temperature invariably falls back to 98½° F. In the fever patient, on the contrary, the loss as well as the production of heat is regulated at an abnormal standard, varying according to the malady and the individual, insomuch that, according to Liebermeister, the very essence of fever consists in a regulation of thermogenesis for a temperature more elevated than normal.[1]

But to maintain that heat production in fever depends essentially on heat-regulation is not to solve the problem, but simply to remove it farther back. It becomes us now to ascertain what causes this modification in the mechanism of regulation. Here comes in the influence of the nervous system, and we have to consider what may be called the nervous theories of fever. Claude Bernard[2] in analyzing the phenomena which occur after section of the great sympathetic, was persuaded that there exist thermic nerve fibres possessing a special physiological function with reference to calorification, and placed under the dependence of the sympathetic ganglia. The great sympathetic becomes thus the moderating mechanism of the chemical combustions of the economy. So whenever the functions of this system are enfeebled, the inhibitory check ceasing to operate, the temperature rises; in a word, fever is only one of the manifestations of paralysis of the great sympathetic.

Since Tscheschichin as a result of his curious experiments on the mesocephalon of rabbits, claimed this part of the nervous system as the regulator of

[1] Liebermeister begins by establishing that the temperature of a fever patient is higher than that in a healthy person, and that a great part of the symptoms of fever are the consequence of elevation of temperature; then he shows that in fever there is augmented heat-production. Both thermometric elevation and increased thermogenesis are present. In the well man every artificial elevation of temperature disappears rapidly, for in the normal condition the production of heat is regulated for a temperature of 98½° F. In fever, on the contrary, the regulation is adjusted to a certain degree of temperature, which varies according to the intensity of the fever, and its nature, so that the essential difference between a fever patient and a well person is this, that in the fever patient the loss as well as the production of heat is regulated by the standard of a high temperature, while in the healthy man it is regulated at 98½° F. (*a*)

[2] Claude Bernard was the first to put forth the hypothesis of the existence of nerve fibres, influencing physico-chemical operations and heat production. He showed first that section of the sympathetic augments calorification, without increasing the organic combustions. There is, according to him, a physiological function of calorification, and this function is under the control of nerves belonging for the most part to the sympathetic. Independently of its vaso-motor action, the sympathetic has a thermic action. "Its excitation produces a frigorific effect; its section or paralysis, a calorific effect. It is not only a vaso-constrictor nerve, it is a frigorific nerve." The sympathetic acts then on the physico-chemical phenomena, which engender heat, as a sort of moderator, as a check, or an agent of inhibition. "It cools the parts which it innervates," he says, "hence the name we give it of frigorific nerve. It constricts the vessels, and thus renders the organs pale and exsanguinated, whence its name, vaso-constrictor. It moderates and slows nutritive movements; it merits the name of check, or inhibitory nerve (*nerf refrenateur*).

Fever then, according to Bernard, is a result of paralysis of the great sympathetic. (*b*)

(*a*) Liebermeister, Uebor Warmeregulirung und Fieber (Somml. Klin. Vortr. von Richard Walkmann, no 19, 1871).

(*b*) Claude Bernard, Leçons sur la Chaleur Animale, Paris, 1884.

the combustions of the economy, making the pons Varolii the heat centre, there has been a tendency to consider the thermic elevation of fever as depending, not so much on a disturbance in the function of the great sympathetic, as in that of the annular protuberance. Vulpian rejects both the theory of Claude Bernard, and that of the Russian physiologist. In his opinion, it is not proved that thermic nerve fibres exist, or even moderating centres of thermogenesis; no matter in what part of the cerebro-spinal axis you may locate those centres.[1] According to Vulpian, disturbances occasioned in the vaso-dilators and vaso-constrictors, whether by direct irritation of these nerves, or by irritation of the spinal cord and of the medulla oblongata, or whether by reflex action, suffice to explain the thermal elevation. It is then by modifications effected in the action of the vaso-motor nerves that he would explain the febrile process. At the same time he recognizes that in many cases the starting point of these troubles is in the blood, and this leads us to study the action of alterations of the blood on the production of fever; and to the nervous theories of Claude Bernard, of Tscheschichin,[2] and of Vulpian, we will now oppose the theories called humoral.

