Dr. J. Burdon Sanderson on the process of fever.

APPENDIX.

No. 1.—Dr. J. Burdon Sanderson on the Process of Fever.

On the Process of Fever, by Dr. Burdon Sanderson.

The following Paper is intended to serve as a compendious statement of the knowledge which at present exists as to the nature of fever. The plan I have adopted in its preparation is in accordance with this intention. Although it would have been easier to myself, and probably more agreeable to the reader to have begun by developing in the order of time the views respecting the pathology of fever which have been so warmly discussed in this country and in Germany during the last twenty years, dealing with the facts in connexion with the doctrines which have been founded on them, I do not think that this method of treating the subject would have answered my purpose. I have therefore confined myself, as strictly as I have found it possible, to an exposition of the clinical and experimental observations which relate to the nature of the febrile process, leaving the work of combining them into a theory of fever to a future opportunity. The reader will, however, not find a mere catalogue of dry facts without connexion. I have endeavoured to follow such an order in the setting forth of the subjects treated of as appeared to me in accordance with their mutual relations, nor have I hesitated to refer to existing theories, whenever the opportunity has offered itself of pointing out the objections to which each of them is liable.

The recognised characteristics of fever are those which relate either to the disintegration of the living substance of the body or to the increase and diminished constancy of the bodily temperature. But in addition to these attributes which distinguish the febrile state of the human or animal organism from that of health, it is essential to the correct definition of fever that it should comprehend particulars relating to its origin, progress, and termination. In other words, fever is not merely a state but also a process. It has its beginning in the entrance into or action on the organism of some affecting or infecting cause. After this event, follows a period which by analogy with certain physiological processes, we are in the habit of calling the period of latency, for it is not until it is passed that the first indications within the affected or infected organism begin to manifest themselves. The state of fever once established, it may vary in its course, in its duration, and in the local inflammations which accompany it, indefinitely; but in all cases it has its onset, accession, and declension, each of which is characterised by more or less distinctive phenomena, the onset by shivering, accompanied with rise of temperature of the internal parts of the body; the augment by continued pyrexia and exhausting disorder of the bodily functions; the decline, epicrisis, or defervescence by the restoration of those processes one by one to their normal conditions and relations. The period of convalescence which follows decline, during which the mischief done is gradually compensated and repaired, and the injured organism is brought back again to its normal condition (so far as this is possible) by new growth of tissue, does not form a part of the febrile process.

These considerations afford the key to the natural division of the subject and consequently to its methodical treatment. In stating what is known as to the febrile state, I propose to study first, those facts which

relate to the disintegration of the bodily substance, and secondly, those relating to the general disturbance of bodily function of which the disorder of temperature is the chief, reserving for another opportunity the inquiry into the nature of the agents which produce fever, and the mode and limiting conditions of their action.

Part I.—Textural Disintegration in Fever.

Even to the superficial observer it is obvious that in fever the body wastes. But it is only by the scientific methods of measurement and comparison that we know how this waste takes place—how in a fevered person or animal the living substance of the body is disintegrated. This central attribute or characteristic (as it appears to be) of fever, is known partly from the study of fever artificially induced in the lower animals, partly by the observation of clinical cases. From the former source we obtain facts which are more definite, and thereby better fitted to serve as foundations for our knowledge. But the indications afforded by clinical observation, even though they may be less precise, are often of greater value, because they bring us nearer to the purpose of all pathological inquiry—the learning of the nature and causes of human ailments.

Both in the clinical and in the experimental investigation of diseased processes, measurement without comparison is useless. Thus in health, the discharge of nitrogen in the excreta is exactly counterbalanced by its introduction in food, so that it is only when this is the case that the person or animal can be said to be in a normal state of nutrition, whether the actual quantity of nitrogen which passes through the body in a given time is large or small. If in any disordered condition of health, which is under investigation, it is found that the quantity of nitrogen discharged is absolutely smaller or larger (as the case may be) than in the same individual when well, we can conclude nothing from this, unless it is ascertained at the same time how much nitrogen enters, in order that by balancing the one quantity against the other, we may learn whether the amount which is stored in the body is being wasted on the one hand, or accumulated on the other. Or, to use the ordinary and perfectly convenient language of physiology, we judge whether integration or disintegration of living substance is going on, not by the absolute income or expenditure, but by the nitrogen exchange—by the excess or defect of nitrogen expenditure as compared with nitrogen income.

Section 1.—*Experimental Investigations.*

For the best observations on the disintegration of tissue in fevered animals we are indebted to Dr. Senator, of Berlin,* on the result of whose researches the most important statements contained in this section are founded.

Senator's Researches on the disintegration of tissue in fevered animals.

The purpose of Dr. Senator's inquiry was not merely to determine the exchange of nitrogen, but also its relations with the production of heat and the discharge of carbonic acid. The method was therefore contrived and adapted with a view to these objects. As I shall have occasion in the other sections of this paper to refer to it repeatedly, I shall give the explanation of the plan of investigation so far as is necessary to enable the reader to understand it.

---

* Dr. Senator's contributions to the pathology of fever have been published from time to time during the last 10 years in Virchow's Archiv. They have been recently republished under the title of "Untersuchungen über den fieberhaften "Process und seine Behandlung." Berlin, 1873.

The purpose of the inquiry being to compare the exchange of material and of heat in the febrile state with those of health, it was necessary before proceeding further, to bring the animals to be employed (dogs) into a condition of nutritive equilibrium. With this view each animal was placed for a sufficient time preceding the period of observation, on a diet of carefully-selected horseflesh, which was increased or diminished until the body-weight and daily discharge of nitrogen in urea, and the "insensible" loss became severally constant. After it had been kept on this regulated diet for some days, food was withdrawn for a period of 48 hours, during which the normal discharge of carbonic acid, water, urea, and of heat were measured. The diet was then continued as before until nitrogen equilibrium was once more established. This having been accomplished, fever was induced by the subcutaneous injection of perfectly fresh pus, and determinations of the same kind as had been previously made, were repeated *under exactly similar conditions as regards nutrition* during a second period of 48 hours. The febrile condition induced was well characterized. The temperature (as measured in the rectum) began to rise in from one to two hours after the injection of the purulent liquid, the pyrexia continuing for about two days. During the accession there were rigors, and the skin felt hot to the finger; subsequently the animals were listless and anorexic, and drank water with avidity whenever it was supplied to them.

Each experiment therefore comprised two 48 hours' periods of observation, separated from each other by an interval of several days, during which periods the production of heat, the changes of bodily weight, the daily quantities of urine and urea excreted, and the respiratory and cutaneous discharges of carbonic acid and water were determined.

The carbonic acid determinations, and the calorimetrical observations, however, related only to limited periods of measurement, each lasting an hour, repeated once or twice during the day. The "insensible loss" was computed for each period by adding the weight of ingesta to the total loss of weight in twenty-four hours, and deducting that of the excreta. As thus reckoned the result for any period of observation would, if the weight of oxygen absorbed were equal to that discharged in the form of carbonic acid, express the discharge of water and carbon from lungs and skin. As however the weight of oxygen taken in in respiration is always in excess of the weight given off, it must be borne in mind that this excess, which is a variable one, is comprised in the so-called "insensible loss." Putting this statement into the equation form:—
Insensible loss = H_2O discharge + CO_2 discharge — O absorption.

The collection of the urine in animals is a matter of great difficulty. As regards the dog, the only method that was found to be successful is that of training the animal to empty its bladder at stated intervals. Unfortunately this cannot be done without much trouble. For the continuous collection of the products of respiration and cutaneous exhalation, the animal was placed in a ventilated chamber, which was so arranged as to answer the purpose of a calorimeter. Its construction will be described in the next section. In some instances the carbonic acid was determined volumetrically by Pettenkofer's method, in others by the balance. The water-vapour in the air discharged from the chamber was determined by weight, the apparatus for the purpose being of course interposed between the exit tube and that for the absorption of carbonic acid, so that the air reached the latter in the dry state. In most of the experiments the air as introduced into the chamber was completely saturated, so that its temperature being known, the per-centage per volume of aqueous vapour it contained could be calculated. This being the case, the difference between this per-centage and that of the outflowing air gave the quantity of water exhaled by the animal. It was recognised, however, by Dr. Senator that this determination was not exact, for of the out-going water-vapour much must have been lost by condensation on the wall of the chamber. Considering that in fever the natural ingestion of food is reduced to a minimum, it is obvious that any comparison made between an animal normally fed, and a

fevered animal, would give no exact information. For even if the nitrogen value of the food taken by the animal in the febrile state were accurately determined, no precise estimate of the weight actually assimilated could be founded on it. In health we can do this with precision; for as soon as the physiologist finds by the constancy of the weight of the animal, that the income and expenditure of material balance each other, he knows that the expenditure is a true index of the activity of the nutritive process. But in artificial fever, from the short duration and the variableness of the conditions to be investigated, no such balance is attainable; so that it must always be quite uncertain in the case of an animal which is still digesting a greater or less quantity of food, how much of the nitrogen it discharges is derived from income, and how much from store. In Dr. Senator's experiments the only available method of securing accuracy was adopted. It consisted in observing the same animal after it had been brought to normal equilibrium as above explained, during two successive periods of inanition, separated from each other by an interval, during which the animal was fed as usual, and again brought to nutritive equilibrium.

In the following table I have brought together the results of a long series of these observations, so far as they relate to the discharge of urea and carbonic acid:—

TABLE I.

Showing the Results of Quantitative Determinations of Urea and Carbonic Anhydride discharged respectively by a Normal Animal, and by the same Animal in the Febrile State during successive Periods of Inanition.

	Bodily Temperature in rectum. (Means.)	Discharge of Carbonic Acid in one hour of Observation.	Discharge of Urea in 24 hours.
Experiment 1. Weight of animal, 11 lbs. 10 oz.			
1st Day Normal	39·0	3·6	6·01 Grammes
1st Day Fever	39·3	3·4	9·0
2nd Day Normal	39·0	3·3	No Observation.
2nd Day Fever	40·3	3·7	Do.
Experiment 2. Weight, 13 lbs. 4 oz.			
1st Day Normal	39·1	4·03	No Observation.
1st Day Fever	39·4	3·93	
2nd Day Normal	39·1	4·78	
2nd Day Fever	40·3	4·02	
Experiment 3. Weight, 16 lbs.			
1st Day Normal	39·0	2·88	7.89
1st Day Fever	39·6	2·73	14·48
2nd Day Normal	38·8	2·72	No Observation.
2nd Day Fever	40·7	4·20	
3rd Day Fever	40·7	3·77	
Experiment 4. Weight, 10 lbs. 10 oz.			
1st Day Normal	39·3	2·72	6·39
1st Day Fever	39·5	2·75	10·27
2nd Day Normal	39·3	2·45	No Observation.
2nd Day Fever	40·7	2·88	
3rd Day Fever	39·6	2·91	
Experiment 5. Weight, 9 lbs. 2 oz.			
1st Day Normal	38·9	2·38	6·87
1st Day Fever	39·7 40·3	3·09	11·47
2nd Day Normal	38·9	2·20	4·61
2nd Day Fever	41·0	2·07	No Observation.

		Bodily Temperature in rectum. (Means.)		Discharge of Carbonic Acid in one hour of Observation.		Discharge of Urea in 24 hours.
Experiment 6. Weight, 24 lbs.						
1st Day	Normal	39·0		5·39		10·0
	Fever	39·2		4·38		17·1
2nd Day	Normal	39·6		5·44		8·1
	Fever	40·0		6·47	6·22	10·91
Experiment 7. Weight, 12 lbs. 3 oz.		Morning.	Afternoon.	Morning.	Afternoon.	
1st Day	Normal	38·8	38·8	3·59	4·02	8·86
	Fever	38·7	40·7	2·58	3·26	13·95
2nd Day	Normal	38·8	38·6	4·09	3·31	7·9
	Fever	40·0	40·0	3·13	3·58	9·47
3rd Day	Fever	40·4	39·9	3·07	2·79	No Observation.

In this table the approximate weight of the animal to which each experiment refers is stated in the first column. The term "first day" expresses a twenty-four hours period of observation, commencing in each case twenty-four hours after the last feeding. In the same horizontal line with the word "normal" in the second column are set down, first the temperature of the animal (derived usually from several observations) during the first day of comparative inanition without fever; secondly, its discharge of carbonic acid, measured either during one period of one hour's duration, or during several such periods, as in Obs. VII.; and, lastly, its discharge of urea as measured during the whole twenty-four hours. In the second line, opposite the word "fever," the same particulars are registered in the same order as regards the same animal in the same stage of inanition, but in the febrile state. In the two lines following, the observations relating to the second day of inanition are recorded in a corresponding manner.

The tabular arrangement renders it possible to comprehend at a glance the general bearing of the results. It is seen at once that, although the febrile state as indicated by the temperature, as well as by the general condition of the animal, was thoroughly established, its effect on the rate of discharge of carbonic acid was very inconsiderable. In five, indeed, out of the seven cases, it appeared to exercise no appreciable influence in either direction, and in the other two, although there was during the second day a slight augmentation, it was trifling in amount.

Results of Dr. Senator's researches.—Discharge of nitrogen.

