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Thesis by Lorrain Smith
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Thyroidectomy & Respiratory Exchange.
A contribution to the Pathology of Myxoedema.

Thesis presented for the degree of
Doctor of Medicine

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For a considerable time previous to the year 1883 the investigation of the function of the Thyroid Gland had awakened almost no interest in the minds of Physiologists. Since 1859, the date of Schiff's research on the relation of the Thyroid Gland to the Glycogenic function of the liver and to the still more obscure functions of other so called "blood glands" ("Ueber die Zucker bildung in der Leber." Würzburg 1859), there had been practically no advance towards the solution of the problem. This was partly to be explained by the result of Schiff's work, for he had found that certain animals from which the Thyroid Gland had been removed died in a few days after the operation. This result prevented him from solving the problem he had in view, and in itself suggested no new line

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thenceforward given to the disease.

The conditions described by Reverdin and Kocher were compared with this disease and with allied forms of cretinism, and the comparison opened up a large field of research for experimental Pathologists.

Since 1883 many investigations on the function of the Gland have been conducted, the chief of these being devoted to finding how far the condition which arises in normal animals after Thyroidectomy corresponds to Myxoedema. Hitherto these researches have been for the most part restricted to a careful observation of the symptoms which arise on ablation of the Thyroid Gland. The most conclusive among them is that of Professor Horsley (Proceedings of the Royal Society, 1886 vol.), who succeeded in inducing in monkeys a condition which resembles Myxoedema in human subjects in all essential symptoms. This result obtained by Prof. Horsley justifies the expectation that we may be able to throw light on the nature of

Myxoedema

Myxoedema by a study of all the forms of Cachexia Strumipriva.

In animals where a condition completely resembling Myxoedema cannot be induced, the reason is often to be found in the fact that when the operation succeeds these animals are so severely affected almost immediately thereafter that they do not recover from the acute stage. In the following paper I have regarded the Cachexia Strumipriva as occurring in two stages, (1) the acute (2) the chronic. In the acute stage we have the changes which Prof. Horsley calls "neurotic". In the chronic, we have the gradual failure of nutrition which ends in death, possibly without recurrence of any of the acute symptoms. Myxoedema being a chronic condition can be expected only in those animals which have survived for some considerable time.

When the acute stage becomes pronounced, as in Carnivores, we find very general evidences that the animal is functionally

unstable.

unstable. We have conspicuous changes in Temperature, in Respiration, in the Blood and the Nervous System, and in certain cases these changes assume the most extreme forms. One would therefore naturally expect to find that these functional changes are the expression of modifications in the metabolism of the animal, of such a nature as could be readily detected.

It was with this hope that the following research was undertaken. So far an examination of the Respiratory Exchange only has been taken up. The study of the modifications in Nitrogenous Excretion would be necessary to give materials for a complete account of the metabolism in this form of the Cachexia, but this has not been carried far enough to admit of publication, and it seemed desirable to proceed with a record of what has been already accomplished.

The only work on this question which I have discovered is that of Michaelson

of

of St Petersburg, and of this he gives only a very meagre description in the shape of a preliminary note (Pflüger's Archiv, 1889).

The animals used in the present research were cats. They were anaesthetised by ether, and during the operation the strictest antiseptic precautions were observed. The wound was dressed with collodion, and this proved to be most efficient. The operation was not a severe one in itself and sometimes on the very evening of the day on which it was performed the cat seemed quite comfortable and purred as usual when it was supplied with food.

The method of observation which I adopted at first was that of taking a record (1) of body temperature, (2) of the amount of Carbonic Acid given off and oxygen absorbed in given intervals of time, (3) Along with this careful notes were taken of the time of onset and character of the symptoms induced by the operation.

The Respiration apparatus used for estimating

estimating the Carbonic Acid and Oxygen was that described by Dr. Haldane in the Journal of Physiology vol. XIII page 219.

Of the nine animals operated on, six died in the acute stage of the Cachexia within a week after the operation. The three others survived. Of these, two had shown moderately pronounced symptoms, but recovery from the acute stage took place. In the last, the symptoms were scarcely if at all noticeable. These results confirm the well known observation that the symptoms which are seen in the acute stage in certain animals are much less pronounced than in others. So much is this the case that it is possible to select from a number those animals which will be affected with that degree of acuteness which it is desired to obtain.

. Sometimes, as in the case of the last animal referred to, the typical symptoms are practically absent; yet in such a case it is manifest from the gradual

gradual loss of weight and general appearance of disturbance, that the nutritive balance of the organism has been seriously interfered with.

Animals which show the symptoms in the most acute form are spirited and well nourished, and functionally active in a high degree. It has been observed by Prof. Horsley that old animals do not as a rule suffer in any way from the operation except in the fact that senile changes are somewhat hastened.

By the method of observation which I have indicated, the metabolism of animals in the Cachexia was compared with that of the same animals in the normal condition prior to the operation. The results, however, were strikingly negative, and the difference from the normal metabolism was not sufficiently great to form the basis of a conclusion as to the origin of the symptoms observed. The output of Carbonic Acid and the

absorption

absorption of Oxygen continued almost uniform, and in a fairly constant ratio.

The effect of starvation on an animal is to lower slightly the amount of Carbonic Acid excreted and Oxygen absorbed, and to lower the ratio of the Oxygen absorbed to the Oxygen in the Carbonic Acid – a ratio called the Respiratory Quotient. The slight fall which was here observed could be explained on this ground.

On the other hand, the Temperature remained almost ~~constant~~. It should be noted, however, that a slight fall occurs in each case. Prof. Horsley draws attention to the fact that in certain of the dogs on which he operated he found that at the acme of muscular twitching the temperature was raised sometimes as high as 4°C or 5°C above normal. In the case of one cat only, in this series, was there observed any distinct rise. In Cat No. IX, after a period of extremely marked muscular spasms, the temperature was found

found at 40·6°, or 2° C above normal.

In these animals therefore the variations of temperature were much less than those which have frequently been seen in dogs. But it is perhaps of greater interest to note the variety in the temperatures rather than the rise. Even in dogs and such animals as occasionally show a rise, in given conditions the temperature on the whole steadily declines. To this I will allude later in the paper.