[1] Schiff has made experiments to determine the influence of the vaso-motor system on the activity of thermogenesis. He cuts the principal nerves of an animal on one side; then he lets the wound cicatrize. Then he determines septic fever in the animal, by injecting putrid substances in the blood. On examining the temperature of the members, he finds that it is higher in the side where the nerves were not cut. Vulpian repeats the experiments, but with contrary results. At the same time he believes in the influence of the vaso-motors, though not claiming to give a very complete explanation of the mechanism of heat regulation. "We must admit," he says, "that the nerve centres, irritated by the morbific cause, act upon the vessels to provoke a constriction or dilatation; they determine a constriction of the cutaneous vessels in the period of chill. They produce without doubt a dilatation of the deeper vessels, especially of the viscera, even during the chill and thus contribute to energize the physico-chemical acts, which give rise to heat. But it appears to me incontestable that all is not limited to a direct influence on those operations, by the medium of the vaso-motor apparatus. The nervous centres must act more directly on those physico-chemical phenomena by the fibres of the nerves of animal or organic life which are in more or less immediate relation with the anatomical elements, the organized, living, protoplasmic substances of the different tissues. We must, in fine, admit that morbid causes (pyretogenous agents) may act also on this organized substance, modifying the nutritive, calorifacient processes in a manner quite direct, and consequently without the necessary intermediation of the nervous system. (*a*)

[2] Tscheschichin cut the pons, in hares, just before the point where the medulla oblongata terminates; the rectal temperature rose several degrees, and the respirations were markedly quickened. If, on the contrary, the bulb or the cervical cord were sectioned, the temperature fell. Hence he considers the pons as acting on the rachidian bulb and spinal cord as a centre which regulates and moderates the organic combustions. If you take away the curb by cutting the connections between the pons and the medulla, the combustions acquire a greater intensity.

Experimenters who have repeated these experiments have not all arrived at the same results; some, as Pochoy, obtaining just the opposite results. Moreover, Naunyn and Quincke in sectioning the cervical cord in dogs, have obtained elevation of temperature, and clinical observations in contusions of the cervical cord by fractures, etc., have often demonstrated the existence of hyperpyrexia. In a case of fracture of the 6th cervical vertebra,

(*a*) Vulpian Leçons l, Appareil Vaso-Moteur, 1875, t II, p. 265. §23

There is no doubt that the blood plays an important part in the production of the febrile process, and here physiological experiments as well as clinical researches show us the reality of this action. It suffices, in fact, as you well know, to inject into the blood of animals a very small quantity of septic matter, to determine in them a febrile state, more or less intense, and it is this very process which we employ in our laboratories to obtain experimental fever. It is the same with man, and the chill, often so violent, which supervenes in patients after surgical operations or confinement, is a proof that the blood has been contaminated by putrid matters. I showed you when speaking of transfusion, that in many cases this operation has been followed by rigors and veritable attacks of fever. It is to the same cause, that is, to the presence of particles foreign to the blood, that we must attribute these symptoms. Does the trouble consist in modifications of the fibrine of the blood, which, analogous to processes of fermentation, induce changes in the constitution of that fluid, or does the trouble consist, as Verneuil thinks, in the presence of a definite morbid principle, *sepsine?* Or does it consist in the introduction of organized microbes, microbes, which, since the discoveries of Davaine and Pasteur, have so considerable a part in our infectious diseases? These are questions which are not completely solved, but there none the less exists this fact which we should keep in mind, that there are substances which, introduced into the blood, are capable of determining the febrile process and to which we may give the name of *pyretogeneous.*

Have these pyretogeneous substances a direct action on heat production, or is this action only indirect and secondary, and brought about through the intermediation of the nervous system? Without being able to solve this question by precise experiments, I believe that in many cases this action must be secondary, and that it is by modifying the function of the vaso-motor centres that in all probability, alterations of the blood determine the elevation of temperature of fever.