As regards the excretion of urea, the indications afforded by the results are set forth by Dr. Senator, to the following effect:*—As has been already shown by the investigations of Naunyn,† the febrile augmentation of the urea discharge takes place immediately after subcutaneous injection of pus, *i.e.*, at a time which precedes the elevation of temperature. In observation VII., in which the urine was collected, and its quantity and urea per-centage estimated during the first eight hours after injection, it was found that there was already a very marked increase of both, so that, while, as will be seen later, the discharge of heat, of carbonic acid, and of aqueous vapour, may even be diminished during the initial stage of fever, that of urea is augmented. In the later stages this relation is in the main reversed, all discharges and par-

* Senator, l. c., pp. 59, 60.

† Berliner klinischer Wochenschrift, 1869, March 15

ticularly the "insensible loss" as indicated by the rapid loss of weight, being decidedly increased. In association with this, the urea discharge "remains excessive during the whole course of the fever," while the rate of discharge of urine increases so markedly towards the end of the first day, that, notwithstanding the diminution which is the immediate consequence of the injection, the quantity for the 24 hours is in excess.

Senator further draws attention to the very remarkable fluctuations and inequalities which all the functions investigated exhibit when they are continuously observed. This is seen to be true, not merely of the rate of discharge of urea and carbonic acid, but more strikingly of the loss of weight. When the weighings are repeated at short intervals, it is found, that whereas at one time the loss is scarcely to be estimated, at another it is three or four times as great as that which occurs in health during the same period.

Increased discharge of urea in induced fever is not dependent on accumulation.

The increase of urea discharge in artificial fever cannot possibly be dependent on the excretion of urea which has previously accumulated in the blood or tissues, for, from the well-established fact that in those tissues which constitute the greater part of the weight of the body, viz., muscles and bones, urea is entirely absent, and that in those organs in which it is most abundant, *e.g.*, the liver, its per-centage never exceeds 0·02—0·03, it is clear that even if the whole quantity stored in the body were discharged at once, the effect on the rate of discharge would be barely perceptible. It is therefore obvious that, in the dog at least, its augmentation in the urine is an indication of increased activity of those processes by which it originates in the body, and that the degree of that increased activity may be judged of pretty correctly by the rate of discharge. As, therefore, we are certain that urea derives its nitrogen from albumin, we are also certain that, at all events in artificial fever, albumin of some kind is disintegrated in greater quantity than in health.

Discharge of carbon. Reasons for inferring that if a comparison were made of the carbonic acid discharge of the fevered animal body and that of the normal at the same temperature, it would be found to be greater in the latter.

So far as the frequently ventured assumption goes that in fever the discharge of carbonic acid is necessarily increased, these results go a long way towards negativing it. They have no value, however, as evidences that the carbonic acid discharge is diminished, although from a number of considerations it seems highly probable that it is so. For in the experimental comparison of fever with health, it is to be borne in mind, that however exactly you may assimilate the conditions of observation, there is one important condition which, while it appears to belong to the organism, belongs in reality to the environment, viz., that of temperature. The temperature of the body, although it is a direct consequence of the chemical processes of life, may from another point of view be quite as correctly regarded as their cause, or at all events as a modifying condition, for the very increase of heat which fever produces, reacts on and influences the fevered body. Consequently, in experiments made on Senator's plan, even when the utmost has been done to render the two observations strictly comparable, the living tissue is not really under identical conditions, for every bit of living protoplasm is acted upon by the general pyrexia, just as if heat were communicated to it from outside. Now we know that when heat is communicated to the body from surrounding media, so as to elevate its temperature even very slightly, the effect of such slight elevation is to produce a very considerable augmentation of the discharge of carbonic acid, and that this effect is rapidly increased as the temperature communicated to the body approaches that of pyrexia. It is, indeed, quite possible, that if in Senator's observations the comparison had been made between normal and fevered animals at the same bodily temperature, it would have been found that the carbonic acid discharge in the former would have been largely in defect. Comparative observations of this kind have not yet been made, but in the mean time we need have no hesitation in adopting Senator's conclusion, that there

is no reason for believing that in induced fever in the dog, there is any increased formation of carbonic acid in the body.

From the observations relating to the quantity of urine and from the loss of weight, Senator concludes that the discharge of water is very considerably increased in fevered animals. He attributes the increase in the quantity of urine partly to the presence of an excess of urea in the blood, (which, as Ustimovitsch's experiments have shown, acts diuretically,) partly to the state of the circulation, and (during the rigor) to the suppression of the exhalation of water from the skin. As the febrile process advanced, the rapid loss of weight, (which the carbonic acid determinations during the same period showed not to be attributable to the augmented discharge of that product,) indicated a much increased insensible perspiration, so that we must suppose that during the later stages both channels for the discharge of aqueous vapour are wide open. Here, however, as in the case of the carbonic acid discharge, no ground whatever is afforded for the assumption that a greater production of water by oxidation takes place than in health, for there is reason for believing that the direct influence of increased temperature in favouring the exhalation of water is even greater than that which it exercises on the discharge of carbonic acid. On this point again, positive observations are wanting.

Discharge of water in induced fever.

The results of Senator's observations relating to the loss of weight in fever and health respectively may be stated as follows :—Fevered dogs lost on the whole from 3 to 4 per cent. of their weight during the first 24 hours of fever. Healthy dogs, in the corresponding period of inanition, lost about 1·6 per cent. As there was certainly no increase of carbonic acid discharge, this must have been chiefly due to loss of water.

Section 2.—Clinical Investigations.

It is obvious that the investigation of the exchange of material in fever is much more difficult in man than in the lower animals. This difficulty arises chiefly from the absence of any normal standard with which the condition of the fevered body as regards its income and expenditure can be compared. Just as it was necessary, in the experimental inquiries to which the last section relates, in order to value the results observed in the febrile state to place them side by side with corresponding results relating to animals under precisely similar conditions, fever excepted, so here it is equally plain that if we desire to interpret justly whatever measurements we may be able to make of the physiological products of the human organism under the influence of fever, this can only be done by first ascertaining how much of each product would be yielded by an individual of the same weight under the same circumstances. A patient in fever is in bed and motionless. The food he takes is, as regards the quantity of albuminous material it contains, a mere fraction of his ordinary diet. The first question to be answered in approaching the subject of this section is—What quantities of urea and of carbonic acid ought a normal person in health to discharge from his body when in bed and on fever diet ?*

Discharge of nitrogen.

The basis of fact on which it is possible to found an estimation of the normal discharge of urea by a healthy individual when on fevered diet

* It is remarkable how frequently this fundamental consideration has been neglected in the discussion of clinical observations on fever. Some clinicists are content with a vague notion that in health something like 500 grains of urea are excreted daily, and that if the febrile discharge is greater than this, it must be excessive, and vice versâ, forgetting that, unless by some means or other the influence of diet is estimated, the mere determination of the daily discharge of urea is of no value whatever.

and in bed, is unfortunately very limited. Indeed, the only observations on the subject which are available, are those made by Dr. Unruh* on three patients in Professor Leyden's wards at Königsberg in 1869. The patients in question were affected with non-febrile diseases. The first, a cabman aged 47, suffering from carcinoma ventriculi, weighed 104 lbs. His diet consisted of beef tea or broth, with an egg or two. The quantity was probably excessively small, for the daily discharge of chloride of sodium scarcely exceeded one gramme. He was under observation 19 days, during which his temperature was normal, and the specific gravity of his urine was natural. The mean daily discharge of urea was 17·5 grammes. In two other patients affected with syphilis, each of whom was observed during 13 days, the daily means of urea were severally 18·58 and 16·267, both being on fever diet with milk. Thus we have 17·466 grammes(=270 grains) as the mean of the three observations; or 0·3835 gramme per kilo. of body weight; whereas the normal excretion of urea per kilo. is about half a gramme. The mean discharge of uric acid in the first case was 0·009 per kilo. per diem.

Having obtained this basis, Dr. Unruh proceeded to investigate in a similar way cases of different kinds of febrile disease, of which the results will be found stated in a long series of tables in his mémoire. They are summed up by him as follows:—

Assuming that 0·38 grammes per kilo. per diem (=2·68 grains per lb.) represents sufficiently accurately the normal low diet discharge of urea in health, he found that in one case of relapsing fever, with an evening temperature of 40°·8 C. (105°·4 F.), and a morning temperature of 38°·2 (100°·76 F.), the discharge was on one occasion as great as 65·97 grammes i.e. 1·18 per kilo. per diem, more than three times the normal, this being the highest result obtained. The lowest amount in a case of pneumonia (with a history of previous chronic disease) was 18·6 per diem, which is scarcely above the normal. This condition presented itself only during the first few days of observation. The general result of the whole series was that the normal urea discharge per diem in intense fever may be set down at 30·576 grammes (= about 470 grains,) hence, something like one and a half times as much as would be discharged by a healthy person on fever diet.

Dr. Senator thinks this estimate too low, on the ground that in most of the cases the beginning of the febrile process was not included, and consequently that during the period of observation, the patient having been previously subjected for a length of time to the combined influence of inanition and fever, was already exhausted of his store albumin, so that Dr. Unruh's mean could not be regarded as a fair one; and refers in support of his view to the published urine analyses of Moos and Rosenstein in typhoid and typhus, both of which show that the urea discharge is larger at the very beginning of the attack than it is afterwards. Unfortunately, the number of cases in which the urea discharge has been observed from the beginning to the end, is exceedingly small. Dr. Senator has been able to meet with only two, one observed by himself, the other by Dr. Wachsmuth, which were complete in this respect. He has, however, brought together 13 selected cases in which the observations were begun sufficiently early, and in which the significance of the results was not impaired by any conditions affecting the patient. He has divided these 13 cases, which must be regarded as by far the most important body of clinical evidence which exists on the question of the exchange of nitrogen in fever, into categories

* Unruh, Ueber die Stickstoffausscheidung bei fieberhaften Krankheiten: Virchow's Archiv., vol. xlviii. p. 227.

according to the presence or absence of collateral circumstances which might be supposed to affect the discharge of urea. By doing so, he has been able to estimate the influence of each such condition separately, and thus to add weight to the general conclusions.

One of the most important of these circumstances relates to the previous nutritive condition of the patient. In Voit's well-known observations on inanition, it was found that the time required for the production of a given effect on the exchange of material in any animal varied according to the store of albumin existing in the body, so that *e.g.*, an ill-fed dog was in the same condition after 24 hours as a well-fed after five or six days The same thing holds good in clinical practice: here, as there, it makes a great deal of difference whether the patient enters into fever with his body well supplied with nutritive materials or not, *i.e.*, whether his previous diet has been abundant or indifferent. The first category includes therefore the two cases above referred to, in which it was not only possible to observe the febrile process throughout, but to ascertain the nutritive antecedents with exactitude.

1. Case observed by Dr. Wachsmuth*:—Pneumonia in a male, with temperature varying from 40° (104° F.) to 41°2 (106° F.). The patient, who during the first three days took no nourishment, and during the last two days only milk, excreted in the five days, which comprised the whole of febrile period, 206·44 grammes of urea, *i.e.*, 41·3 grammes daily.

2. Case observed by Dr. Senator in the Charité:—J. H., a male nurse, æt. 25, tolerably robust, took ill on the 16th of February 1870, with relapsing fever. On the following day the temperature had risen to 40°·5 C. (104°·9 F.) the highest point reached. In the course of the 21st, critical defervescence took place, which was accompanied by profuse sweating, lasting over the following day. Up to this time his daily nourishment consisted of from 1,000 to 1,200 cubic centims. (about two pints) of soup, and 400 to 600 cubic centims. of milk. During the six days of the fever, he excreted 240·73 grms. of urea, *i.e.*, 40·1 grms. per diem.

In the case of Dr. Senator's patient, who was a male nurse in the Charité, it was quite certain that the nitrogen value of his previous diet did not correspond to more than about 25 grammes of urea. The other was also an under-fed individual. In each case the febrile condition was over in less than a week; so that the period during which the patients were under observation overlapped that of the duration of fever. The patient was on a diet containing a mere trace of nitrogenous material. The daily quantity of urea as compared with the normal inanition daily discharge above estimated (17 grammes) gives 126 per cent. as the febrile increase.

The second category comprises four cases in which the previous nutrition was similar, but the observation was not begun until two or three days after the accession.

1. Case recorded by Dr. Huppert†:—Pneumonia in a male, whose highest temperature was 39°·9 (103°·8 F.). Quantity of urea discharged between the second and seventh day, both included, 200·69 grammes, *i.e.*, 33·5 grammes per diem.

2. Case observed by Pribram and Robitschek‡:—Relapsing fever in a male, aged 28. Highest temperature recorded 40°·4 C. (104°.72 F.). Between the second and fourth day of his illness he excreted 168·3 grammes of urea, *i.e.*, 56·1 grammes per diem.

---

* Wachsmuth (quoted by Huppert), Archiv der Heilkunde, Vol. VII.

† Huppert, Ueber die Beziehung der Harnstoffausscheidung zur Körpertemperatur im Fieber. Arch. der Heilkunde, vol. vii. p. 1.

‡ For the case of Pribram and Robitschek, Dr. Senator refers to the Prager Vierteljahrschrift for 1869.

3. Case observed by Huppert :—Pneumonia in a male, aged 18, who during the four days following the third of his illness had febrile temperature varying up to 40°·75 C. (105°·3 F.) and took no solid nourishment. The observation was interrupted before the crisis. In the four days he excreted 138·2 grammes of urea; *i.e.*, 34·5 grammes per diem.

4. Case observed by Huppert and Riesell* :—Pneumonia in a male, aged 25. During six days of "high fever," from the third to the eighth day of his attack, both included, the total weight of nitrogen in the nourishment consumed by him amounted to 2·97 grammes, while nearly twice as much was discharged by the alvine evacuations and sputa. In the six days he excreted a quantity of nitrogen by the urine, corresponding to 223·6 grammes of urea; *i.e.*, 37·2 grammes of urea per diem.