It became clear therefore that some further method was needed for testing the functional integrity of the ~~heat system~~ regulating mechanism. The most satisfactory method of obtaining this in the case of the animals I had under observation was to use the reaction to changes in the temperature of the surrounding air which is found in warm blooded animals. It should be remembered that in the warm blooded animal the temperature may remain constant though there has been

been serious injury to the heat regulating mechanism. The readings of the Thermometer indicate the existence of an organic lesion of the heat regulating system only in so far as it leads to abnormal temperatures, but the actual temperatures of the animal may show neither the nature nor the extent of the lesion from which it is suffering.

In these animals a constant temperature is maintained in two ways. (1) Heat loss may be increased or diminished by modifying radiation from the skin, or by sweating, or some other mode of imparting heat to the surrounding medium. (2) By variation in the metabolism of heat production. The amount of this metabolism is measured by estimating the out put of Carbonic Acid for given temperatures or variations of temperature.

It was found by Pflüger and others working with him that when a warm blooded animal is placed in cold air it gives off more Carbonic Acid than it does in warm air in

Similar

similar conditions. Rübner (Inv.-Progamm. Marburg 1887) has lately confirmed the work of Page (Journal of Physiology Vol. II) by showing that in air at a temperature of 30°–35°C, the animal is at its minimum of Carbonic Acid production. The amount increases as the temperature of the air falls. This reaction is naturally regarded as the attempt on the part of the warm blooded ~~animal~~ organism to maintain its high temperature by increased heat production. The reaction might therefore be used as the basis of a method for studying the integrity of the heat control in cases where the organism still retains its normal temperature as well as those in which a departure from the normal is observed.

One of the most frequently observed facts in cases of Myxoedema is a subnormal temperature. Corresponding to this we have the subnormal temperature in the artificial conditions which occur after Thyroidectomy -

be

we have also, in contrast to this fall, a rise of temperature in certain conditions of muscular spasm to which I have already alluded.

Temperature changes are much more sharply defined in small organisms than in large, since in them the demands on the heat regulating system are so much greater. Any lesion therefore tells much more rapidly and shows itself much more clearly in small organisms such as cats than in man and the larger animals in which the chronic form of the disease occurs. It is to be hoped therefore that with the advantage of this fact it may be possible to isolate the Temperature changes and throw some light on the Physiological sequence of the symptoms in the disease in so far as these are due to lesions of the heat regulating system.

To obtain the necessary variations in the temperature of the air I made use of a water jacket round the

animal

animal chamber in Dr. Haldane's apparatus. The jacket was made of tin and the outer wall was covered with thick canvas to minimize radiation. It had the form of a cylinder fitting the chamber fairly closely, and the ends were left open so that the animal could be easily observed. Through this jacket a constant stream of water was kept flowing. The temperature of the water from the tap was in the cold weather of winter sufficiently low to cause a distinct fall in the temperature of the air in the chamber. By this means the animal could be kept in air constantly under 10°C. To get the higher temperatures the stream from the tap, before it entered the jacket, was led through a spiral placed in a cylinder containing water kept at a high temperature. By this means the stream to the jacket was heated, and thus there was established a heated atmosphere in the chamber.

By

By making the water round the spiral as hot as possible with the means at command, it was an easy matter to obtain a constant heating power, and the temperature of the stream to the jacket could then be easily varied by increasing or diminishing its rate of flow. The best results were obtained by having a large heating power and a considerable stream through the jacket.

To make observations of this sort the method I generally adopted was to take a cold air period extending over three hours. Then followed a period of hot air for a similar length of time. This was followed by a final cold period, so as to observe the return to the early conditions. To examine more carefully into the time of the reaction I sometimes estimated the Carbonic Acid for each half hour, to know exactly the time of the response.

Two or three points are to be noted in studying the nature of the reaction —

reaction: — (1) The amount of the reaction, and this is indicated by the relative amounts of the Carbonic Acid given off by the normal and pathological animals in the same variations of temperature. (2) The promptness with which the response takes place. This is most easily tested in the passage from hot to cold, as the condition of cold is so much more quickly established than that of heat. (3) The effect of demands for increased heat production on the normal variations of metabolism. In normal animals, fed once in 24 hours, there is a daily decline from morning till night. If the animal be quiet we find for example the quantities of CO_2 for half hour periods falling from 1·4 grams to 1·1 grams. This rule is often broken if the animal find any occasion to move about. If, for example, it begin to clean its fur after it has been sleeping in the Respiration chamber, the muscular exercise increases the Carbonic

acid.

Acid. It will be seen that in none of the observations I have made on normal animals did the cold at the later part of the time cause such a rise as to make the Carbonic Acid then given off equal to that given off in the cold period at the beginning of the observation. As a rule the Carbonic Acid never rose at all, but decreased even after the cold air was supplied again. The abnormal animal on the other hand, invariably gives results strikingly in contrast with this.

We must also note that in the progress of the Chronic Cachexia, when the animal seems to differ very slightly from the normal, there are occasionally outbreaks of the more severe symptoms. The cause of these outbreaks is not very clear, but associated with the condition we find that the reaction we are discussing is much greater during the onset of the symptoms than it is when the animal has recovered -

It is

It is difficult in the normal cat to get a very distinct reaction in periods such as were amply sufficient for obtaining a perfectly marked effect in the abnormal animals. For example the following may be taken as a typical observation, extending over 9 hours, divided into 3 periods —

Normal Cat.	Temp. of Chamber.	CO_2 Gms. per hour.
Period I Cold	13°C	2·59
" II Hot	30°C	2·48
" III Cold	13°C	2·13

The time of observation was increased in length to find if possible a rise in the second cold period, with the following result —

	Temp. of Chamber.	CO_2 Gms. per hour.
I Cold	10°C	2·73
II Hot	28°C	2·14
III Cold	10°C	1·91

The observations were then continued in hours. The earlier having been in periods of 3 hours —

over

	Temp. of Chamber		CO_2 grms per hour.
IV	Cold	10°C	2·25
V	Cold	10°C	1·80
VI	Cold	10°C	2·02

It is evident therefore that the reaction of the animal to cold after the hot period is delayed and that it never reaches the early figure, owing partly to the daily decline, and to the fact that at the late hour of the day at which the last observation was always taken the quiet of the laboratory was greater than early in the day, and the cat had fewer temptations to move about in its Chamber.

Since the three cats which I observed in the chronic stage of the ~~disease~~ Cachexia were losing weight gradually, I thought a fairer standard for comparison with them would be found if I used a Kitten: because the relation of bulk to surface found in the Kitten corresponds more nearly than that found in the healthy adult, to the condition of emaciation.

