (say) it is capable of warming to a measured extent. This quantity of heat must then be compared with that given out by the normal body under like conditions. The first attempts, made by Liebermeister and others, were open to objections of many kinds, physical as well as physiological. Professor Burdon Sanderson has subjected some of them to criticism, sometimes more severe than they quite deserve, in his excellent memoir on the "Process of Fever," published as a Government paper in 1875. Thus Liebermeister placed a fevered patient in a tepid bath, and noted the amount by which the water was heated in a given time. But the experiment was vitiated as a quantitative test by the changed physiological conditions the contact of the water might cause in the patient's body, and by the fact that the powerful heat-discharging process of evaporation was interfered with. Leyden and Senator, with greater precautions, measured the heat-discharge from fevered limbs and from fevered animals. In the case of the latter, means were found for estimating the quantity of carbonic acid and the quantity of watery vapour exhaled in a given time. Pains were taken to compare the results with those yielded by a normal animal under like conditions as regards food. The net result was to shew that both in the human patient and in the fevered animal pyrexia was accompanied not by *diminished* but by *increased* discharge of heat. Senator, indeed, goes so far as to estimate the average increase of heat-loss in some cases of septicæmic pyrexia at something like 75 per cent. The objections that have been raised to the methods employed touch, as I have hinted, rather the quantitative than the qualitative value of these calorimetric tests. The latter is not at all ambiguous: the increased discharge of heat was unmistakable. Like experiments have been repeated in recent years by Wood of Philadelphia, and by Reichert and Hare under his direction. Their arrangements were admirably designed, the criticisms of 1875 were considered and met, and the work bears every mark of honesty and care. From a physical point of view there seems nothing to which objection can be taken; and the outcome of the last measurements, published only the other day, is the same as that of the older and less perfect ones of fifteen years ago. It is that heat is *not* abnormally retained in the body during fever; on the contrary, it is excessively discharged:

and this is true not of one stage only; it holds for the rise and for the continuance of the fever, as well as for its fall.

This foundation of the retention theory being done away, the theory falls to the ground as an adequate explanation. But we may further ask—Is it indeed a fact that during fever there is an abiding spasm or tetanus of the arterioles of the skin? This question has been minutely investigated, and though the answer is decidedly in the negative, the research has added largely to our understanding of some of the phenomena of fever. Clinical observation prepares us to believe that the cutaneous circulation may vary greatly during the same febrile attack. At one time the skin is pale and dry, at another flushed, at another bathed in perspiration. Direct observation of the vessels, say in the ear of a fevered rabbit, shews that their calibre is constantly altering in a way that is quite different from the quasi-rhythmical contraction and dilatation of health. These changes become irregular and excessive, so that the surface is within an hour or two pale and cool, then intensely hot and hyperæmic, and then pale once more, the body temperature remaining all the while at a febrile height. Less direct, but perhaps not less convincing, is the evidence afforded by the surface temperature. Whatever spot of the skin we choose, and in whatever variety of fever, we find that the surface temperature fluctuates from hour to hour in a remarkable manner, the curve representing its changes having little or nothing in common with the rectal temperature. Of this my own observations have repeatedly convinced me.

From all these facts, and I have only touched on them in the most general way, we gather that in fever the cutaneous vessels are *not* in a state of continuous contraction. The cutaneous blood-supply, on the contrary, fluctuates in an irregular manner: now flushing the surface tissues, raising their temperature, and pouring out heat into the air; now reduced to a minimum, leaving the skin pale and dry, and shutting in the heat of the central parts. All this, of course, betokens that the nervous mechanism which controls the cutaneous discharge of heat is notably disordered. There is, indeed, no constant stimulation of the vaso-constrictor nerves such as Traube imagined; there is no continuous retention of heat, but there are marked irregularities in the rate at which it is discharged. These irregularities have doubtless much to do with determining the type of the febrile temperature, the configuration of the charts, in various diseases. But they leave out-standing and unexplained the two cardinal facts—

first, that the febrile discharge of heat is greater than the normal discharge, and, second, that notwithstanding this greater loss the temperature so often rises and remains high. One possibility only remains—namely, that the production of heat within the body is abnormally increased.

The next question that suggests itself is this—Is the heat-production steady, or is it fluctuating? We have seen that the heat-loss, as gauged by the condition of the surface, is subject to wide and irregular variations, not merely from day to day during the course of the fever, but even from hour to hour in the same day. Is there any similar irregularity in the rate of heat-production? To answer this question we must again fall back on calorimetry. Thermometrical observations are of no service. The daily balance at my banker's tells me nothing of the variations in my receipts. It depends on out-goings as well as in-comings. The temperature of the body is merely a function of the difference between heat-income and heat-expenditure at any moment. Now, we cannot well shut up a fever patient in a calorimeter for hours or days together, so our direct knowledge of variations in human heat-production during fever is of the slightest. We must have recourse to experiments on animals. The only recent investigations which have been conducted with a view to directly answering our question are those of Wood and his assistants. An examination of their numerical results shews that in the septicæmic fever of dogs and rabbits the hourly rate of heat-production does vary in a remarkable way, even under uniform conditions as to feeding or fasting. The variation shews in some animals a tendency to rhythm, being usually higher towards the evening. Feeding introduces a marked increase of heat-production in the normal animal, and the increase is not absent in fever. Further experiments are to be desired, but of the mere fact of fluctuation in heat-production there seems no doubt. Some of the figures, moreover, shew that, as the course of the temperature varies, the rate of heat-production may actually be highest when the temperature is lowest; an excessive rate of heat-loss may overbear and so disguise a simultaneous excessive rate of heat-production. And, conversely, the time when the temperature is high may coincide with a time when the heat-production is low. The inference from this is very important—namely, that the height of the temperature in fever is in great measure dependent on the *momentary relation* of the two processes of heat-production and heat-loss. And inasmuch as these two processes tend to vary irregularly, with but a weak *nisus* towards a daily rhythm,

the fluctuations of the temperature do not afford an accurate measure of the changes in either process. The daily and hourly variations in febrile temperature are wider and more irregular than those in health: febrile temperature is *inconstant.* Moreover, trifling changes in the surroundings of the patient or in his functions readily send his temperature up or down: febrile temperature is *unstable.* The two coöperant factors of the temperature are acting more or less independently: thermotaxis is enfeebled or overpowered.

Dr Hilton Fagge (whose name I mention with sincere and affectionate respect) has in his classical treatise on medicine befriended, or rather perhaps adopted, a suggestion of Liebermeister's which requires some comment in this connexion. The wide acceptance among English students which any theory so endorsed is sure to gain makes me anxious that it should not pass without some critical examination. Liebermeister takes up the position that "pyrexia consists, not in a mere rise of the temperature of the body, still less in increase of heat-generation, or in diminution of loss of heat, but in a change in the normal function of heat-regulation by which the production of heat and its loss are so balanced as to create and maintain, while the pyrexia lasts, a higher temperature instead of the normal temperature. One might imagine the index of the regulating machinery to be shifted upwards, so that it is 'set,' not at 98·4°, but at 101°, 102°, 103°, or even at a still higher point."

The first objection I have to raise is that, if regulation means anything, it means, as I have already indicated, not merely an average uniformity of temperature persisting for any short period of time. Such a uniformity only implies that for a time the average losses of heat by all channels balance the average gains from all sources. So far as we know, it may be a fortuitous equation between two independently varying quantities. Regulation implies more than this—very much more. It implies *stability*; it implies such an intimate correlation of the producing process to the discharging process that their variations are not independent, but connected and concurrent; it implies a *nisus* towards a normal which is potent to overcome disturbing causes. We may know that a system of forces is in *equilibrium* when they keep a body at rest, but this rest is no evidence that the equilibrium is *stable.* To determine that we must disturb the body and note its behaviour. If it always returns to rest again, it has not merely equilibrium, it has stability. But, as I have just said, febrile temperature, even when it is at its

height and oscillating with fair steadiness about a mean level, is marked by its instability. A trifle that in health would have but a vanishing effect will in fever produce a large and enduring variation. A whiff of cold air, a little food, a passing excitement, a feeble muscular effort, will send up or send down the temperature. The thermostatic character of the healthy normal is conspicuously absent in the mean high level of fever. The imperfect daily rhythm of temperature observed in some continued fevers is no evidence of true regulation. We have seen that even the fluctuating heat-production of a fevered animal shewed signs of a periodicity. In health this rhythm is deep-seated, and singularly persistent in spite of the most various disturbances. That it should to some extent "shew through" the irregularities of the fever-heat is not wonderful; it merely proves that not all the thermal processes are utterly perverted in pyrexia; some that are normally rhythmic may be rhythmic still. But regulation has to do with balancing the integral sum of all the processes, and it is that balance which is overthrown, or at least rendered tottering, in fever. Liebermeister would seem, in fact, to have for the moment fixed his attention too closely on the characters of the *temperature curve* during the *fastigium* of some particular fever; and to explain its apparent average constancy threw out a suggestion which has fascinated others more than himself. The cases given in support of his view are, I think, special, and admit of other interpretations. And he has admitted that its application to clinical and pathological facts must be limited and qualified. Dr Hilton Fagge puts it forward as sufficient for all purposes, with an absoluteness which Liebermeister himself would hardly admit. According to Dr Fagge, in fever nothing is changed; the norm of temperature is merely re-set. As Cohnheim puts it, the thermal mechanism of the man is of a sudden transformed into that of a bird. How is the transformation effected?—by what agents, acting on what mechanism? What determines the new fixed point of regulation? Is it fixed at all, or only sliding? How is it ever re-fixed? All these questions follow on the back of Liebermeister's explanation, and the worst of them is that they are not merely unanswered but unanswerable. One cannot conceive a physical or physiological method by which they might be attacked. This, as I understand, is what Cohnheim means when he says the theory has "*ein gewisser mystischer Beigeschmack*," and, in spite of Dr Fagge's gentle protest, I confess I think the epithet not unjust.