Mean daily discharge of urea in the four cases, 40·3 grammes.

Here, again, the mean of the results gives about 124 per cent. as the fever increment, showing that the exclusion of the first day or two had no great influence. But in the third category, comprising cases in which the illness was of longer duration, and the observations related to a more advanced period, the mean urea discharge was only 34·5 grammes, and the increment was therefore 98 per cent.

1. Case observed by Unruh (loc. cit. p. 242) :—Pneumonia in a male aged 21, weighing 122 lbs., whose temperature rose during his attack to 40°·5. (104°·9F.) During the seven days of his illness, beginning with the third and including the crisis, 278·47 grammes of urea were excreted; *i.e.*, 39·8 grammes per diem.

2. Case observed by Huppert (loc. cit. p. 25) :—Acute rheumatism with heart complication, in a male aged 21, weighing 130 lbs. Temperature during the first 10 days from 38° to 40°. During this period the patient's diet consisted of a variable quantity of milk, with the addition during the first two days of a little soup and bread. On two of the following days no food was taken. The excretion of urea during the 10 days amounted to 394·67 grammes; *i.e.*, 39·4 grammes daily.

3. Case observed by Wachsmuth (reported by Huppert, loc. cit.):—Pneumonia in a male, whose highest temperature during the attack was 40°·5. C. (104°·9 F.) Between the second and the eleventh day, during which period the patient took nourishment, he excreted 231·9 grammes of urea; *i.e.*, 23·2 grammes per diem.

4. Case observed by Salkowski†. Erysipelas in a youth of 18, in whom the highest temperature was 40°·2. (104°·4 F.) He was on fever diet from the 3rd to the 12th day. In eight days he excreted 319·44 grammes of urea, *i.e.*, 39·9 grammes per diem.

5. Case observed by Pribram and Robitschek (loc. cit.) :—Relapsing fever in a young man of 22. Highest temperature recorded 40°·4. (104°·7 F.) In the eight days, from the 3rd to the 10th day of the illness, during which the daily diet consisted of soup and a gill of milk, he excreted 218·67 grammes of urea; *i.e.*, 27·3 grammes per diem.

6. Case observed by Senator :—Pneumonia of the right upper lobe in a very robust and well-nourished journeyman slaughterer, aged 24. The patient, who had shivered on the 2nd of March, was admitted into hospital on the 4th. On the 5th and 6th his temperature reached 40°·5. (104°·9. F) On the 8th defervescence took place. During the seven days, from the 3rd to the 9th, inclusive, his diet consisted of soup, coffee, and 600 cubic centims. of milk daily; and he excreted 225·10 grammes of urea, *i.e.*, 37·5 per diem.

It is to be noticed that the cases selected were of very various diseases, diseases, in short, which have nothing in common, except the febrile state.

The general conclusion to be derived from the whole series is that in the early stage of fever a patient excretes about three times as much urea as he would do on the same diet if he were in health, the difference

* Huppert und Riesell, Ueber den Stickstoffumsatz beim Fieber. Arch. der Heilkunde, vol. x. 1869, p. 329.

† Salkowski, Untersuchungen über die Ausscheidung der Alkalisalze. Virchow's Archiv, vol. Liii. p. 209.

between the fevered and the healthy body, consisting chiefly in this, that whereas the former discharges a quantity of nitrogen equal to that taken in, the latter wastes the store of nitrogen contained in its own juices. That this disorder of nutrition is an essential constituent of the febrile process is indicated by the fact that it not only accompanies the other phenomena of fever during their whole course, but precedes the earliest symptoms and follows the latest. That it anticipates the beginning of fever was first demonstrated by Dr. Sidney Ringer * in his investigation of the relation between temperature and the discharge of urea in ague. That the same condition continues after the crisis has past, *i.e.*, the temperature has begun to sink, has been shown by Dr. Squarey from his investigation of eighteen cases of typhus, in all of which the daily excretion of urea was measured, and the variations of temperature were observed during the whole course of the disease, and the observations were continued until convalescence was completely established. In these cases it was found that, whereas the bodily temperature which in this disease rises rapidly at the beginning, and keeps up without sensible abatement during a period which often extends to the middle of the second week, usually begins to fall after the tenth day, the daily rate of discharge of urea, although usually above the normal during the first week did not attain its maximum until the temperature had been falling for some days.†

The question of the source from which the urea increment of fever comes is one which can be better discussed subsequently. At present it is sufficient to notice that the anticipation of the obvious symptoms of illness, particularly of the pyrexia, by the increased excretion of urea, as well as the continuance of the urea excess during the epicritical period, plainly indicate that pyrexia is not the agent by the direct influence of which the increased secretion of urea is produced.

Another consideration suggested by the same facts is this, that the mere increase of the per-centage of urea discharged, affords an inadequate measure of the waste of nitrogen, *i.e.* of albumin, which actually occurs in fever; for to form a just estimate, the overlapping at both ends of the process ought clearly be taken into account. Moreover, in fever there are very frequently losses of nitrogen by the bowels and skin, as well as by exudations, the amount of which scarcely admits of being determined.

It having been established that there is an increased discharge of nitrogen in fever it remains to state what is known as to its source. There are two sources which are open to discussion, viz.: (1) the albumin of the blood and lymph, and (2) that of the tissues; or, to use the expression which the researches of Voit have rendered current in physiology, store albumin, and tissue albumin. By the former we understand the albuminous constituents of the corpuscles and plasma as well as of the tissue juice or lymph; by the latter, the material of protoplasm, including that of the blood corpuscles.

Here the basis of observation is furnished by researches made by Dr. Salkowski, relating to the proportion of potassium salts discharged

* On the connection between the heat of the body and the excreted amounts of urea, chloride of sodium, &c., during a fit of ague. Medico-chirurgical Transactions, vol. XLII. p. 361. In this paper Dr. Ringer recorded more exact observations than had before been made as to the relation between the temperature and the other phenomena of the paroxysm of ague. In the course of them he made the important discovery referred to in the text, viz: that in this disease the augmentation of the urinary discharge of nitrogen not only begins some time before the accession of the cold stage, but even precedes the rise of temperature.

† Observations on the temperature and the urine in Typhus fever. Medico-chirurgical Transactions, vol. L., p. 329.

App. No. 1.

On the Process of Fever, by Dr. Burdon Sanderson.

by the urine in fever, as compared with that of sodium salts. These researches relate to some twenty cases of various forms of febrile disease in Professor Leyden's wards at Königsberg. The research began with an investigation of the relative proportions of potassium and sodium salts discharged by the liquid and solid excreta in health, the observer being himself the subject of observation. The diet being mixed, and the nutritive condition nearly that of nitrogen equilibrium as seen by the constancy of the daily discharge of urea, (min. 25·3, max. 27·2, mean of seven days 25·69) the daily quantity of potassium and sodium salts respectively, reckoned as potash and soda were: potash, 3·094 grammes, soda, 4·207 grammes; so that of the sum of both alkalies potash constituted 41·4 per cent.

In another individual, a clerk, on low diet without meat, affected with syphilis but in good general health, the soda discharge was about the same, but that of the potash much less, so that the potash per-centage varied from 18 to 26. From these and other observations it was concluded that the daily potash discharge of a healthy person on fever diet is less than one gramme.

The febrile cases investigated were one of relapsing fever, one of erysipelas, and several of pneumonia. In the case of relapsing fever, which was observed during part of the first paroxysm, the whole of the first remission, and of the first relapse and second remission, it was most distinctly seen, that whereas during the remission, the potash per-centage of the total discharge of both alkalies sank to about 18·20, it rose during and especially after each crisis to about 90. In the case of erysipelas and in the pneumonia cases there was a corresponding relative and absolute increase of the potash discbarge. There were however, peculiarities in all the cases which have been fully described by the authors, and are of sufficient importance to require notice.

On the whole the absolute quantity of potassium discharged on febrile days, is three or four times as great as on non febrile. As regards soda the results are entirely different. During fever it is seen in most of the tables that the soda discharge is extremely low. As soon as the crisis is passed it at once begins to increase to such an extent that in one day as much soda is eliminated as on all the previous days taken together. Simultaneously the per-centage of potash discharge falls to its lowest.

The augmentation of potash discharge in fever, when little or no meat is being taken, and its rapid decline in defervescence shows that the augmented production of urea in fever must take place at the expense of some source of albumin which contains potash. We have, therefore, in this fact an answer to the question from which we started. The albumin which serves as a source of urea in fever, is not derived from liquor sanguinis, (for the liquor sanguinis abounds in sodium salts, but contains very little potassium,) but either from the blood corpuscles, or from muscle or both.

The very remarkable diminution of the discharge of sodium signifies of course that in fever, the common salt, which constitutes the bulk of the salts of the blood, is retained; for immediately after the crisis, (as shown most distinctly in three of the cases,) it passed into the urine in great abundance.

In addition to increased excretion of potash there is another circumstance which points to the blood corpuscles or to the muscular tissue as the chief seat of disintegration in fever, namely, the increased discharge of colouring matter. Unfortunately as regards this most important question sufficient information is wanting. There are, to the best of my knowledge, no comparative determinations either of the proportion

of blood corpuscles or (what would be as useful) of the iron per-centage of the blood before and after acute fever either in man or in the lower animals. The only facts relating to the subject that I know of are (1) that in all febrile diseases, the colouring matter of the urine, which is probably derived ultimately from the blood hæmoglobin, is three or four times as abundant as in health (*see* Neubauer and Vogel); and (2) that after traumatic fever in dogs, there is a very marked diminution, both of the corpuscles and of the iron of the blood. But these observations are quite inadequate to serve as a basis for an opinion as to the proportion which the breaking down of blood corpuscles bears to the total disintegration of fever. Of the many questions which require answering, there is perhaps none which is of greater importance, for if, as appears probable, the destruction of the coloured corpuscles is a part of the febrile process, the fact must have a very important bearing, not merely on the process itself, but on its after results. The colouring matter of the blood being the means by which oxygen is distributed to the tissues, the destruction of it must impair every function of organic life.

Discharge of carbonic acid in fevers.

As regards the exhalation of carbonic acid in fever, the existing knowledge is much more unsatisfactory than that which relates to the disengagement of nitrogen. Indeed, the only observations on the subject are those of Prof. Leyden.* Their very great importance renders it necessary to give an account of them.

Leyden's observations, although perhaps insufficient in number, were made with an exactitude and completeness approaching more nearly to scientific experiment than any clinical researches with which I am acquainted. Above all, they have the singular merit of being comparative, *i.e.*, that in each case the measurements of carbonic acid discharge in fever were valued, not by a standard derived from averages of observations made on other persons, but by control measurements of the same function in the same individual when in health. Another point of very great importance is that the urea discharge is estimated during the same periods as the carbonic acid discharge, the comparison of the fluctuation of the two functions adding materially to the certainty and value of the results.

The observations were made on four cases, viz., two of relapsing fever, one of typhus, and the other of pneumonia. In the two cases of relapsing fever the quantity of air respired per minute, (one of the patients being a male, æt. 63, the other a female, æt. 20) was on the whole 50 per cent. greater than during the interval of apyrexia, the observation being made in the first case before and during the first remission, in the second during the whole of the first remission as well as during the first relapse and the second remission. In the second case the contrast between the febrile and non-febrile days was extremely striking. Thus in the morning of Jan. 23, the last fever day of the first relapse, when the temperature was 40°·1 (104°·2 F.), and the frequency of breathing 34 per minute, the quantity of air respired per minute was 8·13 litres, and the per-centage of carbonic acid contained in it 3·28. In the evening the temperature had fallen to 36°·8 (98°·2 F), and on the following day (Jan. 24) the temperature was 36°·6, and the rate of breathing 24. It was then found that the respiration per minute was reduced to 4·85 litres, the per- centage being increased to 3·8.†

---

* Leyden. Ueber die Respiration im Fieber. Deutsches Archiv für klinische Medicin, Vol. VII., 1870, pp. 536–562.

† *See* p. 549 and *seq.*

In the third case, which was one of typhus complicated with hypostatic pneumonia, the most important peculiarity was that during the time that the dyspnœa consequent on the pulmonary affection was most marked, although the temperature had subsided and was nearly normal, the quantity of air breathed was large (10·72 litres per minute), and the per-centage very low. Dr. Leyden has divided the observations relating to this case, which commenced at the maximum of the pyrexia, and were continued through the period of defervescence, and the beginning of convalesence, into three parts. In the first, relating to a period during which the temperature ranged from 39°·6 to 40°·1 (103°·3 to 104°·2 F.), the patient breathed 11·7 litres, with a per-centage of carbonic, acid of 2·26, the frequency of breathing being 40 per minute; in the second, with a temperature varying from 37° to 39° (98°·6 to 102° F.), (the rate of respiration being still frequent with some dyspnœa) 9·8 litres were breathed, with a per-centage of 1·76; in the third, with perfectly normal temperature and respiration at 22, 6·66 litres, containing 2·8 per cent. of carbonic acid, were expired. Consequently the total discharge of carbonic acid per minute was greater during convalescence than in the epicrisis, notwithstanding the diminished quantity of air respired, in the proportion of 28 to 26. In the fourth case, one of pneumonia, the effect of dyspnœa in increasing the quantity of air breathed is still more marked. Here the observation was commenced at the height of the disease, when the temperature was 40°·5 (104°·9 F.), the pulse 120, and the respirations were 44 to 48. The patient breathed 9·0 litres, containing 3·05 per cent. of carbonic acid. On the next day his temperature was reduced to 39°·1, his pulse to 104 in the morning, and to 84 in the evening, his respirations to 36 (morning) and 26 (evening). He respired only 6·8 litres with the same per-centage. During the four following days when convalescence established itself, the quantity gradually sank to 3·72 litres, while the per-centage increased, but by no means in the same proportion, the highest being 3·45.