As you see, gentlemen, of all the theories which I have made to pass before you, that which seems to me most comfortable to the facts of clinical medicine and experimental pathology is the theory which makes febrile thermo-

Frerichs noted a rectal temperature of 43.8° C. Bruck and Gunther in the mechanical irritation of the medulla oblongata or pons, determined an elevation of temperature, instead of a lowering, which they should have obtained if the hypothesis of Tscheschichin had been correct. Electric irritation of these parts by Heidenhain, also gave elevation of temperature. Hence Heidenhain rejects the hypothesis of a heat-moderating centre, and Vulpian and Riegel share the same opinion. Murri rejects also the nervous theory of fever, claiming that the excessive thermogenesis results from a trouble in the physico-chemical process of the living elements of the tissues, and not from any special influence of some nervous centre which regulates heat production in the economy. (*a*)

(*a*) Tschechichin, Zur Lehre von der Thicrischen Warme (Reichert's und die Bois-Reymond's Arch..1866) —Pochoy, Recherches expérimentales sur les centres de température (thèse de Paris, 1870, no 120, p. 24).—B. Naunyn et Quincke Rechert's und du Bois-Raymond's Aach., 1869.—Riegel, Uber den Einfluss des centralsservensystems auf die Thierische Warme (Pflüger's Arch., 1871–1872, p. 629–672).—L. Bruck et A. Günter, Versuche über den Enfluss der Verletzung gewisser Klirntheile auf die temperature des Thierköpers (Pflüger's Arch., 1870, d. 578–585).—J. Schreiber, Uber den Einfluss dec Gehirns auf die Kurpertemperatur (Pflüger's Arch., 1874, t. VIII, p. 576),—Vulpian, Leçons sur l'appareil vaso-motor, t. II, p. 250, 1885.—Murri, Salla teoria della febbre, Florence, 1874.

genesis depend on a trouble in the functionating of the vaso-motor system, whether that trouble be primitive or secondary.

These details being once clearly understood (and you will pardon me for having given so much space to their exposition), we can now approach the study of the action of medicaments which combat the febrile process and its principal characteristic, excessive heat-production; in a word, we will examine the bases of the antipyretic treatment. But I must first of all show you the necessity of this antithermic medication, in pointing out the dangers which hyperpyrexia causes.

Here, moreover, we were indebted to Leibermeister for valuable data.[1] Establishing himself on experimental facts and clinical observations, he has assigned to excess of temperature a series of alterations having especially to do with granulo-fatty degenerations of the different viscera, the most important of which, surely is that which affects the cardiac muscle.

I fear that we have gone a little too far in this direction. Remark, first of all, that from an experimental point of view it is difficult, even grounding ourselves on the experiments of Liebermeister, to compare an animal in which the temperature has been made to rise by artificial means, with a person in whom the heat excess is the fact of a febrile process. Moreover, as Hayem has well

[1] The disorders determined by hyperthermia have been studied experimentally and clinically. Claude Bernard has shown that in pigeons death ensues whenever the central temperature attains 48° C. (118° F.). In mammals death takes place when the temperature is 44° or 45° C. (111° or 113° F.); it seems then demonstrated that death always happens to an animal whenever the temperature of the blood exceeds the normal by from 12° to 15°.

In some experiments on dogs Vallin divides into three periods the accidents which supervene in animals whose temperature has been abnormally raised.

In the first period there is acceleration in the respiratory movements. In the second respiration becomes sighing and prostration is marked. In the third convulsions supervene, and death ensues when the temperature attains 44.4° C. (112° F.)