The risk of laying too much stress on the high temperature of the body, and of regarding it *per se* as an index of the heat-production, is, I think, further exemplified in a recent address by Dr Ord to the Medical Society (Oct. 1885). Let me remind you of his words; they are admirably chosen, and state the formal difficulty with great force: "The increased heat of the body in fever is to me a very constant stimulant of thought. When I ask people how it comes about, I am generally told that it is simply a matter of increase of combustion; that the oxidation processes of the body go on with undue vigour in fever; that the system is burning its candle at both ends, and that the two flames give more heat than one. When one looks at a patient who has passed through a febrile illness, one is ready to accept the explanation. He may have had no wasting discharge, hæmorrhage, or other obvious drain, yet there he lies, bloodless and emaciated to a degree which leads one readily to believe that on his bed of fever he has been consumed in all his tissues by an unseen fire . . . . But for some years my acceptance of this ready and most plausible way of accounting for the phenomenon has been hindered by an attentive consideration of an article on the 'Process of Fever,' contributed by Dr Burdon Sanderson to the Reports of the Medical Officer of the Privy Council for the year 1875. The article contains an exhaustive notice of the best observations made up to that time with reference to heat-production in the body during pyrexia . . . . I refrain from recapitulating the complex and very refined data upon which Dr Burdon Sanderson sums up impressively. Suffice it to say that, after careful analysis of his data, he writes thus: 'The general conclusion to which the preceding calculation leads us is a very important one—namely, that although as compared with the heat-production of a normal individual on fever diet the heat-production of a fevered person is excessive, it is not by any means greater than the heat-production of health.' There is in fever, it must be admitted, increased exhalation of carbonic acid and increased excretion of urea, *but after calculation they do not represent a source of heat sufficient to cause the increased temperature of the body.* I have read the article again and again, I have referred to various authorities on the subject, and I am compelled to say that the increased combustion explanation which satisfied me before has no longer the same value. To what, then, as I felt obliged to lose faith in my first belief, should I turn? Might, as some have argued, the increase of heat in the body be brought about by retention, by some state of the surface

which would prevent the liberation of heat from the body and lead to accumulation within? The well-conducted observations of Leyden and Liebermeister tend to shew that, far from being retained, heat is discharged from the surface in larger quantities in fever than in health. And we all know that intense hyperpyrexia constantly co-exists with profuse sweating, involving the freest discharge of heat from the surface of the body, as in severe cases of acute rheumatism. If we are bound to deny the cogency of the two explanations, we are compelled to find a new one." Dr Ord then goes on to suggest what I may call a new *vera causa*—that is, a possible coöperant cause for the liberation of heat in fever,—about which I shall have something to say later on. My object in making this long quotation has been to shew that, while he fully appreciates and admirably states the experimental facts concerning fever which I have already touched on in this lecture (the failure of the retention theory, the increased discharge of heat, the increased production therein inevitably implied—nay more, the indefeasible evidence of increased "combustion" furnished by the increased products of combustion—namely, carbonic acid and urea), he is stumbled by finding that they "do not represent a source of heat sufficient to cause the increased temperature of the body." I venture to suggest that the difficulty is an unreal one. Dr Burdon Sanderson everywhere distinguishes most carefully between thermogenesis and temperature. He even says there is "the strongest possible evidence that increased or diminished temperature has no necessary connexion with increased or diminished production of heat." "A source of heat sufficient to cause the increased temperature of the body" would be a phrase which Dr Burdon Sanderson would hardly recognise as his own; and if we give it the meaning it was probably intended to convey—that the increased production of heat in fever is not accounted for by the increased combustion of the tissues as evidenced by the excreted matters—I can only say that I find nothing in the paper referred to that supports such a statement, and I do not know of any measurements which suggest it. There is high temperature in fever, and there is increased production of heat, but the one is not the measure of the other. There is increased heat-production in fever as compared with the heat-production of health *on the same diet*, but not necessarily as compared with that *on full diet*. Somewhere between these two propositions comes Dr Ord's, and I am afraid that between them it comes to the ground. I shall be glad if a re-examination of the premisses

convinces him that he need not lose faith in his first belief. Dr Sanderson's memoir, taken in conjunction with Professor Wood's which supplements and corrects it, when properly weighed will shew him that his first belief is true, though perhaps not the whole truth. And as a final satisfaction I may add that, even though the preamble of his address is unproved, though the discontent with the existing theory which acted as a stimulus to his research was not well founded, the happy suggestion to which it led him appears to me to be true notwithstanding, in a certain guarded and limited sense.

Let me now recur to the outcome of Dr Burdon Sanderson's analysis above referred to, because in speaking of the experimental evidence of increased heat-production in fever I made no allusion to his results. On the surface they appear to tell against that evidence, but properly considered they are not inconsistent with it. When we say that more heat is produced by a patient in fever than by a patient in health, we must add the proviso—*in like circumstances*. One of the most important of these circumstances is diet. I being in health can, by eating to excess, raise my rate of heat-discharge far above my usual rate, and I can lower the rate by fasting and still remain in health. If I become fevered I eat less and less, but my rate of heat-discharge does not fall accordingly. In the report already mentioned, Dr Sanderson, from the data before him, finds that the heat-production of a fevered patient might be about 50 per cent. higher than in the same patient in health on a low diet. And if that is the case, some "increased combustion explanation" is not only satisfying but inevitable. Admitting increased heat-discharge, increased exhalation of carbonic acid, increased excretion of urea, we must admit a source whence they are derived. They cannot come from the food consumed, for that is notably reduced in quantity; they can only come from the body-substance itself; there *must* be increased combustion—the tissues *must* be "consumed by an unseen fire." But to go further, there are not wanting grounds for believing that fever-heat is often greater than normal heat even on a full diet. The Philadelphia experiments, made since Dr Sanderson's paper was written, enable us to follow the thermal history of an animal for several successive days under varying conditions of diet and in varying degrees of pyrexia. The outcome is that in dogs and rabbits at least the fundamental part of the febrile process is an increase in heat-production "by chemical movements in the accumulated material of the

organism." And though, to use Professor Wood's expression, this increase was usually insufficient "to overplus the loss of production from abstinence from food," in some cases it was more than sufficient. Moreover, reasons are given—valid reasons, as I think—for surmising that what is occasional in the lower animals is probably common in man, in whom febrile movement is more pronounced and severe. In other words, it is probable that in the fevered man there is sometimes an absolute, and not merely a relative, increase in heat-production.

Allow me, in conclusion, to suggest an image; it is not perfect; it is far from being an argument; it is only an illustration of one aspect of the question before us. Some of us, in travelling by railway or by steamer, have been startled by the sudden stoppage of the engine. On enquiry we are told that the "bearings have heated," and we have perforce to be patient till they are cooled down. The normal temperature of the engine is dependent on the consumption of the fuel in its furnace, and when it is in good order its parts work together with but little wear and tear. But from unequal stress, or excessive speed, or defective lubrication, the friction at some bearing-point increases, and soon the bearing becomes an abnormal source of heat, useless to the engine as a motive power and fraught with danger to its structure, for it means increased wear of the working parts, deterioration of their temper and their strength, and, as the heat mounts high, actual consumption and oxidation of their substance. The hot bearing is in a state of fever, its heat is wasted, and it is wasting. The warmth, the carbonic acid, the urea of health are evidence of so much food-fuel usefully transformed; the excessive heat and the excessive waste-products of fever are evidence that the fabric itself is being wastefully consumed.

LECTURE II.

LET me recal to your memory the point we have now reached in our discussion of the nature of fever. Perhaps I can best do so by reciting the conclusions arrived at in 1875 by Dr Burdon Sanderson in the important memoir I have already referred to. These conclusions will not only serve to indicate the first stage of our argument, they will be useful as a starting-point for the considerations that are yet to come. "Two possibilities [as to the origin of fever] are open to us. One is that fever originates in disorder of the nervous centres, that by means of the influence of the nervous system on the systemic functions the liberation of heat at the surface of the body is controlled or restrained, so that 'by retention' the temperature rises, and finally that the increased temperature so produced acts on the living substance of the body so as to disorder its nutrition. The other alternative is that fever originates in the living tissues, that it is from first to last a disorder of protoplasm, and that all the systemic disturbances are secondary. . . . The facts and considerations we have had before us are, I think, sufficient to justify the definitive rejection of the first hypothesis in all its forms; for, on the one hand, we have seen that no disorder of the systemic functions or of the nervous centres which preside over them is capable of inducing a state which can be identified with febrile pyrexia; and on the other, that it is possible for such a state to originate and persist in the organism after the influence of the central nervous system has been withdrawn from the tissues by the severance of the spinal cord. We are therefore at liberty to adopt the tissue origin of fever as the basis on which we hope *eventually* to construct an explanation of the process. But if we attempt to do so *now*, we shall at once find ourselves in face of an unsolved physiological problem—that of the normal relation between temperature and thermogenesis,—for the elucidation of which it is necessary to investigate much more completely than has yet been found possible the influence of temperature variations on those chemical processes in living tissue with which thermogenesis is necessarily associated."

As these sentences are somewhat condensed in expression a word or two of comment may prevent misunderstanding. In the first place, the "disorder of the nervous centres," which is without hesitation condemned as inadequate to explain the genesis of fever, means primarily disorder of that part of the nervous system which governs the circulation and the respiration—"the systemic functions," as they are called. This is clear from the whole course of the previous argument. The apparently sweeping rejection of the hypothesis of nervous disorder "in all its forms" is really levelled at the hypothesis of merely vaso-motor disorder, which is associated with the names of Traube and Marey; hence if we are led hereafter to consider a theory involving another kind of nervous disorder we shall not necessarily come under Dr Sanderson's condemnation. In the next place, since 1875 something has been done to supply the missing physiological data for the establishment of the tissue-origin of fever, and something more has been done on other lines which help us to get round the outstanding problems. Moreover, as I explained in my last lecture, we have had an authoritative re-examination and re-determination of some of the points in regard to febrile thermogenesis which Dr Sanderson was inclined to regard as doubtful or not proven in the earlier experiments of Leyden and Senator, with the result of shewing that though the methods were imperfect quantitatively the deductions from them were qualitatively correct. Thirdly, we have had from various quarters—England, France, Germany, and America—valuable researches on the relation of the body-temperature and the body-heat to certain parts of the central nervous system, researches which were not before Dr Sanderson when he wrote, and which open up new lines of thought regarding the mechanism of fever. Lastly, some light has been thrown on the relation of the nervous system in general to the "chemical processes in living tissue with which thermogenesis is necessarily connected." All these gains to knowledge enable us to advance further towards a true theory of fever than was thought twelve years ago to be possible, though the "unsolved physiological problem of the normal relation of temperature to thermogenesis" is not yet fully solved. I shall endeavour to shew the bearing of these later contributions, and so lead step by step to a theory of the "tissue-origin of fever," such as Dr Sanderson forecasts.