In

In cats suffering from the Cachexia the condition of emaciation gradually comes on even where the animal continues to enjoy a good appetite. With the loss in weight we have a decrease in bulk without a corresponding decrease in surface. This alters the demands on the heat regulating ~~system~~ mechanism and brings the animal to a condition more or less resembling that of a kitten.
The kitten, however, which was six months old and weighed a little over 1 Kilo, gave for the periods observed a reaction similar to that found in the normal adult cat —

	Temp. of Chamber	CO_2 grms. per hour.
I	9° C	1·75
II	28° C	1·45
III	9° C	1·38

The first conclusion from this series of observations, the whole of which are tabulated at the end of the paper, is that normal cats rely for their regulation as far as possible chiefly on variations

variations of heat loss. This is what one would naturally expect. The power of minimising heat loss from radiation by simple modifications of surface such as are very familiar to observers of the habits of the cat, apparently has a great function in regulating temperature. Further, variation of the supply of blood to the skin and to the exposed areas is another factor which, though less conspicuous than the former, has probably also considerable influence in regulating heat loss. Such physiological factors as these are evidently brought into use before the demand for increase of heat production is felt by the organism.

In cats which are suffering from the Cachexia, either these factors are not called into play in the same order as in the normal animal, or those which are connected with heat loss become relatively insufficient. Here the reaction

by

by increased heat production in response to a fall in the temperature of the outside air is very marked both in its promptness and in the amount of variation in the output of Carbonic Acid which it causes. In addition it is manifest that this abnormality varies with the gravity of the symptoms, and that it more or less disappears on the recovery of the animal. In illustration of this above conclusions we may take the following —

A Cat (No IV) which had never been very ill but which was gradually losing its health gave these results —

I Cold Period at 9·5°C — 2·46 grms. per hour
II Hot Period 29°C — 2·23 " "
III Cold Period 9·5°C — 2·69 " "

This result shows two striking things. The return to increased heat production more prompt than that of the normal animal. And also, in this case, the amount of Carbonic Acid produced at the end of the day in response to the cold is

greater

greater than that obtained in the earlier part of the day. This is characteristic of the Cachectic condition.

The relation of this reaction to the severity of the condition is proved also by the following observations—

Cat No VI when it was extremely ill gave the following result—

Cold Period	14°C	2·19 grms. per hour
Hot Period	33°C	1·03 " "
Cold Period	13°C	2·49 " "

The same animal recovered from this condition to a large extent and in the improved condition it gave a quite different result—

Cold Period	12·5°C	2·44 grms. per hour
Hot Period	27°C	2·31 " "
Cold Period	11°C	2·45 " "

Here the reaction is prompt and thereby differs in character from that obtained in the case of a normal animal, but it is much nearer the normal than it was during the time of its severe symptoms.

A further observation of some interest

interest in this connection I was able to make in the case of Cat No VI. It had never been very much disturbed even in the acute stage, though the tremors were quite distinct. It had lost 25% of its body weight, and when the cold weather came it became very ill, showing general failure. It could not move about and lost its appetite. It occurred to me that an examination of the heat system at this stage might show that the power of heat regulation was gradually being lost. The temperature of the animal was too low to be registered by a thermometer reading as low as 35° C. The CO_2 excretion had fallen in a few days from 1·75 grms. per hour to ·4 grms. per hour. It died on the day following the observation to which I am referring. Here if anywhere the loss of power to regulate heat might be expected to show itself -

I	Cold Period	13° C	1·20 grms. in 3 hours
II	Hot Period	28° C	·99 " "
III	Cold Period	12·5° C	1·01 " "

This

This shows that even when the animal was reduced to extremities the heat regulating function was still dominating the metabolism, and that in spite of the decline which presumably must have been then in rapid progress considering that the animal was so nearly approaching its death.

The cat was very passive during this observation and there was throughout no modification of surface affecting heat loss.

The conclusion to be drawn from this series of observations is that the heat loss seems to be exaggerated in these animals. When the heat loss is increased in normal animals by giving them cold baths the out put of Carbonic Acid increases till a very low temperature, about 30°C has been reached. Below 30° the amount of CO_2 given off begins rapidly to sink. (Pflüger's Archiv vol XII p. 282).

When the heat loss has been increased by cooling the air a similar increase

of

of the Carbonic Acid output occurs (Colosanti-
Pflüger's Archiv vol XIV p. 92)
In those animals which have
lost their Thyroids, the increase in
the out put of CO_2 is out of pro-
portion to the decrease in the tempera-
ture of the surrounding air, if we
take the normal animal as a stan-
dard. It is therefore reasonable to
conclude that the lesion here is one
affecting the mechanism regulating
heat loss, and that the increased
production of heat is an attempt
on the part of the organism to
counteract the weakness and thereby
preserve its normal temperature.
What exactly the form of the lesion
is which is here indicated has not
been determined; but this will
find explanation as the elucidation
of the various forms of the Cachexia
progresses.

The condition might be generally
described as a hyperaesthesia of the
heat productive mechanism, but
that

that there is actually an increase of the response as well as the existence of a greater necessity for relying on it, can scarcely be said to be the case. It seems much more probable from the general results that while the increased readiness of the response exists, it is rather the correlate of an insufficiency in the so called "physical" factors of heat regulation, than the result of an increased readiness in the power of regulation by means of metabolism.

It will be better however to delay the discussion of that point more fully until I have given the analysis of the results.

Another method of investigation which I used in the case of one animal may be mentioned as it would undoubtedly be of use in pathological research into metabolism. It is known that when an animal is fed on carbohydrate food chiefly the Respiratory Quotient, or the ratio of the oxygen absorbed to the oxygen

excreted

excreted in the form of Carbonic Acid, approaches unity. When on the other hand proteid food is taken, the ratio falls. If the metabolism be affected qualitatively, one would expect that this change would not be observed. In the case of Cat No IV I applied this method of observation and obtained at once the physiological reaction due to the change of food.

Cat fed on Flesh (proteids) Quotient ·80–·75
" Carbohydrates " ·85–1·0
" Flesh " ·82–·74

The fact that the quotient rose as high as 1·0 is of some interest. Pflüger in his research into the Oxydation of Living Matter (Archiv 1878) proved that at low temperatures the Respiratory Quotient rises as high as 1%. This result was confirmed by Voltter (Pflüger's Archiv vol. 21) who carried out the same research in greater detail. Here we have a similar condition at ordinary temperatures. It is not possible, however, to make further

further use of this observation as I had no opportunity of confirming it.