Dr. Leyden sums up the results of the four cases as follows:—

	Febrile period.		Non-febrile period.	
	Quantity of air respired, in litres, per minute.	Per-centage of Carbonic Acid.	Quantity of air respired, in litres, per minute.	Per-centage of Carbonic Acid.
Case 1 - - - -	8·76	3·15	6·146	3·4
„ 2 - - - -	7·526	3·79	5·146	3·8
„ 3 - - - -	11·69	2·26	6·66	2·8
„ 4 - - - -	7·912	3·05	4·492	3·2

Hence we have as the general results of his investigation an increase of from 50 to 75 per cent. of the quantity of air breathed per hour, and a diminution of about 10 per cent. in the carbonic acid. Combining these, we have the febrile augmentation of the carbonic acid discharge amounting to nearly 50 per cent.

Before we accept these facts as evidence that increased discharge of carbonic acid is a characteristic of fever, it is necessary here, as with respect to the discharge of nitrogen, to satisfy ourselves that they are not directly consequent on functional disorders, which, although present in the cases observed and often associated with fever, are unquestionably

not of its essence. Physiologists are aware that any abnormal elevation of bodily temperature, whether produced by interference with the discharge of heat from the surface, or by exposure to an external temperature above the ordinary limits of variation, determines an increased disengagement of carbonic acid. It is also known that this augmentation is associated with increased activity of respiration, but it has not yet been shown whether, on the one hand the increased liberation of carbonic acid is entirely accounted for by the greater frequency and depth of the respiratory movements, or on the other is dependent partly on this cause, but partly also on the increased activity of those chemical processes of which carbonic acid is the product. In other words, it is known that the animal body gives off more carbonic acid when its temperature is slightly elevated above the normal, but it is not yet known whether it produces more.

As regards fever, we are nearly, but not quite, in the same position. In many febrile diseases, no doubt, the increased disengagement of carbonic acid is at first the result of more active respiration, but this explanation cannot apply to any instance in which the fact is observed for more than a few hours. The only way in which increased respiration can produce increased discharge of carbonic acid is by furthering the disengagement of whatever quantity of that body was previously accumulated, an effect which can last only a limited time. We are, therefore, compelled to accept it as a fact that in fever more carbonic acid is actually formed in the body than in health.

General view of the exchange of material in fever.

We are now in a position to take a general view of the febrile process, so far as relates to the exchange of material and the disintegration of tissue. We have seen that it is established on grounds which do not admit of any question, that a fevered man or animal discharges more nitrogen than a healthy person or animal on the same nitrogen income; and, that as regards man, the febrile excess amounts to something like three quarters of the normal expenditure. We have also seen that in man there is during fever an excess of discharge of carbonic acid, and that this cannot be accounted for as the mere result of excessive respiration, but that no such excess is observed in the dog. We have now to bring these facts into relation with each other.

In health, the whole of the nitrogen discharge is derived from food. In inanition, when nitrogen income vanishes, all the nitrogen which passes out as urea or otherwise is derived from stored or tissue albumin. In fever this is also the case, for the nitrogen income is as defective in the one condition as in the other, but besides the using up of stored albumin, there is an additional and altogether abnormal disintegration which, for reasons already stated, we believe to take place at the expense of blood corpuscles, of muscle or other tissue. That fact must be taken as a starting point in any attempt to understand the febrile process as a disorder of nutrition.

A healthy adult on ordinary mixed diet discharges from 30 to 36 grammes of urea daily; a healthy adult, on fever diet, discharges from 15 to 20 grammes; but if he is fevered he discharges, on the same diet, a little more than on ordinary diet in health, say from 35 to 40 grammes. A normal person on fever diet discharges about 22 grammes in an hour, of carbonic acid, in health, about 32·3 grammes in fever. Where does this come from?—To account for the urea excess, one must suppose, (the nitrogen equivalent of one gramme of urea being three grammes of albumin,) that sixty grammes of albumin is disintegrated in 24 hours. These 60 grammes would (the carbon per-centage of albumin being 53) contain 31·8 grammes of carbon of which one fifth of the weight of urea discharge, (the proportion of carbon in any given weight of urea

being $\frac{12}{60} = \frac{1}{5}$,) *i.e.*, four grammes would pass out as urea. The remainder, viz., 27·8 would leave the body in 24 hours in the form of carbonic acid. Now 27·8 grammes of carbon correspond to 102 grammes of carbonic acid, which would therefore express the increase of carbonic acid discharge which would result supposing that all the carbon of the tissue disintegrated to form the febrile excess of urea, left the body in that form. 102 grammes per day is only $4\frac{1}{4}$ grammes per hour; consequently the quantity of carbonic acid produced by the disintegration of albumin in fever is a mere fraction of the total quantity exhaled (32·3 grammes). We have therefore a remainder of 28 grammes which must be derived from the consumption in the body of material not containing nitrogen. The bearing of this fact on the question of febrile thermogenesis will be considered in the next section.

Part II.—Production and Discharge of Heat in Fever.

Section 1.—*Experimental Investigations.*

The constancy of the temperature of the body depends upon the existence of heat equilibrium, *i.e.*, of that condition of the organism in which the processes by which heat is produced, and those by which it is liberated, balance each other. It is certain that increased activity of the former is not in itself a sufficient cause for high temperature, for we know that the thermogenetic functions undergo frequent variations, some of which are accidental, while others take place regularly, without the occurrence of any corresponding changes in the temperature of the body. Thus after a meal, a variety of heat-producing processes come into operation, which were before in abeyance; again, during and after muscular exercise the quantity of material disintegrated is much greater than in repose; but in neither instance is there any permanent elevation of the bodily temperature, because in both the increased production is balanced by the increased liberation of heat at the surface. In like manner it can be shown that an unnaturally high temperature may be maintained although the production of heat is diminished. Thus, it is well known that after certain modes of death, the temperature of the body does not sink for some time after the circulation has ceased, notwithstanding that the heat-producing processes which are dependent on the supply of oxygen are no longer in operation.

Heat stands on the same line with carbonic acid, urea, and water, as a product of chemical work done in the living body. To determine whether or not its production is increased or diminished, we have to proceed by continuous measurement just as in the other cases, with this difference, that the measurement of heat is a much more complicated and difficult problem than that of any of the chemical products of life. There are two methods by which it may be attempted. The first consists in estimating the thermogenesis from what is known as to the quantity and "heat value" of the material daily and hourly consumed in the body, under the conditions to be investigated; the second, in directly measuring the quantity of heat daily or hourly discharged from the body, this quantity being, if the temperature is constant, identical with the quantity produced. In employing the first plan, that of estimation, we depend entirely on certain experiments made about eight years ago at the Royal Institution, by Prof. Frankland, (the accuracy of which has been generally admitted,) by which the "heat value" of the "immediate principles" of food, (albumin fat and some

carbonic hydrates,) *i.e.*, the quantity of heat yielded by each in complete or partial oxidation, was estimated.

Of the values obtained, the most important and the most frequently used are those relating to albumin and its product urea, and to fat. A gramme of albumin, according to Frankland, yields 4·998 kilogramme-units of heat in complete combustion, *i.e.* 4·998 times as much heat as is required to raise a kilogramme of water one degree of temperature. A gramme of urea yields 2·206 kilogramme-units; a gramme of fat 9·069 k.-units. In the disintegration of albumin in the living body, it does not yield the ultimate products (water, ammonia, and carbonic acid) but nearly the whole of its nitrogen passes out in the form of urea. Consequently in estimating the quantity of heat generated by it in the organism, (its "physiological heat value,") we deduct from its total heat value, the heat value of the weight of urea which is derived from it. Now, each gramme of albumin yields one third of a gramme of urea, that being the quantity which would be produced by it if all its nitrogen were, in passing out of the body, to enter into the constitution of urea, for whereas albumin contains 15·5 per cent. of nitrogen, urea contains 46·66 per cent., and $\frac{15\cdot5}{46\cdot66} = \frac{1}{3}$. Hence of the total heat value of every gramme of albumin consumed physiologically, as much as belongs to one third of a gramme of urea, (*i.e.*, $\frac{2\cdot206}{3} = 0\cdot735$ k.-units) is lost to the organism. Deducting this from 4·998, we have 4·263 as the "physiological heat value" of albumin.

Leyden found, as has been already seen, that his fever patients exhaled during the remission, *i.e.*, when free from fever, 83·8 litres (at 0° C and 760 m.m.) of air in 15 minutes, which contained 3·3 per cent., *i.e.*, 2·79 litres of carbonic acid. A litre of carbonic acid weighs 1·9712 gramme. Consequently the discharge of carbonic acid per 15 minutes was 5·5 grammes or 22 grammes per hour. This gives 528 grammes as the discharge per day. In fever the same patients exhaled 134·6 litres in 15 minutes, containing 3·066 per cent. of carbonic acid, or, 4·127 litres. This gives 32·5 grammes per hour, or 780 grammes in 24 hours, supposing the rate of discharge to be constant. Senator, from determinations made in cases strictly comparable with those of Leyden, estimated the daily discharge of urea in patients on fever diet, but free from fever, as 17·5 grammes. We may therefore take 17·5 grammes of urea, (representing 52·5 grammes of albumin,) and 528 grammes of carbonic acid as an approximation as near as can be attained to the true estimate of the discharge of a healthy male person on fever diet.

On these data we may proceed as follows:—The physiological heat value of 52·5 grammes of albumin is 229·0 k.-units. The 52·5 grammes contain 27·82 grammes (53 per cent.) of carbon of which 3·5 take the form of urea in order to leave the organism, (for urea contains one fifth of its weight of carbon, and 17·5 grammes are discharged.) Deducting the remainder of carbon (*i.e.*, the quantity not so discharged) from 144 grammes, (the quantity of carbon contained in 528 grammes of carbonic acid,) we have 119·68 grammes as the quantity of carbon to be accounted for as derived from other sources. Now in inanition or on fever diet there is but one non-nitrogenous source of carbonic acid which we have to consider, namely, the fat of the tissues, consequently it is from fat that the 119·7 grammes of carbon must be derived. Taking the per-centage of carbon in fat as 76·5, we have 156·4 grammes as the weight of fat, which must have been consumed in order to produce the quantity of carbonic acid actually discharged. According to Frankland's estimate 156·4 grammes of fat yield in disintegration 1419 k.-units of heat. Adding this to the quantities derived from the disintegration of albumin we have 1648 k.-units as the total quantity of heat produced by patients on fever diet but in the apyretic state.

By substituting for the numbers given above relating to the discharges

in health, those relating to fever and repeating the process, we arrive at a comparable result as to the febrile production of heat. In fever, according to Senator's estimate, the urea discharge is increased to about 40 grammes daily, *i.e.*, it is about two and a third times as great as it would be on the same diet in health. Leyden's estimate of the carbonic acid discharge has already been given as 780 grammes daily. The physiological heat value of 120 grammes of albumin (the quantity which corresponds to 40 grammes of urea) is 511·56 heat units. The 120 grammes contain 63·6 grammes of carbon, of which 8 grammes leave the organism in the form of urea. The remainder of carbon (55·6 grammes) having been deducted from 212·7 grammes, the total carbon-discharge by respiration (*i.e.*, the quantity of carbon corresponding to 780 grammes of carbonic acid) we have 157·1 grammes as the weight of carbon to be accounted for by the consumption of fat in the body. The weight of fat required for this purpose is 205·3 grammes, which would yield 1862·4 k.-units. Adding this, as before, to the quantity of heat derived from the disintegration of albumin, we have 2373·9 as the total heat production of fever.

Ranke found in his experiments on himself that on an adequate mixed diet, *i.e.*, on a diet sufficient, and not more than sufficient, to maintain nutritive equilibrium, he discharged in twenty-four hours a quantity of nitrogen corresponding to 32·3 grammes of urea, and that his respiratory discharge of carbonic acid was 791 grammes. Proceeding as before we have 413·5 k.-units as the quantity of heat yielded by the disintegration of 97 grammes of albumin, which in this case was of course derived from food. Of the carbon contained in this 97 grammes, 45 grammes would have to be discharged in carbonic acid. Deducting these from the total discharge of carbon, viz. 215·7 grammes, we have 170·7 grammes of carbon, to be accounted for as derived from the non-nitrogenous constituents of food. The diet consisted of 250 grammes of meat, (containing a very small proportion of fat,) 400 grammes of bread, 70 grammes of farinaceous food, 70 grammes of egg-albumen, and 100 grammes of butter and lard. From previous determinations it was estimated that the fat of the meat contained about 2·8 grammes of carbon, the butter and lard about 67·9 grammes, the farinaceous food about 26 grammes. This leaves 74 grammes to be accounted for as having been derived from the bread, for 2·8 + 67·9 + 26 + 74 = 170·7. 170·7 grammes therefore represents the balance of carbon in the expired carbonic acid, not already accounted for as derived from the disintegration of albumin. (The actual quantity of carbon contained in the carbonic hydrates of the bread was 80 grammes, so that we have an excess of 6 grammes unaccounted for.) According to Frankland's table the fat would yield 33·19 k.-units, the butter 852·7 k.-units, the bread and other farinaceous food, (supposing them to contain 156·5 grammes of starch of which the heat value is 5·232,) 819 k.-units. Adding these to the 413·5 k.-units derived from the disintegration of albumin we have 33·19 + 852·7 + 819 + 413·5 = 2118·39 k.-units as the heat production of a healthy adult on a mixed adequate diet. On similar data derived from other experiments on himself, Ranke estimated his own mean heat production on adequate diet at 2,200 k.-units.