We start with this: that fever of necessity implies—(1) A disorder of the thermotaxic mechanism; (2) an excessive production of heat associated with excessive chemical changes

in the tissues, the excessive production being more or less than that of a normal patient on full diet (perhaps oftener less than more), but more than that of a normal patient on fever diet; and (3) that the body-temperature, depending on the state of the balance between production and discharge, fluctuates as one or the other is in the ascendant, and is not *per se* a true *measure* of either, or of the consumption of tissue which may be going on. An essential factor of fever being thus excessive production of heat in proportion to the food consumed, a natural question to ask is, What tissue or tissues in particular are concerned in the excessive thermogenesis? If there is increased combustion, what is the fuel, and where the furnace? To answer this question I shall first have to ask another—the licence is permitted to a Scotsman—What are the sources of heat-production in health?

The older notion, connected with the great name of Liebig, that the hydrocarbons of the food are the "fuel" of the body, being consumed chiefly in the lungs during respiration, while the nitrogenous constituents are mainly plastic or tissue-forming, has been so effectually disproved that I need not pause to discuss it. It still reappears in popular books, and we occasionally see in the medical journals—at least on the outside pages—published analyses of particular foods which are duly parted into "heat-givers" and "flesh-formers." Now, however, to use Professor Foster's words, which I need not paraphrase, because I cannot improve on them, "we may at once affirm that the heat of the body is generated by the oxidation not of any particular substances, but of the tissues at large. Wherever metabolism of protoplasm is going on heat is being set free. . . . In growth and in repair, in the deposition of new material, in the transformation of lifeless pabulum into living tissue, in the constructive metabolism of the body, heat may be undoubtedly to a certain extent absorbed and rendered latent; the energy of the construction may be in part, at least, supplied by the heat present. But all this, and more than this—namely, the heat present in a potential form in the substances themselves so built up into the tissue—is lost to the tissue during its destructive metabolism; so that the whole metabolism, the whole cycle of changes from the lifeless pabulum, through the living tissue, back to the lifeless products of vital action, is eminently a source of heat."* But of the "tissues at large," whose oxidation is in general the immediate source of the body-heat, the

* *Physiology*, p. 461.

muscles for various sufficient reasons must be regarded as the chief contributors. In the first place, the muscles form something like one-half the whole mass of the body. When we reflect that of the other half a large portion is made up of the bony tissues, whose oxidation cannot be active, we see that the muscles must play a very large part in thermogenesis. In the next place, even when the muscles are at rest the blood which leaves them by the veins contains more carbonic acid than the blood even of the right ventricle. The mean rate of oxidation in the muscles is higher than that of the average of all the tissues, including the muscles themselves. And, lastly, muscular exercise, in which the metabolism, as evidenced by the increased excretion of carbonic acid, is markedly increased, is accompanied by a large concomitant increase of heat-production. Fick makes a calculation, based on the actual observation that during severe muscular work the quantity of exhaled carbonic acid may be five times the normal, shewing that of the total energy derived from the food one-sixth goes to the work and five-sixths to the extra production of heat that accompanies it.* I need not enumerate all the other reasons for regarding the muscles as "the thermogenic tissues *par excellence*": those I have given are perhaps enough. Next to the muscles come the various secreting glands, and the alimentary canal in digestion. But when we remember that in fever the functional activity of these latter is to a great extent in abeyance, we shall probably not credit them with any large share in the genesis at least of febrile heat. As regards the muscles, however, they are estimated to contribute four-fifths of the body-heat in health; in fever their proportion must be higher still. Briefly, then, we may say that the muscles are the chief furnaces of the body both in health and in fever. Let us consider more minutely this thermogenic function of the muscles, and the nature of its connexion with the more familiar motor function. The investigation will be worth our pains, even if it only leads us to hesitate in regarding the heat produced in muscles as a mere excretion, a waste-product like urea or carbonic acid.

It has long been known that each contraction of a muscle is accompanied by the production of a certain modicum of heat. The earlier experimenters put forward the idea that as in a steam engine the energy supplied by the hot vapour from the boiler is given out partly as work and partly as heat, so in a muscular contraction the energy set free by a given stimulus

* This and other facts recited in this lecture I owe to the kindness of Dr A. Sheridan Lea.

appears partly as mechanical effect and partly as inevitably waste or degraded energy in the form of heat. It was inferred on the principles of the dynamical theory that if we should add the work done by the muscle to the mechanical equivalent of the heat wasted we should have a constant sum. The more work done in contracting the less waste energy in the form of heat, and *vice versâ*. But when exact quantitative experiments were made, such as those by Fick, Heidenhain, and many others, it was found that no such constant relation could be demonstrated. The proportion of heat to work, and the sum of these two elements, depended not on the intensity of the originating stimulus, but on various external conditions, such as the load the muscle had to bear, the extent to which it was stretched, and so on. In fact, the productive efficiency of the muscle considered as a machine was far more complex in character than that of a steam-engine. Many have been the attempts to determine more precisely the quantitative laws of this efficiency, but they all seem to proceed on the assumption that some necessary thermodynamic connexion exists between the function of work-producing and the function of heat-producing, between the motor and the thermogenic activities of the muscle; and it has been sought to define the nature of the assumed connexion in terms of a small number of variables. For some years I have asked myself the question: Must in *all* circumstances heat be produced when a muscle contracts? If heat is produced without contraction, may not contraction take place without heat? The older methods of investigation offered practical difficulties when I came to seek an answer to this question. The muscle experimented on was generally that of a frog or cold-blooded animal; it was removed from the body, and therefore from the influence of the circulation—in fact, it was a dying muscle rather than a living one. Moreover, the quantities of heat and the temperatures which were measured were on the whole extremely small, being reckoned in hundredths or thousandths of a degree. The limits of error in such measurements are naturally wide, and the measurements require the most sensitive thermoelectric instruments to make them apparent.

Working under the inspiring guidance of Professor Ludwig in 1881, and still possessed for a time with the idea of the thermodynamic interdependence of muscle-work and muscle-heat, I thought it worth while to see whether the heat-production of a frog's muscle still connected with the body and permeated by the circulating blood might not be great enough to admit

of thermometric measurement instead of thermoelectric. Some previous experiments of Dr Meade Smith in the same direction had made this probable. I procured very sensitive thermometers with fine-drawn bulbs, and openly graduated in tenths of a degree Centigrade. I found that one of these could be introduced beneath the skin of a pithed frog into the natural intermuscular cleft between the muscles of the thigh, so as to be surrounded on all sides by living flesh, but without injuring anything. When the sciatic nerve was suitably stimulated, the muscle contracted tetanically and the temperature rose. The rise was easily legible, amounting to four or five tenths of a degree. When several successive tetanic contractions were induced, the rise of temperature grew less and less, and at last could not be read at all, though the contraction was quite marked. In a word, the muscle was fatigued as a heat-producer before it was fatigued as a work-producer. These experiments were performed in winter on frogs collected in autumn, and I observed that as spring came on the heat-production in the muscles under uniform conditions gradually grew less and less, though the tetanic curves given by them on stimulation were excellent. I attributed this to the gradual exhaustion of the frogs by their long winter fast. But the point of interest was that the heat-producing power was sooner exhausted than the work-producing power of the muscles. Fatigue from repeated stimulation, exhaustion from long abstinence, each appeared to differentiate the thermogenic function from the motor function. I next proceeded to enquire whether in warm-blooded animals it might not also be possible to separate the two functions, to shew that though generally called into play together they were capable of being performed independently. Using dogs, guinea-pigs, and rabbits, narcotised with chloral in all cases, I made a number of experiments on the fatigue of the thermogenic function, and almost accidentally discovered another method of practically abolishing it while the motor function remained nearly if not quite intact. By controlling the temperature of the whole animal, including that of the muscle under observation, I found that I could vary within wide limits the relation between the work and the heat produced. It is not necessary to give the experimental details at length. Suffice it to say that by enclosing the profoundly narcotised animal in a box with double walls, through which water of any desired temperature could be made to circulate, I was able to raise or lower its body-temperature at will. Artificial respiration was maintained for hours together. The

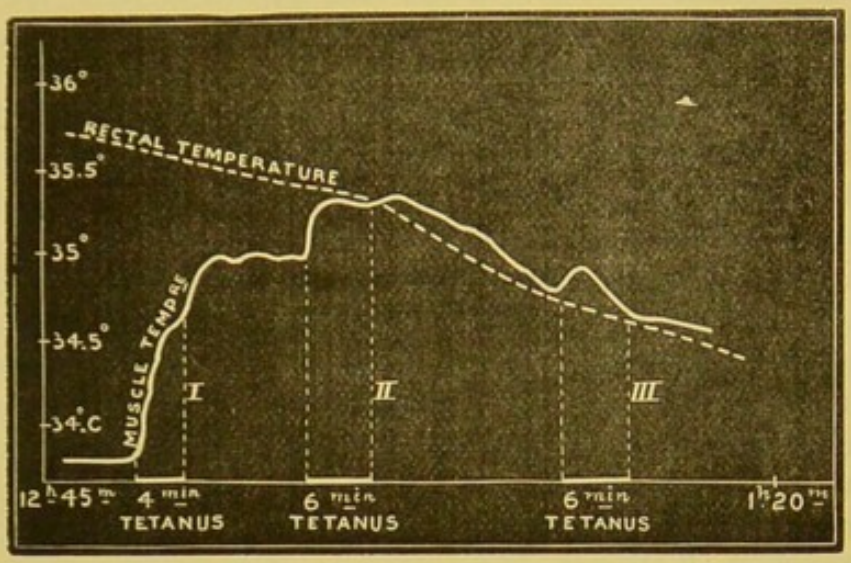
temperature of the blood in the aorta, in the rectum, and in the mass of the calf-muscles could be ascertained from minute to minute by means of fine thermometers; the mechanical work done by the muscles of the calf could be estimated by the motion of a cord fastened to the Achilles tendon; and, lastly, the sciatic nerve, severed from the spine, could be electrically stimulated. The arrangements were elaborate, but after much experience and many failures I succeeded in getting some fairly satisfactory results.