Another problem which is closely associated with this is the effect of certain elements in the food on animals in the Cachectic condition. This is most easily studied in the chronic condition, because in the acute stage the complex of symptoms and the rapid progress of them makes it impossible to isolate the effect of any single factor.

It was pointed out by Breisacher (Archiv für Anatomie und Physiologie 1890) that when dogs from which the Thyroid Gland had been removed were fed on unboiled meat or bouillon the symptoms of the Cachexia were developed in a markedly acute form. On the other hand these symptoms were allayed by substituting for this kind of food boiled flesh or milk. The conclusion drawn from this is that the extractives of flesh have by their influence on the animals'

metabolism

metabolism the power of inducing or increasing the severity of the acute symptoms of the Cachexia.

The precise effect, however, is not further defined by Breinacher's experiments.

The above experiments on the variation of the Respiratory Quotient by means of diet seemed to me to indicate that possibly there was no great qualitative difference between the Cachectic and the normal metabolism, and I proceeded to test the effect of the variations in food which I have described. I found that Liebig's Extract of Meat, which consists largely of extractives of beef, could be given in very large quantity without apparent effect. Boiled and miboiled flesh seemed equally to be without any effect which could be appreciated by observation of the animal's symptoms or by an estimation of their metabolism.

For example, animals IV and VI have in the chronic condition been fed

fed for weeks on raw meat, consisting of lungs or liver of bullocks; or this was varied sometimes by a diet of rabbits' flesh. The rabbits' flesh was obtained from the rabbits which had been used in the practical class in the Physiological Laboratory. Occasionally, when the supply was very large the flesh was boiled for the purpose of keeping it longer, but none of these changes of food had the least visible effect on the animals. Once or twice I tried the effect of a meal of the flesh of a cat which had died in the acute stage of the Cachexia. This I supplied to those which had survived and were now in the chronic condition. It seemed probable that, if the symptoms and death were due to an accumulation of some waste product in the tissues of the animal, a diet of its flesh would be even more potent in arousing symptoms than

than the raw flesh of normal animals such as bullocks. This diet the cats consumed without hesitation and apparently without any unusual effect.

I will now give the notes of the experiments on the different animals. The method of observation was changed essentially as the research progressed, and it finally seemed necessary to concentrate the whole attention on the main question of how to explain the phenomena which are here observed in connection with the heat regulating mechanism.

The best plan in observations of this sort is to supply air far in excess of what the animal requires. There are several advantages in doing so. The atmosphere of the chamber is kept practically in the same condition as outside air, and there is no possibility of discomfort to the animal. There is also a saving

of

of time, for with a rapid current the whole apparatus can at once be put into the condition which enables one to begin an observation. To make the first daily observation comparable with those following, it was necessary to run the current for a few minutes before weighing the animal or commencing the estimation of the Carbonic Acid, so that any of the Carbonic Acid which had accumulated during the introduction of the cat and the sealing up of the Chamber would be carried off. At a given time, which should as nearly as possible be the same on successive days, the current, after this preliminary flow had lasted a sufficient time, was stopped and the chamber was disconnected from the absorption bottles and sealed. Then the animal in the chamber and the absorption bottles were weighed. As soon as this was done, say in 10 minutes,

the

apparatus was again connected up and the current was set going ~~again~~ for a definite ~~another~~ period. The amount of air which was passed through the apparatus was about 600 litres an hour. The measurements were thus made by taking the gases of respiration exchanged during comparable periods.

The weighing presented practically no difficulty. The animals were soon accustomed to the process, and remained perfectly still as a rule. Sometimes they would even remain curled up and apparently sound asleep the whole time. During its first experiences an animal would occasionally be very sensitive to any impurity in its atmosphere, as for example if the time of weighing were so prolonged for any reason, as to allow a small percentage of Carbonic Acid to accumulate in the air of the chamber; but even this they soon learned

learned to disregard.

When the apparatus for hot and cold air was used, the weighing was much simpler, as only the Carbonic Acid was estimated, and in fact after the negative results I got at first in Cats No. I and No II, I ceased to take any trouble to observe the Oxygen absorption.

The relation of Oxygen absorption to the reaction to heat and cold on which I have made so many observations, is not so well known and to take account of it, as well as of the CO_2 output would increase enormously the difficulties in making the observations.

Cat No. I

The day after the operation the cat had slight difficulty in breathing, in the inspiratory phase, and it was thought that this might arise from some obstruction due to inflammatory changes in the air passages. This however was not

the

(Cat No. I)

the case, for on post mortem examination the lining of the air passages was seen to be unaltered.

On the morning of the 3rd day after the operation tremors were first noted, and these were well seen when the cat was lifted up from the ground in such a way that its legs were extended. It then trembled violently especially in the fore legs and fore part of its body.

Five days after the operation there were distinct muscular spasms. These were occasional and did not last long. Vomiting also commenced.

On the 6th day it became much worse, and died in the forenoon. There was a fall in the temperature on the last two days. Otherwise it was almost normal throughout. The excretion of Carbonic Acid and the absorption of Oxygen remained nearly constant, i.e. about 2 grms. per hour. The ratio fell steadily till the last day or two when it became

(Cat No I)

became irregular. This fall was no doubt due to the fact that the onset of the Cachexia meant a corresponding onset of starvation.

The last observation in the table is of some interest. The cat was at a very low temperature, below 35° C, and yet it was giving off as much Carbonic Acid (3.91 per two hours) as had been given off in the days before when its temperature was keeping up to the normal. It was plainly unable to take advantage of the heat production of which it was capable. This therefore points very definitely to an increased heat loss on the part of the animal without corresponding diminution in the power of heat production.

Otherwise this method of observation showed no fact that seemed to have any significance. The temperature did not show any tendency to rise or fall till the day

(Cat No I)

day before death when it had fallen about half a degree.

This animal died in the acute stage of the Cachexia. The observations indicated that there was no very appreciable effect on its metabolism, and it seemed necessary to examine a series of animals for the purpose of extending these negative observations. It was remarkable that though the disturbance was so acute as to lead to death, there was no sign of it in more striking variations of the body temperature, or in any quantitative or qualitative change in the metabolism. The only conclusion that could be drawn from this was that the compensating mechanisms which exist in a warm blooded animal particularly in relation to heat regulation had so dominated the metabolism ~~that~~ any actual change in it which had taken place, was completely masked.

It is striking however to find that

(Cat No I)

that the body temperature of the animal remained as constant as it did.