The lesions determined by hyper-thermia, according to Liebermeister, are characterized essentially by a granulo-fatty degeneration of the different viscera; the liver presents the lesions of acute yellow atrophy; the kidneys, especially the cortical substance, are degenerated. The heart presents notable disorders; it becomes soft and friable, and the fibres are affected with granulo-fatty degeneration.

The lesions observed by Stokes and Hayem in typhus and typhoid fever, by Desnos and Huchard in small-pox, and by Vallin in marsh fevers, are all the consequences of this hyper-thermia; it is the same with the lesions of the muscles described by Zenker and the symptomatic myosites observed by Hayem.

At the same time the latter considers these myosites, not as the result of hyperthermia, but as the consequence of the infectious diseases which modify profoundly the nutrition of the muscular fibres, and this view seems confirmed by a curious observation of Vallin, who in a typhus patient, whose temperature never exceeded 100° F., observed fatty degeneration with rupture and hemorrhage of the muscles of the abdomen and thigh.(*a*)

(*a*) Claude Bernard, Influence de la chaleur sur les animaux (Rev. des cours scient., 1871, p. 134). —Vallin, Recherches expérimentales sur l'insolation et les accidents produits par la chaleur (Arch. gén. de méd.., 1870, p. 138).—Liebermeister, Uber die Werkungen der febrilen temperatur (Deutsch. Archiv, Bd. 1, 1866).—Stokes, Traité des maladies du cœur et de l'aorte, Paris, 1864.—Hayem, Etudes sur les myosites symptomatiques (Arch. phys., 1870).—Desnos et Huchard, Des complications cardiaques dans la variole, Paris, 1871.—Vallin, De la myocardite et de la myostite symptomatique dans les fièvres palustres graves (Un. méd., 1874).—Du Castel, Des températures élevés dans les maladies (thèse d'agrégation, Paris, 1875).

remarked, and as the interesting researches of Vallin show, this alteration of the viscera, and especially these symptomatic *myosites* may depend, not on the thermogenesis, but (with more likelihood) on the infectious or septic agent, which, in altering the blood, has profoundly modified the nutrition of the muscular fibre.

But while combating the exclusive view of those who ascribe to the hyperpyrexia alone the dangers resulting from divers malign febrile processes, I recognize the fact that we ought as far as possible to endeavor to bring back to the normal the temperature of fever patients. To accomplish this we should put in operation the various agencies which constitute the anti-febrile medication.

These medicinal agents may be divided into two principal groups. You will see that this division is based entirely on the physiological deductions, to which we have given development while discussing the pathogeny of fever, and you will at once comprehend how important it was to dwell minutely on this part of our subject.

In the first group we place all remedial measures calculated to remove from the economy the excessive heat; we do not attack the causes of febrile thermogenesis. This group comprehends refrigerants.

The second group comprises methods and medicaments which combat the cause of hyperpyrexia. Since the cause of the exaggeration of physico-chemical phenomena depends, as we have seen, on the two following factors—modifications of the nervous system and modifications of the blood, we may range in two sub-divisions the medicaments which constitute the second group; in the first are those which modify thermogenesis by action on the nervous system, in the second those which are antipyretic by direct action on the blood. There may even be a mixed third group consisting of medicines which, like quinine, belong to both divisions.

This classification being admitted, we may rapidly go over each of these groups, taking only a cursory view, and reserving the more complete details which belong to the application of the different therapeutical agents for the study of specific fevers which is to follow.

I. The anti-thermic methods by abstraction of heat have acquired in these late years a great importance, especially since the promulgation of Brand's experimental researches. Although Hippocrates and Galen[1] have in many

[1] Hippocrates and Galen applied baths and affusions to the treatment of febrile diseases; one may judge of the estimate in which they held them by the following aphorisms: "A fever which does not come from bile gets well under abundant affusions of warm water upon the head," (Aphorisms, sec. 7, § 42). "If the patient is delirious make affusions upon his head," (Epidemics, book III. Sec. 5, page 49). Galen is quite as affirmative; he treats fever by warm or cold baths and by cold drinks internally.