The experiments were made in triads. First, say, at ordinary temperature, the reading of the thermometers shewing that all was steady, a tetanic contraction would be set up, and the muscle-temperature read at intervals of a minute before, during, and after the stimulation. The whole arrangement would then be cooled down, say, to 16° or 18°C (61° or 64°F). When things were once more steady a tetanus of the calf-muscles was again induced, the muscle-temperature being read at short intervals as before. Once more the temperature of the animal as a whole was raised back to the original point, and the experiment repeated. By varying the stimulus the extent of the mechanical contraction was kept as nearly as possible the same in all three experiments. Usually such a triad of experiments lasted the whole day, as the processes of cooling down and warming up occupied several hours each. In some cases I varied the procedure by first cooling the animal, then warming it, and lastly cooling it again; but it was difficult to get very satisfactory results by this method, which was very exhausting to the observer, as well as to the animal. I need hardly say that the latter was never suffered to regain consciousness. The general character of the thermal results may be gathered from the rough diagrams I present. Take first an experiment at about 35°C. As soon as the muscle contracts, its temperature rises, and continues to rise for some time after the contraction ceases. The animal is then cooled to, say 19°C. On stimulation the muscle contracts forcibly, but the rise of temperature is trifling or absent. On re-warming the animal to something like its first temperature, we once more restore the rise of temperature on contraction. There are several other points of interest exhibited in these curves, but I do not propose to dwell on them at present. I will only say that the post-tetanic rise of temperature, when it exists, is due to the post-tetanic flushing of the muscles with blood that is warmer than the muscle. When the blood is cooler than the muscle, as sometimes happened, we have a post-tetanic fall of temperature. Some plethysmographic

experiments convinced me that this explanation, based on what in Germany is sometimes called "*das Gaskell'sche*

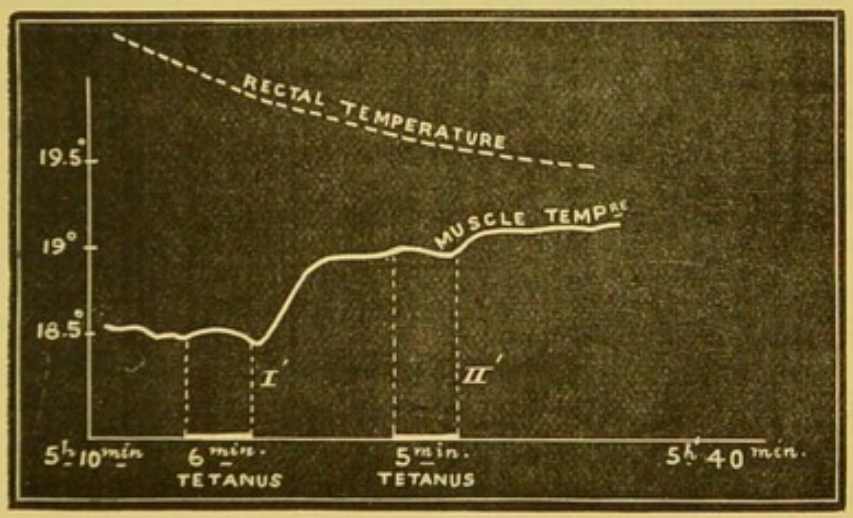
TEMPERATURE CURVE OF MUSCLE: BODY WARM.

Maximum contractions: I = 47 mm.; II = 41 mm.; III = 38 mm.



TEMPERATURE CURVE OF MUSCLE: BODY COLD.

Maximum contractions: I′ = 40 mm.; II′ = 38 mm.



I illustrates the post-tetanic rise of temperature, owing to the flushing of the muscle with warmer blood.

II illustrates the effect of fatigue in reducing the thermogenesis; the tetanic rise is diminished; the post-tetanic rise is almost absent, the blood being scarcely warmer than the muscle.

III illustrates the post-tetanic fall when the blood is cooler than the muscle.

Phänomen," is applicable to all the peculiarities of the curves. A study of these peculiarities, moreover, shews that the absence of thermal phenomena was not due to any percep-

tible impairment of the vaso-motor mechanism of the muscle at the lower temperatures. The lesson taught by these experiments appears to be—first, that the motor function may persist while the thermogenic function is in abeyance; and secondly, that *cold* is capable of abolishing or notably depressing the latter function, while the former is still but little or not at all affected. The therapeutic bearing of the second lesson is not unimportant.

Since 1881, two investigators also working in Professor Ludwig's laboratory have carried on the research in other directions. Dr Meade Smith, and Dr Lukjanow* in a memoir that has lately been published, display in minute detail the laws which govern the fatigue of the thermogenic function of a living muscle—(1) with the blood-supply shut off for a time, and (2) with the blood in full circulation. They also investigate the law of recovery of this function when it is completely exhausted, so far as it is effected by simple rest with or without blood-supply. The outcome of these experiments may thus be expressed: 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 the performance of mechanical work; the other more continuous, and manifested by the increased development of heat. Each process has its own laws as regards (1) the influence of external conditions—such as intensity of stimulus, load, extension, and so on; (2) the influence of fatigue from repeated stimulation; (3) the influence of general exhaustion from inanition or other debilitating causes; (4) the influence of the general temperature of the protoplasm of the muscle; and (5) the influence of rest and of the circulating blood in restoring lost power. This independence, I think, justifies us in assuming that the two processes are largely independent and coördinate. The heat developed in the second or thermogenic process is not simply a thermodynamic waste-product, an excretion of no greater dignity than urea or carbonic acid. On mechanical principles, the dislocation of the parts of the muscle on contraction, and again on relaxation, must give rise to a small quantity of heat, which one might call thermodynamic waste. It is the outcome of the degradation of the kinetic energy of contraction, such as occurs when any moving mass overcomes friction or is reduced to rest. But the amount of this waste-heat is calculable, and it comes out as perfectly trifling in comparison

* Du Bois Reymond's *Archiv* 1886.

with what I may call the thermogenic heat. In some of the experiments of Lukjanow it was much less than 1 per cent. of the heat liberated simultaneously with contraction.

The processes which issue in motion on the one hand and in thermogenesis on the other are of course associated with chemical movements in the muscle, with metabolisms whose terminal steps are the accretion of oxygen and the excretion of carbonic acid and water. The considerations I have adduced, and especially those relating to the power of recovery in a fatigued muscle under the influence respectively of rest and of the blood-supply, point to the conclusion that the two metabolisms are in some way different. In other words, that the "contractile stuff" in the muscle is not the same as the "thermogenic stuff." Both of them are stored in the muscle; so far as function is concerned they *are* the muscle. The store of each can be exhausted by repeated stimulation, but in some cases the thermogenic store sooner than the other. Both can be upbuilt again by the circulating blood, but in some cases the contractile store sooner than the thermogenic. Both the metabolisms are affected by cold, but the thermogenic much sooner and much more intensely than the contractile. We know little of the exact nature of the chemical changes involved in either form of metabolism. Oxygen is taken up in each, and carbonic acid is discharged, but the processes passed through between these terminal stages are much more complex than simple oxidations. The evidence rather goes to shew that it is the living substance as a whole, contractile stuff and thermogenic stuff, which is continually being decomposed and as continually being recomposed by the blood. The net balance shews only gain of carbonic acid and loss of oxygen, but the nitrogenous parts also of the working substance have in the process undergone partial destruction and equivalent reconstruction. This is in health; but if the reconstructive part of the process is inadequate or absent, the balance of accounts will give evidence of a nitrogenous residuum which is morbid. The muscle-substance will appear to be itself consumed; it will no longer be what I may call merely the circulating medium of consumption. I say it will *appear* to be consumed; this only means that the *net* result is loss of nitrogenous substance. The cast-out nitrogenised molecules of the muscle are not really excretionary in the sense that carbonic acid is excretionary. They have merely failed of that immediate upbuilding into muscle-substance again which is characteristic of the healthy metabolism. This incessant upbuilding of the muscle-substance,

which is a necessary consequence of the fact that no increase of urea or other nitrogenous matter is produced in the ordinary processes of muscular metabolism, must require the expenditure of a certain amount of energy. If in any measure the upbuilding is checked or abolished, so much energy is of course unexpended. It was on some such asset of energy as this that, as I presume, Dr Ord fixed his attention in the suggestive paper* of which I spoke in the last lecture. He asks: "Is the increment of heat of the body in fever due not only to combustion or other disintegrative processes thereto allied, but also to the persistence in the form of heat of energy which should have taken another form?" I believe that Dr Ord's claim on this asset must be allowed, at least so far as it refers to that part of the muscle-substance which in fever fails to be reconstructed. But I fear the asset is a very small one at the best, and quite inadequate to provide a large addition to the heat-production of fever. Moreover, it would be measured in a rough way by the loss of nitrogenous substance in the muscle—in other words, by that very combustion of the tissues which Dr Ord himself regards as already inadequate to account for febrile heat. When he goes further and extends his claim over the whole field of the tissues, in which normal constructive metabolism implies the locking up of energy, and when he infers from the absence of tissue-formation in fever that the locked-up energy must therefore all "run wild" and take the form of heat, I fail to follow his argument. Granted that in fever tissue-formation is to some extent in abeyance, are the materials and the energy for tissue-formation still being supplied in normal quantity? We cannot credit ourselves with the possession of unused energy till we are sure that the full tale of energy is being supplied and not used. In other words, until account is taken of the low diet of fever we cannot say with Dr Ord that the energy which in health is utilised in tissue-forming is in fever all available for heat-producing.