Temperature regulation may be regarded as one of the chief factors in the metabolism of the warm blooded animal and the observations of a constant gaseous exchange correspond to and confirm those of a constant temperature, and since the heat regulation of such animals is so largely due to variations in metabolism it is the more easily understood how in the ordinary summer temperatures of 18°C—20°C in which the animal was when these observations were taken, there should be a uniform metabolism. If there were a lesion of the heat regulating mechanism as a result of the operation, the summer temperature of 18°C—20°C which was constantly maintained was the best means for hiding it, since in that temperature the regulating mechanism is at or near its

minimal

(Cat No I)

minimal activity. It seemed that whatever injury to the heat regulating mechanism there was from Thyroidectomy, it could be brought out only when the animal was subjected to variations in temperature of a more or less extreme kind.

There is, however, in the last observation evidence that the animal's resources for heat regulation were much exhausted. As I have already said, this observation showed that the animal was unable to take advantage of the heat production of which it was capable, but not only was this so but the power of increasing metabolism as the temperature decreased had been lost. According to Pflüger the amount of Carbonic Acid given off increases till the very low temperature of about 30°C has been reached. In this case however there was decline of the temperature for at least 6°C, and yet the

(Cat No. I)

the Carbonic Acid given off was no greater than the ordinary amount for normal temperatures. This suggests that the animal was, as I have said exhausted, and was therefore unable to keep up its temperature longer. It will be necessary to return to these points in the notes on some of the other animals.

After death the animal passed ~~extremely~~ very rapidly into extremely marked rigor mortis. On post mortem examination there was no discoverable local lesion of any sort. The microscopic investigation of the tissues has not been carried far enough to permit of a report on the minute changes.

Cat No II.

The table shows a great uniformity in the observations of temperature and gaseous exchange. This animal was not nearly so ill as No I, and

Survived

(Cat No II.)

survived the acute stage. While in the acute stage it suffered from twitchings which were fairly marked especially on exposing it to cold by placing the Respiration Chamber in iced water. But it never had the general convulsions which were seen in some of the other animals. The tremors passed off after 4 weeks and its appetite returned. It never got perfectly over the effects of the operation however, though it did not seem to suffer the least pain. Its fur was always a little out of order, and it gradually lost its weight. When I came back to Oxford in October it had become distinctly worse and the progress of the Cachexia seemed to be much hastened by the approach of the cold weather. The effect of the cold in increasing the tremors had been observed in the acute stage of the Cachexia in the same animal.

It died 4 months after the operation. Before its death it was

Quite

(Cat No II)

quite stupid, and mucus gathered a little about its eyes.

On post mortem examination the whole of the body was found to be much wasted. The muscles were very pale in colour, almost white in places. There was no Accessory Thyroid Gland. Further examination of the changes by means of the Microscope has not yet been carried out.

The observation of its reaction to cold was tried in the acute stage but it showed at that time no change from the normal condition. The same experiment was done the day before it died with the result to which I have already alluded. It was this last result which suggested to me that a lesion of the heat losing mechanism was probably the form of the disease in so far as it is a disturbance of heat regulation. In this animal also, as in the first, we have two days before death a temperature of 36·6°C.

This

(Cat No II)

This is a fall of 1·5° — 2°C below normal, and yet the Carbonic Acid metabolism keeps as high as it was, say, 4 months before, when the temperature was normal. The air was at the same or nearly the same temperature as on the earlier occasion. There must therefore have been an increase of the heat loss by the animal and with this it was unable to cope.

(Cat No III.

Here we have an example of the extremely acute form of the Cachexia. The symptoms could not have been more pronounced. The interest of the observations is that the Carbonic Acid excretion keeps uniform throughout. The temperature again falls 1·5°C or more during the time the cat lived after the operation, and yet the excretion of Carbonic Acid continues about the same in amount.

The

(Cat No III)

The temperature of this animal showed no tendency to rise though it was taken before and after the most marked convulsions. One must therefore conclude that the rise of temperature sometimes seen in dogs is not a necessary correlate of the muscular twitchings in all animals suffering from the Cachexia, even in the most acute form.

Here also one must remark that the uniformity of the Carbonic Acid excretion during the occurrence of fits so extreme in type and involving so much muscular effort is also surprising. It suggests the need for an enquiry into the Physiological Sequence of the symptoms in this condition. Had the convulsions been a part of the primary lesion one might have expected to find that with their occurrence there was a great rise in the output of Carbonic Acid. It is impossible however to do more here than indicate

(Cat No III.)

indicate the bearings of these observations on such problems as convulsions in their relation to Metabolism.

No further examination was made with reference to heat regulation.

This animal was apparently young, but as it was purchased with five others from a place at some distance from Oxford, it was impossible to make out its age exactly. It was the most vigorous animal as yet used.

I found it a rule that the Cachexia developed in its most pronounced form invariably in such animals, and that after a little experience of the animals one could almost a certainty foretell the result of the operation as regards the gravity of the symptoms ensuing. Cats with great vigour, and especially when that expressed itself in a very bad temper, were found to be the best subjects for developing the most acute forms of the Cachexia.

Another

(Cat No III.)

Another feature of the Cachexia which I began to observe in the cases which I was examining is its rapid onset. In this animal the tremors were observed the day after the operation. This or something very similar may be expected as a rule in cases where the Cachexia is about to develope in a severe form.

This animal showed profuse salivation, a more or less rare derangement which has been noted by Prof. Horsley. Though not entirely connected with the occurrence of attacks of convulsions, this was definitely increased on the occasion of such attacks. It was seen that generally when the crisis of the convulsions was past the saliva dropped from the cat's mouth.

It also suffered from marked Dyspnoea. That this was not due to a disturbance of the mucous membrane of the trachea was found on making a post mortem examination,

and

(Cat No III)

and it was also observed that occasionally the obstruction to the breathing seemed suddenly to disappear for a while. It was always found that, as in this animal, when the general nervous disturbances are marked, the Dyspnoea also assumes a pronounced form. Another fact of interest in regard to the Dyspnoea is that it may pass off before other symptoms occurring with it in the acute stage do, so that even in animals which die, the Dyspnoea has occasionally begun to disappear before death. It also became less marked after an attack of convulsions. It was found that the lungs had patches of Emphysema in such cases. The post mortem examination by naked eye showed no changes in the tissues. The wound was perfectly healthy.

Cat No IV

Cat No IV.