Thus we have for the three conditions we have been considering, namely, inadequate or fever diet without fever, inadequate diet with fever, and adequate diet in health, the following results:—

Inanition - -	1648·0 k.-units
Fever - - -	2373·9 k.-units
Health - - -	2118·4 k.-units

The general result to which the preceding calculation leads us, is a very important one, namely that, although as compared with the heat-production of an 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, for the highest difference indicated by the numbers stated is, as we shall see immediately, insignificant.

In estimating the value of this result, there are several considerations to which it is requisite to call attention. In the first place, it is to be noticed that the data employed as representing respectively the discharges of nitrogen and of carbon in fever, are the highest that could be taken; thus, those relating to urea were founded on observations of fevers of short duration, and referred to periods during which the characters of the febrile state showed themselves in their fullest intensity. It is still more important to remember that the estimate of the febrile discharge of carbonic acid in 24 hours, is founded on determinations relating to the rate of discharge during the day only. In comparing the results with those relating to the same patients when free from fever, this error was got rid of, for both sets of observations were made in exactly the same way. Consequently the numbers given above, representing the relation between heat-production on fever diet without fever, and on the same diet in the febrile state, may be regarded as accurate; but if we compare either of these numbers with that representing the heat-production of health with adequate diet, a correction is required.

Taken absolutely, both of them are unquestionably too high, for it is well known that the rate of carbonic acid discharge is considerably higher in the day than in the night, so that any estimate of the total discharge from measurements made only during the day is certain to be excessive. Pettenkofer and Voit found that in health the mean discharge during the whole 24 hours falls short of the mean rate during the day by 14 per cent. If we make a deduction of 14 per cent. from the estimated febrile discharge of carbonic acid which was taken as the basis of our estimate given above, of the heat production in fever, we have to take off 109 grammes from our total of 780 grammes. Now the heat discharge corresponding to each gramme of carbonic acid derived from the consumption of fat is 3·23 k.-units; consequently if in fever the difference between day and night is as great as in health, we must take off 352 ($=3{\cdot}23 \times 109$) k.-units from our estimate. Thus corrected the numbers stand thus:—

Heat production in fever on fever diet -	2021 k.-units.
Heat production in health on adequate diet	2118 k.-units.

It is further to be borne in mind that the state of things which is understood by the term "adequate diet" is not that of ordinary life. By adequate diet is meant a diet which is just sufficient to maintain nutritive equilibrium, *i.e.*, to balance expenditure by income. Under ordinary circumstances we consume a great deal more food than is required for this purpose. In Professor Ranke's experiment, the diet of a young man of 24 consisted as we have seen of half a pound of meat, and a pound of bread, besides small quantities of butter and eggs, &c., an amount of aliment which, although it was proved experimentally to be "adequate" would, in ordinary language be described as insufficient, and is certainly very inconsiderable as compared with the usual requirements of persons of the same age and sex. From the results of his experiment on more abundant dietaries Ranke inferred that the activity of the thermogenetic processes of his body could be increased to as much

as 2,700 k.-units per diem, an amount far exceeding the highest estimate that could be made of the possible production of heat in fever.

Up to the present time no one has attempted to determine the quantity of heat produced in the human body by direct calorimetrical measurement. The only approach to such measurement is to be found in the clinical observations of Prof. Leyden as to the relative quantity of heat given off by the skin in fevers and in health, of which an account will be given in the next section; but in the dog, as has been already stated, the total heat production has been made the subject of an elaborate investigation, extending over many years, by Dr. Senator. As these measurements are the only ones which have as yet been made of this function in the higher animals, it will be necessary to give the reader a sufficiently complete account of them to enable him to understand their bearing.

In Dr. Senator's, as in all other methods of physiological calorimetry the quantity of heat given off by an animal in a given time is ascertained by measuring the loss of heat at its surface; and this measurement is effected by placing it in a ventilated chamber of which the wall is hollow and contains water.

The calorimeter consists essentially of two copper boxes, an internal and an external, resembling each other in form. The internal serves for the reception of the animal, and is provided with a cover which closes air-tight; the external contains the water, to which heat is to be communicated from the body of the animal. The inner case is suspended in the water in such a way that it is in contact with water on all sides, so that the animal occupies an air cavity which is completely surrounded by water. This cavity communicates with the external air by two ventilating channels, one for the entrance, the other for the discharge of air. The temperature of the inner box is measured by two thermometers, its contents being thoroughly agitated before the measurement. The whole apparatus is contained in a wooden case, between which and the external surface of the water-box there is a packing of non-conducting material, in order to diminish as much as possible the loss of heat. As a preliminary step, this loss was determined in a number of experiments in which the difference between the temperature of the water contained in the chamber and that of the environment varied as much as possible. From these a series of corrections for "temperature difference" were obtained. In all the experiments the chamber contained the same quantity of water, 37 litres. From the weight and specific heat of the metal contained in the boxes their calorimetrical value was estimated as equivalent to that of 2·5 litres of water, so that the total water-value of the apparatus was 39·5 litres. The term "coefficient of cooling" is used by Senator to indicate the number of kilogramme-heat-units lost by the apparatus in one hour for any given number of degrees of "temperature-difference." This was learnt by multiplying the correction for difference, by 39·5. The quantity of heat in k.-units lost by the air passing through the apparatus was of course obtained by multiplying its estimated weight by the specific heat of air (0·237) and the increase of temperature, (*i.e.*, the difference of temperature between the air entering and that passing out of the apparatus.) The ventilation was effected by a Bunsen's water-air-pump and measured by a gas meter; from this measurement the weight was estimated, the proper corrections for pressure and temperature having been made. The methods by which the carbonic acid and water were determined have been already described. From the hourly discharge of water the quantity of heat lost by evaporation was estimated.

In calorimetrical, as in all other quantitative measurements of the products

of life, it is necessary that for each result two experiments should be made, of which one is the exact counterpart of the other, with the exception that in the former the condition to be investigated is present, in the latter absent. All Dr. Senator's observations were made on this principle, that is, each measurement of the febrile heat production of an animal was compared, not with an estimated normal, representing the mean results of a number of similar experiments on other animals, but from an experiment made previously on the same animal under exactly similar conditions, fever excepted. Considering however, how important it is that a normal standard for future use in pathological inquiries should be obtained, he has recently made a series of determinations on a sufficient number of healthy animals, with this object in view. I subjoin a summary of one of these observations, which may serve as an example of the method employed in the whole research.

A dog, weighing 4,270 grm., which had been kept for four weeks on a diet of 250 grammes of selected horseflesh, with five grammes of lard, and 100 cubic centimeters of water, was introduced into the calorimetrical chamber at 9.34 a.m. The temperature of the animal when introduced was 39°·0 C., and that of the water of the calorimeter 27°·35. It remained in the chamber for four hours, during which the temperatures of the calorimetrical water, of the air on entering and leaving, and of the surrounding air, were observed every 10 minutes. The results of each hour were reckoned separately as follows: the calorimetrical value of the calorimeter, (*i.e.*, the quantity of heat required to augment its temperature by one degree,) being 3·94 k.-units and the increase of temperature during the hour being 0°·02 C., the heat communicated to it by the animal was 0·79 k.-units. Secondly, 144 litres of air having passed through it, of which the temperature was raised by 4°·48, the heat communicated to it, (= the product of the weight of 144 litres at the temperature at which it entered, the specific heat of air, viz., 0·237, and the increment of temperature,) was computed as 0·18 k.-units. Thirdly, the air on entering the calorimeter being dry, and having taken up from the animal 0·75 gramme moisture, this quantity, multiplied by 0·582, gave 0·44 k.-units.* Lastly, the quantity of heat given off by the apparatus to external media as previously determined empirically, for the difference of temperature between the temperature of the calorimetrical water and that of the external air was 11·22. Hence the total quantity of heat given off by the animal to its surroundings during the hour (= 0·79 + 0·18 + 0·44 + 11·22) was 12·63 k.-units. Similarly estimated, the discharges of heat in k.-units for the second, third, and fourth hours were severally 12·26, 11·54, and 11·92. From 26 similar measurements of six healthy animals, the following results were obtained in k.-units as representing the heat production of the dog per kilogramme of body weight, viz., 2·34, 2·71, 2·24, 2·88, 2·18, 2·85, giving a mean of 2·53 k.-units as the quantity of heat produced by a dog when fasting during summer.

In experiments relating to the influence of food on heat production it was found that the same dog which in the fasting state yielded 23·28 k.-units of heat per hour, and 5·2 to 5·5 grammes of carbonic acid, produced six hours after feeding 35·43 k.-units and 9·5 grammes of carbonic acid, its temperature remaining the same throughout. In this, as in other observations, the food given was the daily ration of flesh and fat which was sufficient to maintain nutritive equilibrium.

Production of heat in induced fever.

We are now in a position to proceed with the examination of Senator's results as to the production of heat in the fevered organism of the dog. With this view, comparative observations were made on the same animals in respect of which those relating to the discharge of carbonic acid and urea have already been given (p. 4); the measurement of heat production and of carbonic acid discharge being carried out simultaneously, that is, during periods of observation of which each lasted an hour. As was before explained, the normal heat production of each

---

* With reference to the determination of the heat loss by evaporation the method employed will probably be found to be open to objections, the discussion of which must for the present be reserved.

animal was first ascertained by measuring it on two successive days of privation of food. The observations were then repeated after the animal had been brought back again to nutritive equilibrium, under conditions which differed only in one respect from those of the first, namely, in the previous induction of the febrile state by the injection of fresh pus.

The following is a tabular summary of the results stated in the same form as in Table I.

Table II.

Table showing the Quantity of Heat produced per Hour by Fevered Dogs as compared with the Quantity by the same Animals when free from Fever but under the same Conditions of Nourishment.

—		Bodily Temperature (in rectum). Means	Heat Production.
Observation 1. Weight of animal 11 lbs. 10 oz.			
1st day	Normal	39·0	13·32
	Fever	39·3	12·46
2nd day	Normal	39·0	11·50
	Fever	40·3	11·58
Observation 2. Weight 13 lbs. 4 oz.			
1st day	Normal	39·1	15·67
	Fever	39·4	15·29
2nd day	Normal	39·1	17·32
	Fever	40·3	15·57
Observation 3. Weight 16 lbs.			
1st day	Normal	39·0	12·64
	Fever	39·6	9·91
2nd day	Normal	38·8	11·87
	Fever	40·7	14·52
3rd day	Fever	40·7	11·87
Observation 4. Weight 10 lbs. 10 oz.			
1st day	Normal	39·3	8·67
	Fever	39·5	9·59
2nd day	Normal	39·3	10·24
	Fever	40·7	11·86
3rd day	Fever	39·6	9·43
Observation 5. Weight 9 lbs. 2 oz.			
1st day	Normal	38·9	12·31
	Fever	39·7–40·3	11·97
2nd day	Normal	38·9	12·67
	Fever	41·0	15·22
Observation 6. Weight 24 lbs.			
1st day	Normal	39·0	24·18
	Fever	39·2	25·46
2nd day	Normal	39·0	24·48
	Fever	40·0	23·59

Observation 7. Weight 12 lbs. 9 oz.		Morning.	Afternoon.	Morning.	Afternoon.
1st day	Normal	38·8	38·8	15·94	16·20
	Fever	38·7	40·7	15·34	17·44
2nd day	Normal	38·8	38·6	16·47	17·06
	Fever	40·0	40·0	15·48	19·50
3rd day	Fever	40·4	39·9	17·41	15·57

A glance at the above results is sufficient to show that they afford no ground for concluding that in the induced fever of the dog there is on the whole any increase of heat production. One or two instances no doubt, as for example the observations relating to the second day of fever in the first series, and to the third day in the third and seventh series, might be referred to in favour of increased production; for in these cases the discharge of heat was increased, at the same time that the temperature of the animal rose. But in others, as in those relating to the second day in series 2, 6, and 7, although the temperature in each instance remained unaltered, the calorimetrical result was decidedly less than normal.

In series 7, the observations were more complete than in any of the others. The period during which the heat production and the discharge of carbonic acid was measured was extended to four hours, of which three were consecutive (10 a.m. to 1 p.m.), and the fourth separated by a four-hours' interval (5 to 6 p.m.). The "insensible loss" was also determined for each day of observation. The insensible loss was increased more than 50 per cent., it being 85 and 75 grammes respectively on the first and second normal days, and 142 and 151 grammes during the corresponding days of fever. All of this increased loss of weight must have been due to increased discharge of water, for the determinations of carbonic acid for the same days show that the rate of discharge of this product was rather diminished than increased. Notwithstanding this fact, the weight of aqueous vapour taken up during each hour of observation by the air transmitted through the chamber, was not greater in the fever series than in the others. As, however, in all the observations the total quantity of aqueous vapour discharged by this channel (two or three grammes) is shown by the detailed results of the experiments to have been small as compared with the very considerable "insensible loss" per hour, the discrepancy may perhaps be attributed to the insufficiency of the ventilation employed (about 150 litres per hour).