To return now to the thermogenic metabolism of the muscles. I have already implied, but may usefully state here in so many words, that in ordinary conditions it is continually going on as a quiescent but unceasing process. Contraction is accompanied by an increase of it, but contraction is not necessary to it. So long as the blood-supply and the nerve-supply are intact, the muscle, whether visibly moving or visibly resting, works unceasingly at its business

* *British Medical Journal* ii. 1885.

of heat-production. I say so long as the blood-supply and the nerve-supply are intact; we have already touched on some of the ways in which the blood-supply is related to the thermogenic function; we have now to consider the relation of the nerve-supply.

When we stimulate the nerve going to a muscle, two obvious processes are set up in the muscle-substance. The one issues in temporary contraction; the other temporarily increases the production of heat. When a muscle is poisoned by curare, both these effects of the stimulation are done away. As we know, curare abolishes the function of the peripheral nerve-endings, and thus blocks the way for the transmission of impulses from the nerve-trunk to the muscle. The thermal behaviour of an animal in whom the thermogenic tissues are thus cut off from the influence of the nervous system is very remarkable. The vaso-motor mechanism is intact, but the animal can no longer maintain its temperature. If it is plunged in a cooler medium, its temperature steadily falls; in a warmer medium it steadily rises. It is, in fact, the plaything of the external conditions; it is to all intents a cold-blooded animal. Still more remarkable is the change in the quantity of its oxidative metabolism, as manifested by the consumption of oxygen and the exhalation of carbonic acid. Both of these fall in the cooler medium to a mere fraction of the normal.* The circulation remains unaffected; the respiration can be artificially maintained. The cause of the change can only be the interception of the nervous influences that normally reach the muscles. Two inferences are inevitable: (1) that the thermogenic function of the muscles is primarily dependent on their innervation; and (2) that the share of the muscles in the oxidative metabolism, in the combustion-processes of the body, is so great that when they are excluded a mere fraction of the whole alone remains. This second inference confirms and justifies the attention we have concentrated on the muscles as the chief sources of heat, normal and febrile. The first inference leads us from the muscle to the nerve. But if when no contraction is going on the normal muscle is continually undergoing an active oxidative metabolism, and if this metabolism is dependent on active innervation, we must conclude that through the nerve-trunks at all times there is kept up a continuous stream of nervous influence. In other words, that in the resting muscle a constant *thermogenic tonus* is maintained. The old arguments for the

* Röhrig and Zuntz, *Pflüger's Archiv* 1871.

existence of a constant motor tonus in muscle now appear to be inadequate, though its impossibility is by no means proved. As regards the vaso-motor muscular system, however, there seems no doubt that such a tonus, such a degree of steady moderate contraction, does exist. There is, if I may so call it, a state of strained equilibrium between the vaso-constricting and the vaso-dilating influences, and the result is that mean condition—ready to be altered either way as one influence or the other preponderates—which we call arterial tone. And in the case of the respiration we have something very similar. In ordinary automatic breathing there is a steady rhythmic balance between the inspiratory and the expiratory impulses sent to the muscles of respiration—rhythmic but yet balanced, as are the impulses that maintain a planet in its elliptic orbit round the sun. Indeed, as I have already hinted in passing, it is possible to explain the automatic mechanism of respiration by regarding the balanced impulses as simply motor and inhibitory of the inspiratory muscles. The periodic equilibrium is capable of perturbation by various reflex and volitional causes; the breathing can be augmented or depressed in various ways; but in the normal self-regulated condition we have what we may call a *nervous tonus* of the respiratory centres. Now, as the vascular tonus is the result of a strained equilibrium between the opposing impulses given to the unstriped muscle of the arterial wall—the opposing impulses sent along the vaso-constrictor and the vaso-motor fibres,—and as the nervous tonus of the respiratory centres is in like manner due to what I have called a rhythmic balance or periodic equilibrium between motor and inhibitory influences, so I am fain to regard the thermogenic tonus of the muscles as the manifestation of a balance between two opposing innervations. But you will perhaps say, Granted that in respiration there is a balance between two tendencies, the nature of these tendencies is obvious—there is inspiration and there is expiration; and in the tonus of the arteries the two opposing tendencies are equally obvious—there is constriction and there is dilatation. What are the two tendencies that are balanced in the thermogenic tonus? The answer is: first, the tendency to the upbuilding and storing of what I have bluntly called the "thermogenic stuff" of the muscle—the *thermogen*, if I may coin the word; and second, the tendency to disintegrate this by a process involving oxidation. At Cambridge we are accustomed to speak of the upbuilding aspect of metabolism as anabolic, and the unbuilding aspect as catabolic. If I were to compress what I have ventured to

suggest to you into a formula, it would be: the thermogenic tonus of a resting muscle is dependent on a balance between the nervous impulses subserving anabolism and those subserving catabolism of thermogen. The words have a formidable sound, but I trust the idea they are meant to convey is clear enough. They emphasise the *particular* processes referred to in general terms by Dr Broadbent in his admirably terse article in *Quain's Dictionary of Medicine*. "If a theory of the febrile process is to be formed," he says, "it must be based upon a theory of the relation between the nervous system and the processes of nutrition and oxidation, and especially the latter." A few years ago such a theory of the relation of the nervous system to the processes of anabolism and catabolism would have been at best a pure speculation. Imperfect understanding of the true nature of one whole side of the relation—namely, the anabolic side—stood in the way of every attempt at demonstration. Now, however, thanks in great part to the suggestive work of my colleague Dr Gaskell, we are beginning to have clearer light on the subject; he has given a basis of facts for a new and comprehensive generalisation, and has opened out a vista for research whose limits we cannot now estimate. I will here ask your attention only to so much of his investigation as may help us to an insight into thermogenesis.

As examples of a tonus or balance of opposing tendencies, I have mentioned, first, the tonus of the arterioles maintained by the joint continuous action of the motor and inhibitory nerves subserving contraction of the vascular muscles; and, secondly, the tonus of the respiratory apparatus maintained by the joint rhythmic action of the motor and inhibitory centres controlling inspiration. There is a third example which is hardly less familiar, though it is only of late that we have approached a consistent theory of it. I refer to the action of the cardio-motor and cardio-inhibitory nerves in maintaining the rhythmic contraction of the heart. The complicated apparatus of intrinsic ganglia, of local inhibitory mechanisms, and so on, is being gradually simplified as our knowledge of the cardiac nerves increases. Suffice it here to say that to maintain the heat at its normal rate only two concurrent and continuously acting *central* influences need now be assumed. The one is exerted through the branches of the cervical sympathetic—the motor nerves of the heart. Dr Gaskell, in his epoch-making memoir* on the sympathetic

* *Journal of Physiology* 1886.

system, shews that we may class these nerves as functionally, structurally, and morphologically equivalent to the motor nerves of the vessels—the vaso-constrictors. The other influence is exerted through the vagus nerve, and, as we all know, its action is to check the heart's beat; when the nerve is cut the rhythm is suddenly quickened; when we stimulate the nerve the heart remains motionless and flaccid. It is the typical inhibitory nerve; it corresponds to the vaso-dilators.

But what is the nature of the influence on the cardiac muscle exerted through the motor nerve? and how does it differ from the apparently opposite influence exerted through the vagus? The characteristic effects of motor stimulation on the heart are primarily increased rhythm, increased vigour, and increased conduction of the beat through the muscular tissue. "But our knowledge of the action of any nerve is not complete so long as we only know its primary action; the chemical changes which the action of the nerve sets up in the tissue must manifest themselves in a more or less permanent after-effect, which must be recognisable apart from the more temporary primary effect of stimulation .... A motor nerve causes a muscular contraction by means of chemical changes in the muscle which are of a destructive nature, so that the after-effect upon the muscle is in the direction of exhaustion; and if the activity of the muscle be long continued this exhaustion becomes very manifest .... The subsequent exhaustion is as important a factor as the contraction." Dr Gaskell shews that the sympathetic nerves of the heart are motor in this sense also—that their continued stimulation leads to exhaustion of its muscle. He describes such a nerve as the *catabolic* nerve of the tissue, the nerve which produces its motor effect by augmenting suddenly the destructive metabolism of the resting muscle, and thus by excessive repeated action exhausts the store of "contractile stuff" within it. What now is the after-effect of vagus-stimulation when the primary and temporary effect of stopping the beat is gone by? Dr Gaskell has shewn that as regards all the functions of the muscle "the after-effect is nothing but beneficial." If before the stoppage the heart was beating at its normal rate, the rhythm afterwards is perfectly maintained or even quickened; the contraction-power is maintained, or, if it was weak before, increased; the conduction-power is restored if from exhaustion it was impaired; in a word, the tissue, if damaged, is repaired and restored as the result of stimulation of the inhibitory fibres. In fact, the result of vagus-action is exactly opposite to that of sympathetic-action; from the

latter we have increased activity followed by exhaustion—symptoms of catabolic action; from the former diminished activity followed by repair of function—symptoms of anabolic action.

There is thus "no greater mystery involved in the conception of a nerve of inhibition than in the conception of a nerve of contraction. In the former case, the cessation of function, the relaxation of tissue, is a symptom of constructive chemical changes going on in the tissue—that is, of anabolism, or assimilation, or trophic action—in precisely the same way as the activity of function, the contraction of the tissue, is a symptom of destructive changes—that is, of catabolism or dissimilation . . . . . The evidence is daily becoming stronger that every tissue is innervated by two sets of nerve-fibres of opposite characters, so that I look forward hopefully to the time when the whole nervous system shall be mapped out into two great districts, of which the one is catabolic, the other anabolic, to the peripheral tissues; two great divisions of the nervous system which are occupied with chemical changes of a synthetical and analytical character respectively, which, therefore, in their action must shew the characteristic signs of such opposite chemical characters . . . . . The decisive proof that inhibition is a symptom of anabolism in the same way as contraction is a symptom of catabolism will, in all probability, (first) be found in the heart; and perhaps the most important investigation that must be done before this theory of anabolic nerves is based on an absolutely firm footing is to find out what are the electrical and thermal changes in the heart-muscle which accompany the stimulation of its inhibitory nerve-fibres." Since this was first written a remarkable confirmation of the doctrine has been obtained. When the motor nerve of a quiescent muscle is stimulated, the contracting muscle assumes an electrical condition different from that of the uncontracted—the *negative* variation. Dr Gaskell finds that when the inhibitory nerve of a piece of quiescent heart muscle is stimulated, the muscle exhibits an electrical change of precisely the opposite character—a decided *positive* variation. He is now at work on the thermal changes accompanying inhibition, and I shall not be surprised to hear that, as on stimulating a motor nerve we have a simultaneous evolution of heat, so on stimulating the inhibitory nerve the muscle becomes cooler.