The fourth cat was a contrast to the third one in every way. It was a cranky ill nourished cat possessing an imperturbable temper. It submitted to observations in perfect good will, and disturbed itself for nothing but to display the state of its appetite which was invariably perfectly sound. It had almost no symptoms, but a general failure of nutrition set in slowly, and seemed the only evidence that the balance of the organism had been interfered with. It had soon after the operation also a little hoarseness and difficulty in breathing. The first effect of the operation was to cause a great increase in the cat's appetite, a result which has sometimes been observed by other investigators.

No distinct tremors could be made out. Its gait was rather curious when it walked about.

It

(Cat No IV)

It would lift up its paws from the ground continually and shake them as cats do when they are shaking off water. It also shook its head with considerable frequency, but these were rather the accompaniments of the Cachexia than the actual symptoms. The animal has throughout suffered from vomiting occasionally, but this not very frequently. It has failed markedly in body weight in spite of its continued appetite. In December it weighed 3·103 grammes, and at the end of March it weighed 2·570 grms. Towards the end of April it weighed 2·2778 grms.

On this animal I tried the effect of diet on the Respiratory Quotient. What one might expect was that a derangement of nutrition would cause some modifications of the relation which the Quotient bears to the nature of the food taken. This animal however, reacted in the most prompt manner.

But

(Cat No IV)

But I have not yet had opportunity to study this reaction sufficiently to show to what extent it can be used.

I did experiments also on the heat regulating mechanism. I found that the reaction obtained differed very markedly from that given by the normal animal; but that compared with other cats in which the other symptoms had assumed the most acute form, the reaction did not show the marked difference in the quantities of Carbonic Acid.

Cat found dead on the morning of April 20th 1893. 8 months after the operation. A careful post mortem examination was conducted, particularly in order to find if possible any evidence of accessory Thyroid Tissue.

The temperature of the animal the night before it died was 39·6°, and this puzzled me a good deal as I could find nothing that might occasion

(Cat No IV)

occasion such a rise. Its temperature when last observed had been distinctly lower than this. On March 16th, it was 38°C and 38·2°, at the beginning and end of the day. On the 17th it was again 38°. So that a temperature of 39·6° meant that there had been a rise of 1·5°.
Next day, (April 20th) on making the post mortem examination, I made the following notes —

Cat's fur was very unkempt — The skin was thin and wasted — There was exceedingly little subcutaneous tissue. Here and there there was a small strand of fatty tissue. The whole tissue was abnormally dry and seemed almost free from Lymph and Blood. The larger blood vessels contained a little fluid blood, venous in colour, but there was a great deficiency in the amount of blood distributed through the tissues. The neck was carefully examined for remains of the Thyroid or ~~and~~

(Cat No IV)

or accessory glands. There was not the slightest trace of anything of this nature. The whole of the tissue of neck was dry and white, and nothing would have been easier than to detect the least trace of Thyroid tissue. The muscles were very pale in colour. A few of the lymphatic glands of the neck were enlarged. One very much enlarged was situated about the upper level of the Thyroid Cartilage, on the right hand side. The Cerebro-spinal nerves in the neck seemed to be wasted. The Sympathetic ganglia in the neck seemed normal. There was no enlargement of the Carotid ganglia. The organs of the abdomen were next examined. They also were dry and anaemic. The wall of the intestine was thin & wasted, and very white. The liver was of normal size, dark in colour, with traces of fatty degeneration. The spleen was apparently normal. It showed no

wasy

(Cat No IV)

waxy degeneration by the Iodine test. The pancreas was exceedingly white in colour, but of normal size. The Kidney was extremely white. The cortex was very pliable and showed great anaemia and fatty degeneration. The Suprarenal capsules were fairly large. They had the same pallor as the Kidneys. The mesenteric glands were enlarged, and had a grey gelatinous appearance. When the chest was opened it was found that both pleural cavities contained an enormous Quantity of purulent fluid. There were remains of serous inflammation on the diaphragmatic and mediastinal pleurae, but more on the surface of the lungs. The lungs were greyish in appearance and much compressed by the surrounding fluid. They were not at all consolidated, nor was there any trace of tubercle visible. There was a certain amount of oedema but the whole tissue was crepitant.

The

(Cat No IV)

The first suggestion was that the cat had died of pleurisy and empyema of a tubercular form, and a diligent search was made for tubercle bacilli in the old granulation tissue. The tissue was swarming with micrococci of various sorts and a few scattered bacilli of the large rounded type often ~~found~~ present in sputum were found, but no tubercle bacilli.

The tissues of the body are being hardened for a thorough microscopic Examination.

There was no hypertrophy of the pituitary body. The cord was covered with a plentiful layer of greyish fat. No abnormalities were seen in it.

What must first be decided is the question whether the Empyema was due to tubercle or not. This can be done by a careful examination of the lungs with the microscope.

The fact of the double empyema was striking, but since doing the Examination I have heard on the authority

(Cat No IV)

authority of Prof. Smith of Aldershot that very often the double character of an Empyema has no significance in the lower animals as their pleural cavities so often unite.

Should it so happen that there is no tubercle present it will be possible to regard the morbid changes as one form in which a small animal may be affected in Chronic Cachexia Strumipriva and interesting matter will be obtained for comparison with Myxoedema.

Cat No V

In the case of the fifth animal the facts were exactly parallel to those seen in No III. The cat was a vigorous male which was fully grown. It is interesting to note in the first days' observations the effect on the Carbonic Acid of different factors. To begin with the animal was very restless and

anxious

(Cat No V)

anxious to make its way out of the Respiratory Chamber. During this activity it gave 4·8 grms. of Carbonic Acid in the hour, as compared with 2·14 grms. at the end of the day when the laboratory was quite quiet. The muscular tremors began to appear on the day following the operation. They were fully more severe in this animal than in No III. There was no salivation. During a fit the pupils were widely dilated. There was also quick shallow breathing with dilated nostrils. These symptoms disappeared when the fit had passed off.

Occasionally when the muscular spasms were less pronounced, they were seen to be distributed in definite groups of muscles. Affecting one side or one limb. Sometimes they were most marked in the hind limbs and again in the fore limbs.

In this animal the difficulty of breathing was never so marked as in

(Cat No V)

in other animals which showed the other acute symptoms of the Cachexia.

The examination made post mortem revealed no abnormality. There were some small patches of Emphysema in the lungs, and patches which were apparently collapsed, but there was no general change. The rest of the organs showed no changes apparent to the naked eye.