Rhazés advised to combat the fever of small-pox by baths and cold drinks. All these facts had, however, been forgotten and abandoned by the followers of Hippocrates and of Galen; and we have to come down to the end of the eighteenth century to see James Currie, a Scotch physician, practising at Liverpool, establish, on new bases, the treatment of fever by cold water. It is thus that James Currie combated what was then described under the name of grave contagious fever or "typhus," what we now call typhoid fever, and even intermittent fevers. Currie examined the results of his medications by means of a thermometer which he placed in the mouth and armpit of the patient.

He employed cold affusions, *i. e.*, with water at 15° C. (59° F.) and affusions of warm water, whose temperature varied from 30° to 35° C. (86° to 95° F). He believes these latter affusions to produce as satisfactory a lowering of the temperature of the body as cold affusions; he joined to them also the internal usage of cold drinks.

When one reads attentively the work of Currie it is plainly evident that he employed cold or tepid lotions not so much to abstract heat as to tonify the organism, and it was rather the reaction which he sought than the thermic depression.

The doctrine of Currie fell into oblivion. Forty-nine years elapsed before attention was again called to this practice, and this time in France. Jacques, of Lure, revived Currie's method in 1846; a method which he had adopted since 1839 in the treatment of typhoid fever, and which consisted in applying over the forehead and abdomen and different parts of the body compresses of cold water; these he ordered to be renewed every ten minutes; he also administered cold lavements and cold drinks. Out of 143 patients affected with typhoid fever and treated after this manner he had but nine fatal cases, while out of 349 typhoid patients treated by the other methods he had had 91 deaths.

In 1849, Wanner set forth a treatment of typhoid fever which consisted in giving cold water for the only drink, and applying lotions over the whole body of ice-cold water; and from this time onward, in successive memoirs Wanner affirms that with his method persistently carried out of lotions and ice water, which he calls "passes," he has the experimental certainty of triumphing over every case of typhoid fever whose date of invasion does not exceed one week.

In 1852 Leroy, of Bethune, maintained that by cold water internally and externally one could almost certainly cure typhoid fever.

In 1851, Brand, a physician in Stetin, published his first treatise on the employ of cold water in the treatment of typhoid fever. His first affirmations are a little hesitating, and he expresses himself thus: "If typhoid fever is treated from the commencement by cold water, there is in general nothing to fear, and even in cases the most grave one may yet many times obtain cure by cold water." In 1863 Brand becomes still more positive, and he now says: "Every case of typhoid fever treated regularly, according to my method, takes on a light character and almost never terminates by death, so that in fact we may say that Clinical Medicine is in condition to preserve with certainty the lives of all patients entrusted to its care." In 1868 he assures us an absolute cure by his method, in the following terms: "The treatment by cold baths, methodically employed from the commencement, gives a success positively ensured, and always enables one to ward off death." Glenard, of

places insisted on the employment of cold, internally and externally, in the treatment of fevers; although Rhazes called attention to cold baths as beneficial in small-pox, it is certain that these precepts had fallen into desuetude and oblivion, and we have to come down to the end of the eighteenth century to find the remedial value of cold water in fevers recognized, and James Currie proclaiming a new method of treatment of pyrexias, namely by cold baths. Currie aimed to obtain, it is true, by his cold applications, not so much a lowering of heat as a tonic and reconstituent effect. Despite the great efforts of the Scotch physician, his mode of treatment was little followed, if at all, and despite attempts renewed since in France, by Jacquez, Wanner, Leroy, to treat fever by external cold, this practice was virtually abandoned. It is then in reality to Brand that we are indebted for the revival and formulization of this ancient method.

I do not mean here to decide concerning this therapeutic measure, or estimate its results; such actual examination I shall make in another lecture,