Dr. Senator concludes his discussion of his calorimetrical results as follows:—

In the first stage of fever the discharge of heat is rather diminished than increased, so that at this period it is probable that there is an abnormal retention. As the febrile process progresses, and when it is at its height, fluctuations exhibit themselves in the quantity of heat liberated, which resemble those which are observed in the discharge of carbonic acid and of aqueous vapour; but it cannot as yet be determined whether the amount of heat given off during the whole course of the febrile process is greater or less than the quantity of heat given off during the same period of apyrexia.

In judging of the significance of the fact last stated, it must be borne in mind that the normal with which the febrile thermogenesis is here compared, is that of inanition. In the dog, when on adequate diet, the production of heat is at least 50 per cent. more active. If, therefore, we were to take the animal in the ordinary condition of nourishment as our standard of comparison, we should find the heat production in fever very considerably diminished.

Section 2.—Clinical Investigations of the Discharge of Heat from the Skin.

It has been seen in the last section that in the fevered animal, in respect of which the conditions are such as to admit of exactitude of measurement, such measurement affords no support to the hypothesis

that increased thermogenesis is a characteristic of the febrile state. In man no attempt has yet been made to measure the heat production of the whole body. It has, however, been concluded from the results of observations as to the emission of heat from the cutaneous surface in those fevers which come under clinical observation, that the production of heat in the whole body is augmented. Here, again, as with regard to the discharge of carbonic acid, the pathologist depends almost entirely on the observations of Professor Leyden.

The series of researches to which we have now to refer were made in 1868.* They were directed exclusively to the relation between pyrexia, loss of weight, and discharge of heat from the surface in fever, the subjects of observation being for the most part persons affected with relapsing fever, typhoid fever, or pneumonia.

For the investigation of the surface loss of heat, a water calorimeter was employed, which was constructed on the same principle as that already described as applicable for the investigation of the discharge of heat in animals, with the exception that there was no provision for the continuous passage through it of a current of air. The apparatus is of such form and dimensions as to contain one limb instead of the whole body.

The copper chamber in which the limb is contained during the observation is 2 feet long and 1 foot wide. It is surrounded by a cylinder of zinc of corresponding form, but from 3 to 4 inches wide. The outer wall of the water chamber is protected from abstraction of heat by a thick padding of non-conducting material enclosed in a wooden case. The equal distribution of heat in the water contained in the chamber is secured by two agitators, turned by a winch, which revolve round the outer surface of the cylinder, so as to maintain a continuous current in the direction of rotation. The open end of the chamber is lined by an annular air cushion of india rubber, which, when the limb is introduced, occupies the space between its surface and that of the copper, so as to close the chamber air tight. The part of the body observed is the leg, the lower extremity being introduced into the chamber to such a distance that the india rubber cushion gently presses round the knee immediately above the joint.

Each observation lasted two hours. Before beginning it the water in the calorimeter was brought to the temperature of the room, the variations of which were of course noted. The greatest pains were taken that the limb, as placed in the chamber, should be under otherwise normal conditions, and particularly that it should be carefully supported on a kind of wooden tray contained in the chamber, so as to avoid contact with the metal, and that it should be clothed with blanket of the same thickness as the leg of the opposite side. When these precautions were attended to, it was found not only that its introduction into the calorimeter did not at all interfere with the comfort of the patient, but that the conditions and temperature of the limb were at the end of the two hours the same as those of its fellow.

The mode of estimating the results of the observations was as follows :—According to Funke † the surface of a grown person is 2,254 square inches, that of the leg alone 149 square inches, the two numbers being in the ratio of 15 : 1. The calorimetrical value of the chamber is 55 k.-units. The mean rise of temperature produced in an hour by

* Leyden. Untersuchungen über das Fieber. Deutsches Archiv Vol. V. pp. 273–371.

† Quoted by Leyden. I am not able to ascertain in what paper of Funke's these facts are recorded.

the introduction of the limb of a healthy person was 0°12 C. Hence 6·6 k.-units (55 × 0·12) must have been given off to it by the limb in one hour. Assuming that the quantity given off was in the same proportion to its surface, we have 99 k.-units as the hourly heat discharge, *i.e.*, production of the body. This corresponds pretty closely with the estimate already given of the normal heat discharge in health, viz., 2,200 to 2,600 k.-units ; for 24 × 99 = 2,376. This is probably high; for if we add to it the 400 k.-units which, according to Helmholtz's estimate are given off by the lungs, we have a total of more than 2,700 k.-units for the total heat loss.

The following is a tabular summary of the most complete of the series of observations reported in Professor Leyden's paper. It relates to two cases of relapsing fever and two of pneumonia. The table scarcely requires explanation. In the first case the observations were made during the accession, during the first remission, and the following relapse ; in the second case the observations were begun during the first remission and continued during the second relapse and the second remission. In the table each line gives the result of an observation ; the patient's temperature and pulse are stated in columns 4 and 5, while column 6 shows the rise of temperature produced in the calorimetrical water in the course of one hour. As has already been stated it was found that in a healthy person the mean rise of temperature produced in the course of one hour was 0°·12 C. when the ward was at the ordinary temperature, viz., 17°·3 C. (63°1 F.).

Table Showing the Results of Observations relating to the Discharge of Heat from the Surface of the Skin in Fever.

1. No.	2. Date.	3. Temperature of ward.	4. Temperature of patient.	5. Pulse.	6. Increment of temperature.	Remarks.
						Case I.—Relapsing Fever.
1	Oct. 19	18·8	40·0	120	0·19	M. æt.? Weight, 96 lbs.
2	„ 29	18·1	40·5	124	0·14	The periods of observations 2 and 3 followed at an interval of half an hour during which a rigor occurred. State of skin not noted.
3	„ 29	18·1	?	?	0·18	
4	„ 30	18·5	40·3	124	0·15	
5	„ 31	19·7	41·4	120	0·13	
6	„ 31	19·8	39·5	not stated	0·20	Observations 5 and 6 were made during the relapse at 12h. 15m. and 1h. 45m. of the same day. Before observation 5 the patient had had a rigor, and the skin was hot and dry. At 1h. 15m. sweating came on, which continued during the period of observation. Observation 7 was made at 5h. 35m. the same day; observation 8 at mid-day when convalescence was established.
7	„ 31	19·9	36·1	80	0·06	
8	Nov. 8	17·5	37·3	80	0·105	
						Case II.—Relapsing Fever.
1	Nov. 14	20·5 mean	39·8	108	0·16	M. æt. 18, weight 101 lbs. The numbers bracketed relate to a period of observation of 5 hours, during which the bodily temperature was gradually sinking. The patient
			38·7	88	0·19	
			—	—	0·24	
			37·2	64	0·16	
			37·2	—	0·15	

1. No.	2. Date.	3. Temperature of ward.	4. Temperature of patient.	5. Pulse.	6. Increment of temperature.	Remarks.
2	„ 15	20·5	36·8	64	0·075	was sweating the whole time, most
3	„ 16	20·3	36·5	68	0·10	profusely during the middle hour,
4	„ 17	20·5	36·5	64	0·06	when, as seen in column 6, the sur-
5	„ 18	20·0	36·5	68	0·10	face loss of heat was greatest.
6	„ 19	20·0	36·5	68	0·10	Observations 2 to 6 were made on
7	„ 20	19·6	40·6	106	0·145	different days during the non-febrile
8	„ 21	19·4	40·4	108	0·145	interval. Each observation lasted
9	„ 22	19·4	39·0 to 40·7	110 104	0·142	two hours, of which the mean result is given in each case. The patient was perfectly free from fever.
10	„ 23	—	40·5	not	0·10	Observations 7 and 8 were made at
11				stated		11 a.m. and 6 p.m. of the first day
12	„ 23	19·5	38·9	104	0·20	of the relapse. The skin was dry
	„ 23	—	37·4	88	0·18	and hot, moaning constant, excessive thirst. In the afternoon the temperature rose to 41°·0.
						Observation 9 was continued for four hours, viz., from noon to 4 p.m. During the whole time the skin was hot and dry.
						Observation 10 lasted two hours, commencing at 11 a.m. The skin was hot and dry. Observation 11 lasted also two hours, commencing at 5h. 45m. p.m. In the course of it the patient began to sweat, and continued to do so all the evening. At 8h. 15m. observation 12 was taken.
						Case III.—Pneumonia.
1	Jan. 8	18·8	40·0	100	0·192	M. æt. 19. Weight 101 lbs.
2	„ 8	18·8	39·2 to 37·2	92 to 76	0·26	Observation 1 was made at mid-day, the skin being moist.
						Observation 2 at 6h. 30m. p.m., the
	„ 11	18·6	37·1	not stated	0·105	perspiration being general over the whole body.
						Observation 3 relates to convalescence.
						Case IV.—Pneunomia.
1	Jan. 11	19·5	39·7 to 40·5	100 —	0·14	M. æt. 30. Weight 130 lbs.
2	„ 12	19·9	40·3	100	0·175	
3	„ 13	19·5	39·3 to 38·4	100 —	0·225	
4	„ 14	19·5	40·2	108	0·23	
5	„ 20	17·0	Normal.	Normal.	0·11	

Before proceeding to examine the results contained in this table, it will be advantageous to state the signification attached to them by the author, and accepted by other authorities on the pathology of fever. Dr. Leyden expresses his conclusions as follows:—"The discharge of

" heat is increased in fever whether the temperature is constant, falls " or rises. Consequently it is certain that the production of heat is " increased. In high fever the quantity of heat given off is from half " as much again as the normal to twice as much. The most rapid " discharge of heat takes place in the critical stage when the tem- " perature is rapidly sinking. It may then be twice or even three " times as great as the normal. Defervescence is associated with " marked sweating and evaporation at the surface; fervescence by the " absence of these phenomena, even when the coverings are air tight."

Senator's conclusion on thermogenesis.

In dealing with the question we have now before us, Senator, in the paper already so often quoted, seeks in Leyden's researches the most important material for the construction of his doctrine of pyrexia. In beginning his chapter on this subject he says:—" By Leyden's observations these two facts " come out prominently. 1. That with the exception of the initial stage, the " discharge of heat is considerably increased, although by no means constantly. " 2. That the activity of the discharge is not proportional to the bodily tem- " perature, for it may be less when the temperature is high, than when it is " lower; it may be normal when the temperature is above the normal, always " attaining its maximum in the stage of defervescence with critical sweating," &c. He then after referring to the confirmatory results of Liebermeister and Hattwich, and giving an explanation of the apparent contradictions between Leyden's general conclusion that in fever the production of heat is nearly doubled, and the contrary results obtained by himself in his calorimetrical measurements of fevered dogs, proceeds to observe that notwithstanding that the observations of Leyden extended at the utmost over a few hours, and related only to the discharge of a part of the body, it appears to him to be permissible to found conclusions upon them, so long as it is understood that they are accepted subject to drawbacks, which may turn out to be more important than they at first sight seem. "We may therefore," he says, " estimate the average increase of heat loss in febrile pyrexia as compared " with the normal as 70–75 per cent. As, moreover, at this time the constant " temperature of the body is higher, it must have at its disposal in pyrexia an " even larger quantity of heat than is required in the non-febrile state to " maintain itself at fever temperature; a quantity which not only exceeds " that produced by a healthy person in inanition or on fever diet, but even that " generated in ordinary conditions of nourishment. In making this estimate " it must, however, be expressly stated that it applies only to the condition of " fervescence, and that it must not be taken as representing the total loss of " heat in the process, from the beginning to the end; for during the defer- " vescence the loss is much greater, and it is much less during the accession." Senator's general conclusion on the subject is stated as follows:—" The discharge " of heat is in the outset of fever during the rigor, not increased but " diminished; during the height of the fever it is on the whole increased in " the ratio (so far as relates to the day hours) of 70–75 per cent., and con- " siderably more during the critical defervescence. During the height the " greater part of the loss occurs by conduction and radiation, during the " crisis by evaporation."

Results corroborative of those of Leyden are furnished by the observations of Liebermeister as to the quantity of heat given off by a fever patient in the tepid bath, as compared with a healthy person. Regarded as calorimetrical experiments, these measurements are subject to objections which cannot now be considered.

I have quoted these passages in order to show that Senator and Leyden, the two greatest authorities on the pathology of fever, are agreed in accepting the fact as certain that production of heat is largely increased, and that both of them found their conclusions simply and exclusively on Leyden's cases, for although both of them refer to Liebermeister's observations in confirmation, each indicates some of the reasons for regarding the results of that observer as inapplicable to the question.

If, therefore, it can be shown that Leyden's facts admit of a different interpretation, the whole foundation of the very generally accepted belief that the heat production is greater in fever than in health under normal circumstances of nutrition, falls to the ground.

Statement of the question.

The question we have before us is not whether the fact that in febrile pyrexia the temperature is as a rule increased both in man and animals by two or three degrees, is due to this or that cause, but simply whether in fever along with the increased temperature, there is also increased production.

That *cæteris paribus* there is, in fever, an increased activity of *certain processes* which produce heat can be proved without calorimetrical measurement. Supposing the state of the heat discharging surfaces to remain the same, the fever patient must necessarily produce more heat to keep his body up to the higher mark as regards temperature than the healthy person. In other words, supposing the quantity and quality of clothing, and the temperature and moisture of the air to remain the same, and the discharge of watery liquid from the sweat glands to be also the same, the fevered person would give off a somewhat larger quantity of heat from the surface than a healthy person; for the difference between the temperature of his body and that of the environment being greater, the loss by radiation and convection would be proportionally greater. The difference, however, would certainly be small, greater somewhat in summer than in winter, and greater in bed than in clothing.