The only remaining fact to note here is that the temperature slowly but steadily fell during the 8 days on which the animal remained alive. Even when the temperature had fallen at least 5°C the output of Carbonic Acid was still almost the same as it had been when the temperature was normal. It seems difficult to interpret this result in any other way than by saying that the animal had an exaggerated heat loss. For if we

may

(Cat No V)

may take the amount of Carbonic Acid given off as an index of the amount of heat produced, the animal was producing heat enough to keep its body at the normal temperature, had its been able to make use of it to the same extent as it did before it had lost its Thyroid Gland. This observation should also be compared with that of Pflüger, referred to above, in which he shows that warm blooded animals whose temperature is lowered artificially increase the amount of Carbonic Acid excreted till a temperature of about 30° is reached. That this did not here occur is evident from the fact that the animal produces not more Carbonic Acid than it had given off in the normal condition, or when the temperature of the air and that of its body were both normal. It therefore seems that the limits of its heat production were

(Cat No VI)

were more easily reached than in a normal animal. This helps to explain the fact which was discovered by Prof. Horsley that cold had a most harmful effect on these animals, and that the fatal effects of the operation could be long delayed by keeping them in a moderately warm atmosphere. The same observation has been made on No I and No III and it will be referred to again in relation to further experiments to test the heat regulating function.

Cat No VI.

The sixth animal was of great interest because though it had its Thyroid Gland removed on August 8th 1892, it is still alive, April 1893.

It had also a fairly marked acute stage. When the cold weather of winter set in it had a recrudescence of the acute symptoms, and again it

(Cat No VI)

it has apparently recovered more or less completely.

In the case of this animal I have been able to confirm the observations which I made on former animals in all respects. In regard to the heat regulating function I was able to take a series of observations when the animal showed the acute symptoms, and again when it had recovered. What is to be noted is the extremely pronounced character of the reaction both in its extent, and in its promptness. When the animal recovered from the more acute symptoms the striking character of the reaction tended to disappear. Thus for example when it was ill in November it gave a reaction which was very striking —

Cold Period	14·5° C	2·19 grms. CO_2
Hot Period	30°	1·03 " "
Cold Period	13·5°	2·49 " "

Thus

(No VI)

This means that for a fall of under 20° C in the surrounding air the metabolism goes up to over 100% above what it was while the air was hot. Colosanti (Pflüger's Archiv vol XXV) calculates from his observations on normal animals that for a fall of 1° C there is a rise of 3% in the metabolism of guinea pigs. A guinea pig being a much smaller animal than a cat must possess a much more sensitive heat regulating mechanism, yet in this cat we have a condition where the reaction for cold even in the short period of three hours is found to be nearly double that of normal guinea pigs.

The observations on this cat are particularly interesting because in January when the animal seemed to have completely recovered, the reaction which it gave, though differing essentially from that of the normal cat, was much

nearer

(No VI)

nearer it than that given at the time of the observations in November.

The cat, except that it lacks activity, seems now to have recovered altogether and its weight is increasing.

In December 92 it weighed 2·927 Grms.
" January 93 " 2·957 "
" April 93 " 3·097 "

It is now kept under careful observation as to food, temperature, etc. It is difficult to account for its recovery. But it is by no means certain that its recovery is permanent. Its neighbour No IV has just died April 20th, and it may be that this appearance of recovery is merely a temporary one.

On the other hand it may be that an accessory Thyroid Gland exists in this animal. Such an abnormality has not yet been observed in the cat; but as it does exist frequently in other animals, it naturally occurs to one to explain the

exception

exception in this way. Other reasons for its survival are not apparent.

Cat No VII

The observations on this animal, which are five in number, are all simply for the purpose of finding a standard for comparison of the normal and abnormal animals.

It will be seen that in each case the observation shows that in the nine hours usually taken for one observation, the increase of metabolism for cold is never so great nor is it so promptly brought about as in the animals suffering from Cachexia Strumipriva.

In one case (5·12·92) where I prolonged the observation further and took estimations for each hour, it was seen that the metabolism increased a little as compared with that for the period when the animal

(No VII)

animal had hot air; but this was still far from the condition of the Cachectic animals where in the three hours succeeding the hot air period we find a metabolism as great, sometimes even greater than that seen in the first period of cold. That it should sometimes be greater suggests that such an animal becomes less able to resist the cold as it becomes hungry or as the immediate supply of food is exhausted. This characteristic of the Cachexia shows generally what may in many cases be the Physiological reason why cold tells so much faster on men and animals suffering from any wasting disease than on those which are in perfect health. For among these observations is one which I took after the cat had had no food for three days. The results noted in this observation on the fourth day

(No VII)

day (16·12·92) do not differ essentially from those given by the cat when fed in the usual manner.

No VIII. Kitten.

It is interesting in the same connection also to show in the case of a Kitten the effect of variations in Temperature. By this series of observations I hoped to eliminate the fallacy which exists in the conclusions drawn from the other results because of the condition of emaciation which supervenes after the operation of Thyroidectomy if the animal live for some time. The kitten has a much larger surface compared with its bulk than a cat has. As emaciation progresses in the adult cat, the surface remaining constant the bulk continually decreases, and the animal comes to resemble a Kitten. It will be seen, however, that

(No VIII.)

that in this respect a kitten is not so different from the adult cat as one might expect. The kitten I used was about 1 kilogram in weight and was six months old, i.e. about half grown. The reaction closely resembles that given by the adult cat.

The observation on December 21st was an extremely long one, but even at the end the amount of Carbonic Acid given off was not brought up to that given off in the morning, though cold air had been supplied for 7½ hours.

It may therefore be concluded that the reaction which the cats give in the Cachexia differs Physiologically from that given by a normal cat in any condition, and that in this difference we have one of the characteristics of the condition.

The remaining point to be determined in completing the study of the Heat Regulation was whether or not

(No VIII)

or not this Physiological difference had already established itself in the acute stage of the Cachexia. That I had not already examined this point was due to the fact that only when I was studying the condition of these in the chronic stage of the Cachexia did I get a hint as to the existence of a Physiological lesion of this form. What therefore might logically be regarded as the first came actually to be the last step in this research.

Cat No IX January 1893.

The question which remained to be settled at this point was what is the behaviour of the heat regulating system in the acute stage of the Cachexia. In the case of the sixth animal I made a number of observations on the normal ~~animal~~ reaction and confirmed the results I had

(No IX)

I had already obtained in the case of other animals.