It seems to me that from the considerations advanced in this lecture it is not rash to proceed to a provisional generalisation. It is this: that not the visceral and vascular muscles

only, but all the muscles of the body, have their double nerve-supply. The one set of fibres are essentially catabolic; they set up disintegrative changes in the muscle, which are manifested first by thermogenesis, and secondly by contraction. The other set of fibres, whose path is perhaps anatomically different, are essentially anabolic; they set up reconstructive changes in the muscle, which are manifested by inhibition of motion on the one hand, and the absorption of energy on the other. Does the motor fibre also subserve the thermogenic function? Does the same catabolic nerve convey the stimulus which determines motion and the stimulus which determines the evolution of heat? Or are the stimuli only quantitatively, not qualitatively, different? Or again, as I have suggested, is the stimulus the same, but the "stuffs"—contractile and thermogenic—different, one impulse starting two kinds of catabolism, as when the same electric spark simultaneously fires a mixture of two explosives? These questions are as yet unanswered, though I am persuaded that the answer is not far off. Meanwhile we have brought our argument to this, that the heat-production in the muscles, the chief furnaces of fever, is probably carried on under the influence of a twofold nervous mechanism; the one part exciting to thermogenesis, accompanied by destructive metabolism; the other staying thermogenesis, and subserving constructive metabolism. The thermogenic tonus is the manifestation of the normal balance between these two parts. In other words, the character of the nervous mechanisms subserving heat-loss is paralleled by an analogous twofold character in the nervous mechanism subserving heat-production. The relations of this nervous mechanism to the central nervous system and to the thermotaxic mechanism will occupy us in the next lecture.

LECTURE III.

In the last lecture I gave at some length my reasons for believing that the thermogenic function of the skeletal muscles, the chief sources of heat in health and in disease, is dependent on their innervation. I spoke of this innervation as twofold, corresponding to the motor and inhibitory innervation of the vascular and visceral muscles and of the heart. From the point of view of the chemical changes which take place in thermogenesis, I spoke of the nerves concerned as respectively catabolic and anabolic. The latter nerves were inhibitory of heat-production, inasmuch as their influence is towards the upbuilding of the hypothetical "thermogen" and the simultaneous absorption of energy. The former were excitors of heat-production inasmuch as they induce destructive metabolism with oxidation and the liberation of energy. Briefly this view of thermogenesis was suggested (1) by the chemical fact that in the normal thermogenic, as in the normal contractile, metabolism of muscle there is no adequate evidence of increased nitrogenous waste, but only of the absorption of oxygen and the liberation of carbonic acid and water; the nitrogenous molecule of the muscle-substance must be continuously upbuilt again as it is continuously being unbuilt, anabolism going hand-in-hand with catabolism; and (2) by the cardinal physiological doctrine taught us by Dr Gaskell, that catabolism or disintegration is the symptom of "motor" or "excitor" nervous action, and anabolism or restoration of "inhibitory" nervous action. The physiological doctrine was, you will remember, strongly supported by the phenomena presented by the heart-muscle and its double nerve-supply through the sympathetic and the vagus; it was rendered probable in the case of the visceral and vascular involuntary muscles, and on analogical and other grounds inferred in the case of the voluntary muscles and the secreting glands.

Another line of analogical reasoning to which you may or may not be inclined to give weight suggested that, as the nervous mechanisms of heat-loss—namely, those subserving circulation and respiration—had a twofold character, and

were maintained in balance by the joint action of opposing influences, respectively motor and inhibitory, so too the nervous mechanism of heat-production was twofold, and in health maintained a "thermogenic tonus," a balance between tendencies towards the liberation of thermal energy on the one hand and its repression or absorption on the other.

I have to confess that we know little or nothing as yet of the anatomical course of the thermal nerves of the muscles. The motor trunks would appear to contain the thermogenic fibres—if, indeed, they are not identical with the motor fibres. But as to the course of the anabolic fibres we can only conjecture, and the analogies which we have to guide us are too obscure for me to dwell on here. This ignorance would be more depressing if we held to the notion that anatomy had fulfilled its task and explored exhaustively the whole field of the peripheral nervous system. But when I remember that it is only since the other day that the physiological, anatomical, and morphological relations of the so-called sympathetic system to the spinal nerves have been at all clearly understood, I do not despair of further great discoveries. In my own opinion the work of anatomy, guided by the light of physiological research, is in this domain scarcely even begun. When it is complete I have little doubt that the relations, anatomical and morphological, of the anabolic nerves to the central system will appear as definite as those of the motor nerves.

I proceed to consider some of the attempts that have been made to trace the thermal nerves into and through the central nervous system. I do not for a moment profess to give a complete summary of all that has been done, even in recent times, to investigate the relations of the cerebro-spinal system to thermogenesis. A very large number of these researches are to my mind vitiated, in that they are merely thermometrical. Without calorimetry, or—what in a sense we may regard as equivalent—the measurement of the oxidative or other destructive metabolism accompanying experimental lesions of the nervous centres, we can infer little that is certain as to the mechanism of heat-production. The concurrent effects of the processes of heat-loss are not easily to be eliminated or allowed for, and the results thus complicated are at best ambiguous.

To take a familiar example: it has been known from the time of Sir Benjamin Brodie that section of the spinal cord is in some cases followed by a surprising rise of the body-temperature. In other instances the temperature falls; and

some observers have found that according as the animal is exposed to a warmer or cooler medium, according as it is wrapped up or naked, its temperature will ultimately rise high or sink low. Wood has shewn how these inconsistencies may be reconciled by measuring the actual heat produced by an animal before and after section. As the result of many rigorous experiments, he is able to state as demonstrated, that "section of the spinal cord above the origin of the splanchnic nerves is usually followed by an immediate very decided increase in the amount of heat dissipated from the body, and also by a decided lessening of the amount of heat produced." The vaso-motor tracts being divided in these experiments, it is certain that vaso-motor paralysis has a great deal to do with the increased loss of heat, while the paralysed muscles, being cut off from their regulating nerve-supply, are apt to have their thermogenesis increased or diminished by the high or low temperature of the surrounding medium, much as when they are poisoned with curare. The temperature of the body is thus the resultant of a number of diverse thermal tendencies; and as one or the other is in the ascendant the temperature rises or falls. Successively higher and higher sections of the cord at length carry us to a level above the highest or dominating vaso-motor centre in the medulla, and not till then do we get results that are fairly uniform and intelligible. If the medulla is partially divided close to its junction with the pons, the vaso-motor mechanism appears to remain intact; at any rate, the usual physiological test of its integrity—marked rise of blood-pressure when a sensory nerve is stimulated—is readily obtained. The operation itself is not easy, but when it is successfully performed the thermal consequences are remarkable. I attach little importance to the alleged results of Tschetschichin, now twenty years old, or to the alleged failure of others since to confirm them. Both the discoverer and his critics seem to have tested merely the temperature of the animals operated on; and this varies according to circumstances. But when we come to measure the thermogenesis the case is different. In the dog at least there is generally a rise of temperature; but whether this happens or not, the rate of heat-production is invariably augmented. Heat-loss is also increased, but it seldom keeps pace with the heat-production. Moreover, the increased heat-production is not simply transient; it goes on for a long time, and in some instances is greater twenty-four hours after operation than it is at first. Again, when the same region—namely, the part of the medulla which imme-

diately adjoins the pons—is mechanically irritated by a puncture, in several instances a marked temporary fall in the rate of heat-production has been observed (Wood), though in others electrical stimulation of the part is said to have been followed by a prompt rise of temperature at least.

These experiments certainly suggest the hypothesis that the region in question is traversed by some of the anabolic or inhibitory fibres. Severance of them is followed by a disturbance of the balance I have called thermogenic tonus; the inhibitory influence being cut off, the excitor influence has full sway. Irritation of the same tract is followed by a temporary diminution of thermogenesis, just as irritation of the vagus tract is followed by a temporary diminution of the contractile activity of the heart. I have scrutinised the tabulated results of the published experiments to see whether there were any traces of an increased vigour of the thermogenic function following the temporary diminution, such as might be expected to result from the stimulation of an anabolic nerve, and such as we find to follow the vagus-inhibition of the heart (see Lecture II p. 30). The figures are unfortunately insufficient for the purpose, with one exception given in Wood's series. In this case puncture of the pons-medulla at first lessened the heat-production by no less than two-thirds. But in twenty-four hours, in spite of the exhaustion of the animal, in spite too of its prolonged abstinence from food, the rate of heat-production increased again to within one-fifth of the normal rate. This at least suggests considerable vigour in the thermogenic function, and it may be an instance of improvement following inhibition.