It is also certain that the process of disintegration of tissue of which the evidence has already been presented to us, is in its nature thermogenetic. In the preceding section I have estimated that increase, and have shown that there is unquestionably a very considerable difference between the heat production of a febrile and of a non-febrile person on the same febrile diet. I have also pointed out that this holds true only so long as the comparison is made under similar conditions of nutrition, for if we compare the heat production of a fevered patient with that of a person in health on ordinary diet, we find that whatever difference presents itself is quite within the limits of normal variation.

The fact of the greater consumption of material in fever may therefore be dismissed entirely from our minds in entering on the consideration of observations similar to those of Professor Leyden, for in those observations the comparison between fever and health is made, not in regard of the discharge of heat from the whole body (pulmonary and cutaneous), but in regard of the quantity of heat liberated by a given area of skin, in fever and in health. Whatever may be the result of a comparison between these two conditions as regards the activity of the process by which heat is given off by the skin, there is no reason for supposing that a well-fed person would, if the skin were in a natural state, emit more heat from a square inch of surface than an ill-fed, or that the quantity of heat given off by the skin is dependent on any other cause than on changes in its own temperature or moisture, or in that of the atmosphere with which it is in contact.

The careful study of Professor Leyden's results has led me to an interpretation which differs materially from that which he has embodied in his main conclusion. He admits throughout the great importance of visible perspiration, *i.e.*, of the secretion of watery liquid by the sweat glands as a condition favouring the discharge of heat from the skin. He points out that in all those of his experiments in which the heating of the calorimetrical water was most rapid, the result could be connected with rapid cooling of the accessible parts of the body, and with profuse sweating. But he finds that there were other cases in which, notwithstanding the dryness of the skin, the fevered body parted with its heat to the calorimeter with a rapidity which could not possibly be accounted for as the mere result of the greater heat of the surface. In looking through the cases, I am unable to find a single instance in which the

state of the skin being noted, it was found that in the absence of perspiration, the loss from the surface was considerably in excess. This being so, I am compelled to associate increased discharge from the surface, not with pyrexia, but with sweating, for while on the one hand I find instances in which the patient was in high fever, with only an average of heat loss, I find in the same patient on another day a very active discharge of heat from the surface, but no fever.

In so far as it can be shown that the increased rate at which the fever patient's heat was communicated from the limb to the calorimeter in which it was enclosed, is dependent on sweating, the result is of little value or significance as an index of increased production of heat in the living tissues. Under the conditions of the experiment, *i.e.*, when a limb is enclosed in an air-tight chamber, the air which occupies the space between the cutaneous surface and that of the chamber, soon becomes saturated with moisture. As soon as this state of things is established there is no further loss of heat by the conversion of sweat into vapour; the effect of sweating therefore resolves itself into the mere abstraction from the limb of a certain quantity of watery liquid, of which the whole of the heat goes to the good of the calorimeter. So far as the body of the patient is concerned, the process is attended with the loss of a certain quantity of water, and manifests itself in a corresponding loss of weight, but so far as relates to the chemical processes by which heat is produced, it fails to afford any information. If for every gramme of water sweated out at the surface, it were the law of the animal economy that an equal quantity of cold water should be ingested, then it might be said with truth that for every gramme discharged a quantity of heat must be generated in the body sufficient to warm a gramme of water from the ordinary temperature to that of the blood. So far from this being the case, the loss of water is, as a rule, supplied in the diet of fever by liquid, of which the temperature is as high as, or higher than that which it has to acquire in order to be discharged, in which case it is obvious that the water as it actually leaves the body cooler than it entered it, must, (in so far as it has any appreciable action on the temperature of the body,) tend rather to favour the accumulation of heat than to promote its discharge.

Professor Leyden's observations are of great value, as affording a more complete understanding than we before possessed of the function of the sweat glands in defervescence. In this respect some of the observations (as *e.g.* the second case in the table) are particularly striking. In that instance, as in many others, it was seen that the temperature of the patient's body sank very rapidly as that of the calorimeter rose, the transference of heat from one to the other being effected either by the trickling down of drops of hot moisture from the limb on to the floor of the chamber, or through the air by a process of distillation, in which for every quantity of water condensed on the metal surface a similar quantity is evaporated from the skin. In those parts of the surface which are not enclosed in a chamber, it is clear that the sweating must be more effectual than in the chamber itself; for here the air which is in contact with the skin is not saturated, so that, in addition to the loss of heat by the discharge of warm sweat, there is an additional loss due to the conversion of the whole or part of it into aqueous vapour. In either case the activity of the process is dependent entirely on the secreting function of the sweat glands, *i.e.*, on the quantity of watery liquid which they throw out on the surface, and has no direct connexion with any heat-producing or other nutritive processes having their seats in the tissues. Whether the watery discharge is converted into vapour or soaks into the patient's

blankets, it is discharged without any arrangement existing or being required for its continuous replacement, so that, if I may be permitted to use the expression, the loss of heat by sweating is payment out of capital; it may go on for a very long period without any appreciable effect excepting loss of weight. For this very reason, of all functional fluctuations, those of sweating are the most valueless as outward indications of inward changes.

Part III.—Pyrexia.

Section 1.—*The Norma of Temperature.*

The temperature of the healthy human body has been recently determined by Jürgensen* on a larger basis of accurate measurements than before existed. The mean temperature of day and night of a healthy person, as measured in the rectum, is 37°·2 C. If the whole period of 24 hours is divided into two, of which one, commencing at the moment that the bodily temperature reaches its morning minimum, ends with the attainment of the evening maximum, the other, corresponding to the interval, it is found that in the diurnal period, viz., between 7 or 8 a.m. and 9 p.m., the mean temperature is 37°·34, while in the nocturnal period, of which the duration is shorter in the proportion 100 to 136, the mean temperature is 36°·94.

In relation to our present inquiry, Jürgensen's researches have led to a most remarkable result, which was entirely unexpected, viz., that the *mean* temperature of the human body is remarkably independent of the conditions which temporarily affect the production of heat, even when their influence is most powerful. Thus, by observations on a vigorous and healthy person who voluntarily submitted to inanition for 63 hours, it was found, not only that the mean temperature of the two days was exactly the same as in ordinary conditions of nutrition, but that the diurnal temperature course was not modified in its character.† Again, it was ascertained by the most accurate observations on the same patient, who submitted to a succession of cold baths, each lasting 25 minutes, at temperatures varying from 9° to 11° C. (50° F.) that notwithstanding the rapid abstraction of heat, which gave rise to a shivering lasting for several hours, the diminution of bodily temperature which occurred during the bath was followed, after an interval of four or five hours, by an elevation which precisely compensated it, so that if the average was taken of observations extending over a sufficiently long period, the mean was the same as under normal conditions.

An exactly similar result was come to as regards muscular work, showing that as in the former case the depression, so here the elevation of temperature by active exercise is, in the long run, completely made up for.

When it is remembered that all these conditions—inanition, abstraction of heat by the cold bath, and muscular work—are known to produce very considerable effects on the exchange of material in the body and consequently on the thermogenesis, they afford the strongest possible evidence that increased or diminished temperature has no necessary connexion with increased or diminished production of heat.

The extension of Jürgensen's observations to fever, led him to the remarkable discovery that in continued fever, and particularly in typhoid,

---

* Jürgensen, Die Körperwärme des gesunden Menschen. Leipzig, 1873, p. 9.

† Jürgensen, l. c. p. 21.

the diurnal variation of bodily temperature closely resembles that of health; so that if two curves representing these variations are inscribed one above the other over the same abscissa, they are seen to run parallel to each other with a constancy which is very remarkable. In other words, the only material difference between the two conditions is that in fever, the normal is 3° higher (40°·1 to 40°·3 instead of 37°·2). Whatever be the explanation of this, the fact comes out so clearly as the result of observation, that it cannot be disputed. It affords evidence that the laws which regulate the temperature of our body, and to which even the chemical activity of our protoplasm is subject, are not upset in the febrile state, and gives us ground for anticipating that, whenever those laws shall have been fully investigated, they will be found to be the expressions of the most fundamental and specific endowments of our being.

That the shifting of the abscissa of the temperature curve three degrees upwards, does not, as Liebermeister thinks, signify that in fever the organism has "forgotten" the "habit" of temperature, is proved by the observations of the most accurate clinicists as to the influence of anti-pyretic remedies, and particularly of cold and quinine. We have already seen that in health "the law of temperature" is strong enough to withstand even the most rapid abstraction of heat from the surface; but this is not so in fever. Clinical observation has established the fact (whatever may be its therapeutical value) that in typhoid and other fevers the temperature can be brought down and kept down nearly to the normal by the systematic use of the cold bath, or of the cold affusion. Hence we are justified in concluding that in fever, conformity with the law of temperature is not abolished, but merely weakened; that just as in health a *nisus* constantly exists towards excess, which is restrained by the controlling influence of that "*schützendes Etwas*," the existence of which we unconsciously refer to when we call it the law of temperature; so in fever that influence still exists and needs only to be strengthened or aided; strengthened when we administer large doses of of quinine, aided when by the cold bath we abstract heat from the surface. It is on this principle only that we can understand how it is that those anti-pyretic agents, of which the action is so certain in fever, have no permanent effect on temperature in health.

Section 2.—Relation between Pyrexia and the other Functional Disorders of the Febrile State.

Whenever two actions or groups of phenomena are associated so as to constitute a process, the theory or explanation of that process consists in determining what is the nature of the association. And if we designate the two associated actions or phenomena respectively *a* and *b*, then the possibilities to be considered are that *a* may be the consequence of *b*, that *b* may be the consequence of *a*, or that both may stand side by side as collateral products of some other antecedent. So in the case of fever with its two chief phenomena pyrexia and textural disintegration, the theory of the process is involved in the question whether the former or the latter is primary, or whether both are not the results of an action originating independently of either.

I have referred to these questions not with a view to their immediate discussion, but for the purpose of indicating what form should be given to our investigation of the subject, in order that eventually we may find ourselves in a position to answer them.

The temperature of the body being dependent on the balance of the production and discharge of heat, of which the former is a function of

living protoplasm, the latter a function of the organs of circulation, respiration, and secretion, the question whether pyrexia or textural disintegration is primary, comes to assume the form in which it has been frequently discussed by pathological authors, viz., whether it is production or discharge which is primarily disordered.

Want of information as to the normal relation between the former of these processes and the bodily temperature, renders it impossible to answer the question in either of its forms, in other words, to frame a theory of fever. All that can be attempted is to study the mutual reactions on each other of the two sets of functional disorders, in order that when these relations have been ascertained by observation, we may be furnished with such anticipations as to their nature, as may guide us in clinical and experimental researches. With this view I shall occupy the remainder of this section, by giving an account of the agencies which exist in the animal body for regulating the discharge of heat, stating with respect to each of them what is known as to its nature; for inasmuch as we as yet *do not* know by observation or experiment of any mechanism, any endowment of living protoplasm by which it can regulate or limit its own chemical, *i.e.*, thermogenetic processes, and *do* know how the escape of heat from the surface is limited, it is clearly necessary to satisfy ourselves by the most careful observation that these agencies are inadequate, before we fall back, as I anticipate we shall eventually do, on a process having its seat in protoplasm, and seek for the explanation of the regulation of temperature in the establishment of a direct relation between it and the functional activity of living tissue.

a.—Discharge of Heat by Sweating from the Skin.

This subject has already been discussed in connexion with Leyden's researches on febrile thermogenesis. No precise measurements exist of the quantity of moisture (aqueous vapour) discharged by the human skin in health, and consequently no estimate can be formed of the heat normally lost in this way. According to Helmholtz's calorimetrical investigations the total loss of heat by the skin, amounts to about 1,800 to 2,000 kil.-units daily; Leyden's experiments have shown that this loss would be doubled in the moderate sweating of the febrile crisis, if the whole of the heat contained in the perspired water were abstracted from the organism. As has been already pointed out, this is never likely to be the case, for however well the body of a patient may be ventilated, the ventilation is never sufficient under ordinary conditions to carry away the secreted water as vapour, as fast as it is discharged by the sweat glands. If it were sufficient, the abstraction of heat from the body would be extremely rapid. We have no data for estimating it in fever, because we have no measurements of the quantity of water actually discharged. In the Turkish bath the loss of water often amounts to 500 to 600 grammes per hour. If this weight of water were entirely converted into vapour it would imply a loss of heat amounting to some 300 to 360 k.-units, which, (supposing the specific heat of the body to be nearly equal to that of water,) would cool it 6° or 7°. In fever the quantity of liquid sweated can never or very rarely be comparable to that discharged in the Turkish bath, but even here, if it were completely converted into vapour the heat loss would be very rapid.

b.—Discharge of Heat by Respiration.

The normal loss by respiration may be estimated as about 320 to 330 k.-units daily, made up of 80 to 90 k.-units, spent in warming some

10,000 litres by about 25° C. and 240 k.-units used in evaporating 412 grammes of water. This loss may obviously be increased by any cause which increases the activity of respiration.

Thus in fever, when in general the quantity of air breathed has been shown by Leyden's researches to be increased by more than 50 per cent., it is probable that other things being equal, both the evaporation loss, and that incurred in warming the air respired, will be correspondingly increased ; but, considering that the total respiration loss, according to Helmholtz, amounts to about 20 per cent., the pulmonary cooling is without doubt of little importance as compared with that which takes place by the surface of the skin.

In the dog the influence of respiration on temperature has been shown by Dr. Riegel to be much more considerable, and has an unquestionable importance as a regulating agency. In that animal any cause which elevates the bodily temperature, whether this is effected by clothing the body in non-conducting material, or placing it in a warm environment, excites respiration in a very remarkable manner, so that the animal not only breathes more frequently, but inhales a larger quantity of air at each breath. This effect, which must be attributed to the influence of the increased temperature of the blood on the intra-cranial nervous centres, was first described by Ackermann under the term heat-dyspnœa. It is not, however, so much with reference to the mode in which it is produced, or to its teleological significance that it is now referred to. Riegel* has shown that in the heat economy of the dog, the function of respiration is the most important means which exists for the maintenance of constancy of temperature. When a dog is observed in a moderately overheated room, say at 25° R. (88° F.), a temperature which to the human organism is not uncomfortably high, it soon becomes distressed and breathes with extraordinary rapidity. If under these circumstances its temperature is observed continuously, it is found scarcely to exceed the normal; but if, while still in the warm room, it is placed fully under the influence of chloroform, (a drug which under ordinary circumstances invariably decreases the temperature of the dog,) its temperature rises at once to that of pyrexia. In this experiment the reason why the temperature rises, is evidently that the narcotic renders the nervous system incapable of reacting against the stimulus to which it is exposed. Consequently the rise of the temperature of the blood is no longer the signal for that more active breathing by which, if the animal were not narcotized, the normal state of things would be restored.

c.—Influence of Changes in the Circulation on the Discharge of Heat.

The explanation which is commonly given of the nature and cause of febrile pyrexia is founded on the supposition that in health the constancy of the bodily temperature is dependent on the power which the organism possesses of regulating the circulation, that is to say, that the faculty which man in common with other homoiothermic animals enjoys of maintaining equability of temperature, depends on the existence in his nervous system of apparatus by which the relative quantity of blood contained in those parts of the vascular system which are exposed to the influence of external media, (particularly in the vessels of the lungs and skin,) can be increased or diminished according to the requirements of the organism. In constructing a theory of fever on this basis, it is

* Riegel. Ueber den Einfluss des central Nervensystems auf die thierische Wärme. Pflüger's Archiv, Vol. V., p. 651.

assumed that the disorder of the circulation is the first link in the chain of phenomena of which the febrile process consists, and consequently, that fever has its origin in disorder of the nervous system. For inasmuch as it is known experimentally that the distribution of the blood is entirely regulated by "vasomotor centres," it is clear that no departure from the normal condition of the circulation can happen otherwise, than by virtue of an antecedent disturbance of the functions of those centres.

Until a very recent period the knowledge which existed as to the influence exercised by variations of the velocity of the blood stream and of the distribution of the blood on the bodily temperature was chiefly theoretical, consisting rather of deductions from what was known as to the mechanism of the circulation than of results derived directly from observation. During the last few years a more or less complete experimental basis has been furnished by the physiological researches of Heidenhain, as well as by the pathological inquiries of Riegel and Naunyn,* so that although there are still questions which must be left open, there are some points on which it is possible to speak with confidence.

One of the most satisfactory and (if I may be permitted the expression) one of the most elegant proofs that by increasing the quantity of blood in circulation in an exposed part, the temperature of the whole body can be diminished, is afforded when the vessels of an exposed organ are paralysed by the severance of its vasomotor nerves, so that while the capacity of its relaxed blood channels is largely increased, the force of the circulation remains unimpaired. Thus, when in the well-known experiment which 20 years ago led to the discovery of the vasomotor nervous system, the vascular nerves of the rabbit's ear are divided, the increased warmth thereby produced in the ear is associated with a diminution of the temperature of the whole body, which though small in amount is perfectly measurable. It is small because the quantity of blood which is in circulation at any moment in the paralysed organ is a mere fraction of the whole mass of the contents of the vascular system.

When the vessels of the whole or of the greater part of the body are thrown into a state of relaxation by severance of the spinal cord, the resulting abnormalities of bodily temperature are much more considerable, but their nature and degree depend rather on the secondary effect which the total disappearance of arterial tonus exercises on the circulation, than on the altered distribution of the blood-current. For when all the arteries are relaxed, the velocity of the circulation, *i.e.*, the quantity of blood discharged by the heart in a given time, is necessarily diminished, the reason of this being that, while the mass of blood contained in the whole circulatory apparatus (heart and blood vessels) remains unchanged, the capacity of the vascular system is augmented, and consequently that of the heart diminished. The heart, therefore, containing a smaller quantity of blood at the commencement of each contraction, discharges less, *i.e.*, works with less effect.

Although it might have been anticipated from previously existing knowledge as to the mechanical conditions of the circulation, that this would be the case, *i. e.*, that abolition of arterial tonus would be disadvantageous to the circulation, the fact that it is so was not only not recognized, but, by many physiological writers, distinctly denied. The mechanical physiologists of the French school, whose doctrines have

* Dubczcanski und Naunyn. Beiträge zur Lehre von der fieberhaften Temperaturerhöhung. Archiv für Pathologie ; Vol. I., p. 181.

been popularized in this country by the works of M. Marey,* teach without any reservation that the effect of general relaxation of the blood vessels is to increase the force of the pulse, and to augment the frequency of the contractions of the heart, and found upon this notion their theory of fever.

d.—Comparison of the State of the Circulation in Fever with its State after Injury of the Spinal Cord.

If in man or in an animal, severance of the cord takes place below the origin of the phrenic nerves, the respiratory movements, although altered in their character by the paralysis of the muscles of the trunk, continue, and consequently, life is preserved. The phenomena which present themselves in these cases, from their extreme interest in connexion with the heat economy of the living body, have of late years concentrated upon themselves the attention of pathologists. Those which are of most importance in relation to our present inquiry are the following:—

For the reason already stated, section of the cord at the level of the seventh vertebra, or accidental destruction of the organ in man, produces as its primary effect an enormous diminution of the pressure on the arteries in consequence of which the circulation diminishes. The influence exercised by this diminution on the temperature of the body varies both in degree and direction, according to the animal observed, and the nature of its environment. In man, as is well known from the historical case recorded by Sir Benjamin Brodie, as well as from others published since, it often happens that the bodily heat rises above the normal, sometimes above that of fever. In small animals, such as rabbits, the temperature falls rapidly, notwithstanding that they are so well clothed in fur, and that the observation is made in summer weather. In animals of intermediate size, such as dogs, the result varies according to the outside temperature and the protection which is afforded against surface cooling, either by the natural covering or by artificial clothing. Thus, if the creature is invested in an envelope of non-conducting material, and kept in an ordinary room, the temperature of the blood inevitably rises to a height which often exceeds that of fever. Without clothing, especially if it be of relatively small size, its temperature rapidly sinks until it dies in collapse.

From these facts it is obvious that the most striking difference between the heat economy of the injured and that of the normal animal consists in this, that in the latter the bodily temperature is independent of external conditions, whereas in the former it is affected even by very slight changes in the environment. We have already seen to what an almost incredible extent this is true of man. Similarly, it is found that a healthy dog accustomed to the temperature of summer may be exposed to that of a winter's day without the slightest variation. After the cord is divided, the same animal must be clothed, even when in a warm room, else it cools too much; while if the room is only a very little too warm, it passes into a state of intense pyrexia. To prevent either result, depression on the one hand or collapse on the other, the surface loss has to be accurately adjusted to the thermogenesis by artificial means; for the animal has lost its powers of making any adjustment for itself.

As regards the heat economy of animals after section of the cord at

* *See* Marey's Physiol. de la Circulation, chap. xviii. p. 3,501.

the level of the sixth or seventh vertebra, there has been much dispute. Most observers have been content to assume, as a sufficient explanation in the case of depression of temperature, that the result is attributable to the paralysed condition of the cutaneous vessels and to the consequent increased discharge of heat at the surface. As regards the other cases, it has been generally taken for granted that there is a close correspondence between the condition induced by the injury and that of fever, and accordingly that there is, along with the augmented disengagement of heat from the surface, an associated increased activity of those powers by which heat is produced ; so that the former is more than compensated by the latter. In order to bring this view into harmony and connexion with Virchow's well-known doctrine of an inhibitory centre situated somewhere in the intra-cranial nervous system, all that is necessary is to suppose that just as in clinical fever the influence of this centre is directly paralysed by the morbific agent, so after section of the cord its influence on the tissues is annulled by the severance of the channels by which it is normally exercised.

It is, fortunately, no longer necessary to occupy space in discussing the theory according to which there is a direct physiological relation between the nervous system and the chemical processes on which the production of heat depends ; for it has now been shown experimentally by Dr. Murri that after severance of the cord, the temperature rises even when the thermogenetic function may undergo a very great diminution. As, therefore, there is no increase of production, the hypothesis of increased discharge, which is necessarily associated with that of increased production, falls to the ground of itself. Dr. Murri has, however, by another series of researches, furnished us with the direct proof that no such increased liberation of heat takes place. It is a fundamental and well known fact in relation to the distribution of temperature in the animal body, that the greater the vigour of the circulation, the less is the difference of temperature between the central and superficial parts, so that by measuring simultaneously the temperature of the skin and that of the rectum, we are enabled to judge very accurately of the velocity of the blood stream. Why this is so, is easy to understand. When the arteries are distended, and the blood current is rapid, a larger quantity of blood is brought to the surface from the warmer central parts of the body than in the contrary case. The mass of blood therefore being greater, the cooling it sustains by exposure to the cooler environment of the body is proportionately less, so that it returns by the veins towards the centre at a temperature which does not differ largely from that which it possessed in its outward course. Consequently if we find the temperature of the surface much less than that of the central parts, we are quite certain that the circulation through the surface vessels is feeble, and that little heat is being given off. Now Murri found that, even when after section of the cord, the internal temperature was normal or excessive, that of the skin was unnaturally low, a proof that the condition of the circulation was such as to be least favourable to the discharge of heat from the surface.

The hypothesis of increased exchange of heat having been got rid of, we fall back on the one fact of which the importance has already been indicated as affording the most striking characteristic of the thermal state of an animal after section of the cord, namely, that the bodily temperature yields with abnormal facility to the influence of outside conditions—that the temperature equilibrium, to use Naunyn's expression, becomes labile. This being the case, it is obvious that the analogy between this condition and that of fever is not sufficiently close to justify

us in following the example of those pathologists who have founded on it a theory of fever. As, however, it may be of use in enabling us to answer some inevitable questions, and particularly may facilitate the understanding of the relation between thermogenesis and temperature in fever, time will not be wasted in instituting a comparison between the two kinds of pyrexia.

In the various fevers which form the subject of clinical observation, no very accurate information exists as to the state of the circulation. The comparison of the central with the surface temperature, which in the study of the effects of section of the spinal cord, affords us such valuable information, would also be of value if it were made in the early stage of fever but as yet clinicists have not recognised its importance; so that the necessary basis of observation is wanting. In the later stages of fever the introduction of another element, that of sweating, a heat-discharging process which is in great measure independent of the circulation, deprives the observation and measurement of the surface temperature of much of its value as a criterion.

As regards thermogenesis it must not be supposed that in fever the diminution of this function is comparable in degree to that which occurs after section of the cord. In the first part of this paper it has been shown that as regards the ordinary sources of heat, viz., those dependent on the ingestion of food, the diminution is so considerable that the total quantity of heat produced in the body in a given time, even when augmented by the quantity arising from the abnormal disintegration of tissue, may still fall short of the average of health. This being the case, it is natural to ask, how it is that we do not meet with instances of fever in which, (as after section of the cord in small animals and under external conditions favourable to cooling,) the temperature remains stationary or sinks instead of rising. The answer to this question is, that although, as might be expected, we have perhaps no counterparts in human pathology to those relatively common cases in which, after accidental injury of the cord, the patient becomes cold instead of hot, such instances are familiar to the experimental pathologist. We have seen that in the dog febrile pyrexia may be induced with certainty by the introduction into the circulation of a known dose of pyrogenic substance. If a dose of the same substance, proportionate in quantity to the smaller weight of the animal, be injected into the circulation of a rabbit or guinea pig, the same succession of disorders occurs with this difference, that the temperature falls *below* the normal instead of rising above it, the amount of depression varying according to the temperature of the environment. Here, namely, just as after section of the cord, we have evidence that the thermogenesis *may fall below the normal limit of adequacy*: the cause, which in a larger animal would produce fever with all its signs, here produces only an intense general disorder with diminished heat of body and diminished thermic discharge.

e.—Concluding Inferences as to the Seat of Origin of Febrile Pyrexia.

A satisfactory explanation of the nature of fever and of its relation to the febrile process is not at present possible, because we are not as yet possessed of the necessary physiological knowledge. We have elsewhere stated that two possibilities 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.

In both hypotheses it is tacitly assumed that fever is the product of a material fever-producing cause contained in the blood or tissue juice, the morbific action of which on the organism is antecedent to all functional disturbances whatever. At bottom we are all humoralists, and believe in infection. It is not until we have to say where and how the infection acts that questions arise.

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. The little that has been already accomplished in this direction is sufficient to show that the living substance of our bodies is, if I may so express myself, delicately sensitive to variations in the temperature of its environment, so that very slight deviations from the normal may produce effects of surprising magnitude.