Professor Wood has gone further in his attempts to trace upwards the inhibitory tract. He has sought, following Eulenburg and Landois, to determine the influence of certain cortical and subcortical lesions upon thermogenesis. His methods for producing the experimental lesions are no doubt less refined and precise than those to which the classical researches of Dr Ferrier have accustomed us. But his results, extending to some twenty laborious experiments, are so uniform and so striking that, if we accept his statement of them at all, it is difficult to resist the conclusion that severe injury of certain regions in the cortex or beneath it is, in the dog at least, followed not merely by rise of temperature—that is of secondary importance—but by increased production of heat. The cortical area is just posterior to the crucial sulcus, and corresponds in Hitzig's and Ferrier's scheme to the motor region for the muscular masses of the limbs. The experi-

ments in which stimulation rather than destructive injury of this region was attempted are neither numerous nor altogether satisfactory, but so far as they go they agree with the older experiments of Eulenburg and Landois, in which local electrical stimulation of one of the areas was followed by a slight temporary *cooling* of the opposite extremities. Dr Ferrier, in the last edition of his great work,* regards this as due to contraction of the blood-vessels, and the long enduring and considerable increase of heat-production which follows destruction of the areas as due to dilatation of the vessels. Changes in the distribution of temperature may and do result from changes in the vascularity of the tissues; but I know of nothing that justifies us in straightway assuming that such changes affect thermogenesis. The *mere* flushing of a muscle with blood need not increase the metabolism of the muscle-substance, unless the latter is simultaneously stimulated to functional activity, unless it is moved *ab extra* to take advantage of the opportunities for assimilation which are offered to it. Cut off the innervation of a muscle by curare, and you may cause the arterial blood to rush through its vessels without appreciably increasing its oxidative metabolism. For this reason, in addition to those given by Professor Wood, I am unable to correlate the thermogenic phenomena resulting from destruction or stimulation of the cortex with vaso-motor changes; I say nothing for the present of the thermometric phenomena. So far, then, it would appear that there is experimental evidence that the tract containing the nerve-fibres inhibitory of the thermogenic function of the muscles runs through the medulla into the pons; there is, moreover, experimental evidence that, in the dog at least, a cortical or subcortical region coinciding in part with the motor region is concerned with thermogenesis, and is probably in connexion with the inhibitory tract.

Allow me next to call your attention to an interesting series of experiments by Messrs Aronsohn and Sachs, of Berlin. They are thermometric, not calorimetric, and therefore at first sight bear on temperature rather than thermogenesis; but as simultaneous measurements were made of the oxygen consumed and the carbonic acid discharged, we are able to draw from them certain conclusions of interest as regards febrile heat. Some of the striking phenomena in question were shewn to a number of the visitors to the Berlin Medical Congress in 1885.

* *Functions of the Brain* (ed. 1886), pp. 87, 253.

When a puncture with a fine needle is made through the brain of a rabbit in such wise as to pass vertically through the medial side of the corpus striatum near the *nodus cursorius* of Nothnagel, the temperature in the muscles and in the rectum promptly rises from 1½° to 2½°C, or say 2½° to 4½°F, and remains high for many hours, returning ultimately to the normal again. The animal appears to be but little affected by the operation, and eats and moves about gaily. It need not be tied up or confined in any way, and the temperature of the room may be ordinary. But the result seems invariably to follow, and it can be reproduced again and again in the same animal. It is not due to irritation or injury of the cortex or of the white matter immediately underlying it, for superficial or shallow punctures are without effect. The sensitive region is of no great extent, and can be defined with considerable precision. The question that always rises in experiments of the kind rises here also: Is the result due to stimulation or to destruction of the nervous elements that are punctured? Our experimenters have apparently answered this question in a satisfactory way. By a highly ingenious method they succeeded in passing a weak electric current through the sensitive region, and that without exciting any of the neighbouring parts. The result was striking. The temperature in the muscles rose with every passage of the current, and could at will be kept at a febrile height for many hours together. The rise of temperature appeared thus to be unmistakably due to stimulation, and not to injury. And here remark that the febrile condition could hardly be due to any contraction of the cutaneous vessels, to any *retention* of heat, for it was observed that the temperatures of the skin, the muscles, and the rectum rose and fell together. Moreover, when means were provided for estimating the oxygen consumed and the carbonic acid given off, they were found to be increased during the artificial fever to about the same extent as in ordinary fever of like intensity, and the nitrogen excreted in the twenty-four hours after the puncture was something like 25 per cent. greater than in the twenty-four hours before the puncture. From all these facts the conclusion is hardly to be resisted—that by the stimulation of a particular region to the inner side of the corpus striatum the thermogenic function of the muscles is abnormally increased, and therewith their catabolic or oxidative metabolism; and this without encroaching on the motor tract, without exciting the motor function, and without any action that can fairly be called vaso-motor coming into play. I am not going to say

that the circumscribed region of the brain so carefully explored by Messrs Aronsohn and Sachs is a thermogenic "centre," for I know that by some pathologists the word is banned. But I do say that, if the evidence is worth anything, it proves that the region is connected intimately with the thermogenic tract; that the catabolic fibres which proceed to the muscles, and in them excite the thermogenic function, are here capable of being reached and stimulated apart from the motor nerves. It is this fact which makes one hesitate at once to say that the thermogenic fibres to the muscles are identical with the motor fibres. It is not easy to see how they can dichotomise again at their central terminations, the motor running through the internal capsule, the thermogenic quite to the inner side of the corpus striatum.

There is another aspect in which we may view these experiments. During the period in which the sensitive spot is being at intervals electrically stimulated, the animal's temperature is markedly raised, its rate of heat-production is apparently increased, it is consuming more oxygen and giving off more carbonic acid than is normal; by all the signs of disordered body-heat, by all the symptoms which imply pyrexia, the animal is in a state of fever. When the stimulation ceases the fever subsides. In other words, by exciting to excessive action a particular spot within the brain, we can bring about a fever of moderate intensity indistinguishable while it lasts from any other produced in more familiar ways. We have generated a fever by a direct action on the central nervous system.

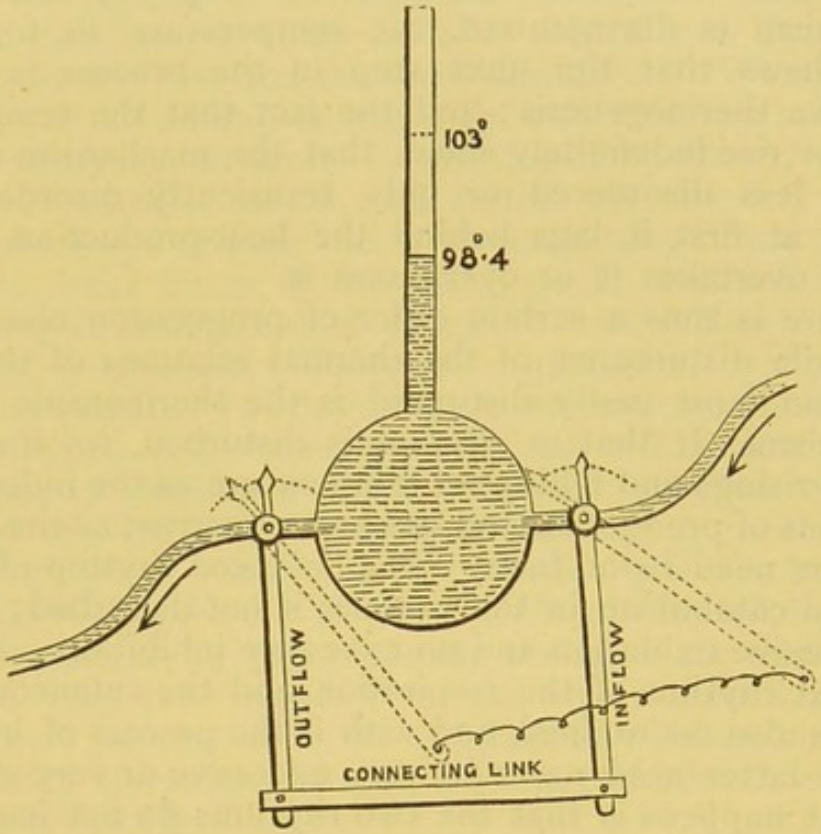
Before I proceed to suggest to you my own belief that all fever is due to an action on the central nervous system, I must anticipate a possible misunderstanding. I have more than once remarked, in passing, on the distinction between high temperature and increased heat-production. It is due to you, and necessary to my remaining arguments, that I should make clear wherein the distinction is of importance. In my first lecture I spoke of disorder of the body-heat as the essential condition of fever, whose frequent and most manifest system is high temperature. But I now go further, and say that high temperature is not necessarily fever, and that fever is not necessarily accompanied by high temperature. We may have a *febris sine febre*, a morbid thermogenesis without high temperature, the increased heat-production being compensated or more than compensated by increased heat-loss. And we may have a rise of temperature even with diminished thermogenesis, if the heat-loss is so

diminished as no longer to balance even the diminished production. The former would be fever, though the patient were cool; the latter would not be fever, even though the patient were hot. It is the excessive thermogenesis, with the excessive catabolism of nitrogenous tissue which that involves, that constitute fever. Without this condition the mere temperature may run for a time to a "paradoxical" height, to a point at which we might expect the albumens of the body to coagulate; and yet the patient may recover, and promptly too, for there has been no excessive combustion, no consuming of the tissues.

Consider on how slight a dislocation of the normal relation of gain to loss a marked rise of temperature may depend. An adult man in ordinary health breeds enough heat in half an hour to raise his own temperature one degree Centigrade. In half an hour he discharges an equal amount of heat into the air, and so his temperature is *not* raised. But suppose for a moment that all automatic connexion between the two processes were broken for the space of an hour, that the two could work independently of each other and of the temperature. Suppose further that the heat-loss were somehow checked entirely for the hour and then restored to its normal rate. The heat-production need not alter a jot, but it would all go to raise the temperature; at the end of the hour the temperature would be higher by 2°C or 3·6°F. Open now the channels of heat-loss; they will carry off at the old rate, and the temperature will rise no further; but it will now remain permanently at 102°F. This rise of temperature has been produced, not by any increase of thermogenesis, not by any ultimate diminution of heat-loss, but simply by a little "lagging" of the latter process behind the former. The two have become balanced again, but the temperature does not fall unless the loss goes beyond the balancing point. And what is thus true of lagging in time is obviously true of lagging in degree. If the heat-loss is not in abeyance, but merely a little less than the heat-gain, the temperature will rise until it reaches a point at which the two are balanced again, and will remain there if the balance once obtained is maintained. In other words, the difference between the rate of heat-production and the rate of heat-loss at any moment is measured not by the temperature, but by the *gradient* of the temperature. The temperature itself, when it reaches its height, indicates the time it has taken for the one process to gain upon and at length overtake the other, but tells nothing as to the absolute activity of either. High temperature may

thus be an indication of mere sluggishness or lagging in the process of adjustment, and is not *per se* an indication of increased heat or of increased combustion.

I have imagined that a working model might be arranged to illustrate this plain but constantly overlooked fact. Suppose a tall vessel containing water; the level of the water



shall represent temperature. Let two pipes be connected with the vessel, the one bringing water to it, the other carrying it off. Let each be provided with a stopcock, and let the two stopcocks be connected by a rigid link which ensures that they always turn together and by the same amount. If, to start with, the inflow and outflow are equal, then however I move the linked stopcocks, the height of the water will remain the same. Loss balances gain in every position. Now remove the link and connect the stopcocks by a weak indiarubber band or a spiral spring. If I now move the inflow stopcock so as to increase the flow, the outflow one will not at once follow, and, the balance being broken, the level of the water will rise. Presently, as the elasticity of the spring comes into play, the outflow will become equal to the inflow, and the rise will cease; but the new high level will be maintained. Every movement of either stopcock will affect the level, which will fluctuate accordingly, but its height at any moment will not

be an index of the amount of inflow at that moment. The inflow may be slight while the level is high. Of course inflow represents heat-production, outflow heat-loss, and the rigid link which first connected the two stopcocks the healthy thermotaxic mechanism. When this latter is weakened, or relaxed, or broken, the steadiness of the normal level is impossible. The fact that in fever, after the thermotaxic mechanism is disorganised, the temperature so frequently rises, shews that the next step in the process is usually excessive thermogenesis; and the fact that the temperature does not rise indefinitely shews that the mechanism of heat-loss is less disordered or only transiently disordered, for though at first it lags behind the heat-production, it ultimately overtakes it or overpasses it.

There is thus a certain order of progression observed in the febrile disturbance of the thermal relations of the body. First and most easily disturbed is the thermotaxic nervous mechanism. If that is all that is disturbed, we shall have strange risings and fallings of temperature as the independent variations of production and loss are concurrent or the reverse, but there need be no fever. The balanced rhythm of anabolism and catabolism in the muscles is not disturbed; there is no excessive oxidation and no excessive inhibition. And the balanced rhythm of the respiration and the cutaneous circulation is also maintained, and with it the process of heat-loss, but the latter need never be very excessive or very deficient. All that happens is that the two rhythms do not harmonise, and the fluctuations of the temperature correspond in a measure to the "beats" which are heard when two tones are sounded together that are nearly but not quite in concord. Cases of this thermal ataxia are not wanting; one such was under my charge for a time when acting for Dr Paget at Addenbrooke's Hospital. He has described it in the *Lancet* of July 4th, 1885. The patient was paraplegic, with at times a remarkably unstable temperature. For instance, on one day, when there was a trifling irregularity of the bowels, it ran up to 109·2° F, the pulse being at 80 and the respiration at 22; in three-quarters of an hour it was down to 97·8°. On another day it reached 110·4°, and in half an hour fell to 98·8° again. But there was no evidence of increased thermogenesis, no wasting, no failure of nutrition. Many similar "paradoxical" fluctuations of temperature, without fever, have been described.

The next degree of disturbance is that in which there is not only thermal ataxia, but disorder of the parts of the

nervous system subserving heat-production; there is under-action of the anabolic nerves with diminished construction and diminished absorption of energy; there is over-action of the catabolic nerves with increased oxidation and thermogenesis. Both factors of the normal thermogenic tonus are probably disordered together, but as I believe there is good reason for regarding the anabolic mechanism as "higher" than the catabolic, so there is reason for the view that it is in many cases the first and the most disordered. Weakening or abolition of the inhibitory influences with defective upbuilding of the "thermogenic stuff" in the muscles probably precedes excessive catabolic action, and to this may be due the pre-febrile discharge of urea which is occasionally observed. But soon the other factor of the thermogenic mechanism is disordered also, and there is excessive heat-production. The net result is apparent wasting or "combustion," and generally high temperature. The thermotaxic mechanism is in abeyance; the immediate adjustment of heat-loss to heat-production is consequently hindered; the thermogenic mechanism gets a start, as it were, before the heat-discharging mechanism is called into play. Once the temperature is somewhat raised, the latter mechanism, if it is not itself disordered, is capable of increased activity, and presently overtakes the work thrown upon it. But the "lagging" of the one process behind the other finds expression in the heightened temperature. This is ordinary pyrexia, and the nervous disorder does not in general go further.

But there is another stage—namely, when the mechanism of heat-loss is also profoundly disordered, so that the rise of temperature from the antecedent excessive thermogenesis does not stimulate it (or does not stimulate it enough) to make it overtake the latter until the temperature reaches an excessive or even a fatal height. This is hyperpyrexia.

To resume. The thermal nervous system has three parts; let us call them briefly the thermotaxic or adjusting, the thermogenic or producing, and the thermolytic or discharging mechanism. Disorder of the first implies irregularity of temperature only; disorder of the first and second implies, in general, heightened temperature and increased body-heat—that is, ordinary fever; disorder of the first, second, and third implies, in general, hyperpyrexia, dangerous increase of heat, and steadily *rising* temperature. In the ascending scale of evolution we seem to rise from the thermolytic to the thermogenic and thence to the thermotaxic nervous system. Cold-blooded animals possess the mechanism that in mammals

becomes thermolytic—a nervous mechanism that controls the vessels and the breathing. The thermogenic system in them is ill-developed, and probably not well differentiated from the system of motor and inhibitory nerves that subserves locomotion. The frog in a normal condition hardly needs to generate heat in his muscles, but when the motor trunks are artificially stimulated heat *can* be produced in them. But his oxidative thermogenic metabolism is at best feeble, and we cannot easily throw him into an enduring fever. In young mammals the thermogenic system is developed before the thermotaxic. The instability of an infant's temperature is its chief characteristic. A little sends it into a high fever; a little restores it again. As the child grows, the range of its power of regulation increases, its temperature grows stable, and the thermotaxic mechanism is evolved.

Time fails me to say more as to the successive evolution of the three mechanisms from what we may call the historical point of view. The consideration of their organisation leads us, however, to a like result. In Dr Hughlings Jackson's words, "Evolution is a passage from the most to the least organised—that is to say, from the lowest well-organised centres up to the highest least-organised centres; putting this otherwise, the progress is from centres comparatively well organised at birth up to those, the highest centres, which are continually organising through life." The order of organisation is, like that of evolution—thermolytic, thermogenic, thermotaxic. The localisation of the thermolytic centres is admitted even by the opponents of localisation; they do not object to speak of the vaso-motor, respiratory, and sweat centres. The best organised and the most automatic centres are the best recognised, and the lowest. The cerebral thermogenic mechanism I have hardly ventured to speak of as consisting of "centres." Yet some observers claim to be able to point to the inhibitory centre, and others, as competent, to the excitor centre. I have laid before you specimens of both claims; that they are not universally admitted is to me evidence that the organisation of these thermogenic centres is less complete and therefore less localised; that they are, in a sense, in process of evolution; that they are higher than the thermolytic. As to the thermotaxic mechanism, no one, so far as I am aware, has been able to say it is at this spot or at that. Least organised, least automatic, least and last developed, its localisation is necessarily the most imperfect. But its existence I take to be as necessary as that of the "highest motor centres," which control and connect and

represent the "middle motor centres" localised in the cortex. It coördinates because it represents the thermogenic and the thermolytic centres.

You will see from what I have said that, regarding the thermal mechanisms as a functional and evolutional hierarchy, I regard fever as a "dissolution," a progressive negative process, a relaxation of control from above downwards, in the same sense (and with the same reserves) that the term is used by Dr Hughlings Jackson in his Croonian Lectures of 1884. The ideas set forth in that most suggestive course with reference to the evolution or dissolution of the motor functions I venture in all deference to apply to the correlative thermogenic function. If I may so express myself, the pains that have been taken to adjust our thermal relations to our environment, the nicety of the balance in widely varying circumstances, the impairment of all the higher functions which ensues when the balance is but a little disturbed in either direction, move me to regard thermogenesis as no mere by-end of our nature, no mere casual but unavoidable concomitant of chemical processes performed for another primary purpose. I would put thermogenesis in the vital scale a little "higher" than circulation and respiration, and a little "lower" than voluntary muscular action. The motor function of the muscles is related to the highest centres; their thermogenic function connects them with the lower or animal centres; and the innumerable variety of causes which disturb or "dissolve" the controlling nervous mechanism, the readiness of "fever" to result from injurious influences of so many kinds, is the expression of the fact that the habit of stable temperature is, so to speak, recently acquired.

As a last test of the "dissolution" hypothesis, consider what happens in recovery from a typical febrile attack. First, the thermolytic mechanism is waked to adequacy, there is a critical sweat or a relaxation of the vessels of the skin, and a gush of heat from the surface brings down the temperature with a run. But the thermogenic centres have not yet recovered, and the temperature will swing backwards and forwards for some days, and an epicritical excretion of urea takes place. Thermogenesis becomes less and less excessive, and is vigilantly counterbalanced by thermolysis; but thermotaxis is yet feeble. The patient's temperature is down, but it is still far from stable. As convalescence proceeds the stability increases, and at length thermotaxis, the first to be disturbed and overthrown, is the last to be restored.

The task which I proposed to myself is fulfilled; it was

to set before you, if not an idea, at least the germ of an idea concerning the nature of fever. At every turn I have been indebted to the work of others; theirs are the pearls of observation and experiment which I have so inadequately displayed to you; only this tenuous filament of a theory on which I have strung them together is mine. But as some coherent theory is better than none,* if only as an aid to the ordering of our facts, and as I have found this manner of looking at fever useful to myself, not only as a pathologist but as a physician, I have ventured thus imperfectly to propound it. I have said nothing of the many clinical facts which might be adduced in support of the nervous origin of fever; Dr Hale White has done so once for all in an excellent paper in the *Guy's Hospital Reports* (1884). I have said nothing of the therapeutics of fever, for indeed there is probably no Fellow of the College here present who could not teach me many lessons as to its treatment. And if, lastly, I have said nothing about etiology, that has at least this advantage, that you have been spared even a single allusion to bacteria.

* "We should follow the method of science, and investigate by the use of hypotheses. This may seem a strange remark to those who erroneously suppose an hypothesis to be a conclusion in which we may rest. It is only used for the methodising of work by observation and experiment."—(HUGHLINGS JACKSON, *Bowman Lecture* 1885.)

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