After the operation I was able unfortunately to make only one observation, owing to the fact that the apparatus I had stopped working, and before I could have it repaired the cat died. The observation I did take, however, showed that the change had taken place in the heat regulating System. But it is not nearly so simple as the modification, which is found in the chronic condition.

The cat was at the stage at which it suffered from Dyspnoea at ordinary temperatures and the Respiratory distress was increased to a most marked extent when the temperature of its atmosphere was raised to near 30°C. This amount of heat was causing the distress though the out put of Carbonic Acid had fallen markedly. The normal cat ~~at 30°~~ in air at a temperature

(No IX)

temperature of 30° usually indulges in a prolonged sleep, and seems to find great pleasure in the warmth.

I had intended to take an observation for an hour further as I had turned on the hot air for two hours only, but considering the amount of discomfort which the rise of temperature was giving the cat I turned on the cold air. This gave instant relief and in a few minutes the cat was breathing with moderate quiet as before.

The amounts of Carbonic Acid given off in the two successive hours contrast very much with each other, and considering the amount of Respiratory distress one must conclude that the animal's blood was storing up the Carbonic Acid. Somehow or other the lungs were, while the heat lasted, unable to get rid of the CO_2. What was exactly the cause of this inability it is not easy

to

(No IX)

to say. It was observed again in the case of the next animal. That it was not a mere storage of CO_2 in the blood and tissues of the body, is evident from the fact that we continue to obtain very large quantities of Carbonic Acid during the time the observations were made afterwards, i.e. for 1½ hours more. These quantities were much larger than what was obtained in the earlier part of the day. This Type of result we have already seen in the case of animals in the chronic condition, and it seems to be a fairly constant one.

The rise of temperature at death is of interest. From all the other observations I have made on Temperature I mean could get evidence that the cat showed a rise of temperature, in the way which has been observed in dogs by Professor Horsley and others. In dogs

the

(No IX)

temperature has been found to rise as high as 4° or 5° C above normal. Taking 38.6° as the normal for a cat we may regard this temperature as a rise of 2° C. he must therefore conclude that this rise is one of the rarer symptoms of the Cachexia in cats. This cat I should add was the only white cat amongst the ten. Its white fur would tend to prevent its skin from radiating so freely as that of coloured animals.

Cat No X.

Seeing I was not able to make further observations on Cat No IX I did the operation on another cat for the same purpose.
This cat was much less vigorous than the former, and I hoped that the symptoms would be less acutely developed, and that I would therefore have a greater

number

(No X)

number of days at my disposal for making observations. In this I succeeded and I made several observations which confirmed the single observation I obtained in the case of the ninth cat. They resembled it more or less exactly, except that as the symptoms were in this cat less in degree, so was the reaction less marked.

The day after the operation the tremors had commenced and I obtained a reaction to change in air temperature which in a measure repeats the one obtained with Cat IX. The amount of Carbonic Acid was greatly increased when the cold was supplied after the period of hot air, and the amounts given off continued large through the three hours of the cold air period during which the observation was made.

Next day however when the cat seemed less disturbed and abnormal

the

(No X)

the reaction resembled that of the normal cat. The fact that the reaction was not obtained with mechanical regularity is what one would expect when it is remembered that the progress of the Cachexia is not absolutely regular.

It should also be noted that with increasing gravity in the symptoms we have a more marked modification in the heat and cold reaction.

On the last occasion when the tremors were more distinct this reaction is again observed. On the remaining occasions we see still the same reaction but in a less marked degree.

It may therefore be concluded that with the establishment of the Cachexia Strumipriva, and while it lasts, we have a lesion of the heat regulating system causing an exaggeration in heat loss.

In the rapid changes which occur in the acute stage we have several points of interest in the form

of

of reaction. Some of these are worthy of attention in detail.

To begin with that given at the date 2·3·93. We note that there is a decline in the output of Carbonic Acid in each of the three periods as they proceed –

	CO_2 grms. per hour		CO_2 grms. per hour		CO_2 grms. per hour.
Cold	2·24	Hot	2·40	Cold	3·45
	2·00		1·99		3·38
					2·85

Contrast with this the observations taken at date 9·3·93, and we have exactly the opposite condition. The reaction has a form which might properly be called the reverse of this –

	CO_2 grms. per hour		CO_2 grms. per hour		CO_2 grms. per hour
Cold	1·33	Hot	1·45	Cold	
	1·74		1·86		1·21
	1·72		1·86		1·88

Here the quantities increase in each of the three periods.

The fact that this change of type has taken place even in the short

time

time during which the animal lived, indicates the great rapidity with which the Cachexia is developing, and explains so far the irregularity of the results as compared with those obtained from animals in the chronic condition.

The meaning however of these variations in type could not be explained by the information we have as yet at our command.

Though Pflüger was the first to point out that in the intact animal a fall in the Temperature of the skin or even of the rectum (if not below 30° C) caused an increase in the animal's metabolism; yet he did not admit that the metabolism of any of the tissues in the body was other than proportional to the rise and fall of temperature directly as in the cold blooded animal. To prove this he ~~did~~ conducted an investigation on animals which had been curarised,

for

for by means of this the control which the nervous system exercises in the metabolism of the body was destroyed. He found in these conditions that with a rise of temperature the out put of Carbonic Acid and absorption of Oxygen rose in proportion. Consequently the fact that the minimum metabolism occurs at 30° C in the warm blooded animal is entirely due to the influence of the nervous system.

Rübner on the other hand, in the paper I have already quoted, brings forward the hypothesis that there are two kinds of metabolism in the warm blooded animal, the muscular and the glandular. At different temperatures these enter into the total metabolism in different proportions.

For animals in starvation he gives the following figures for the respective quantities —

(No X)

	Muscle	Gland
0°C	55.5%	44.5%
10°C	40.7 -	59.3 -
20°C	19.9 -	80.1 -
30°C	0 -	100. -

It is not possible to regard this as more than a hypothesis nor are we able from these theories to come to any conclusion which explains the facts before us. What we observe is that this is not the type of reaction which we have obtained either in the normal animal or in those animals which suffered from the chronic symptoms of the Cachexia.

In this ~~animal~~ cat we have again to note the gradual fall of temperature throughout from 38.2°C to 34.5°C, and get on the day on which it was at 34.5°C it was still giving off Carbonic Acid in amounts equal to those given off when it was in a normal condition. This observation confirms

confirms those made on the other animals and calls for the same remarks in its explanation.

We have now before us the material of the research and it remains for us to consider the bearing of the results so far obtained.

The research has an appearance of empiricism from the fact that for a long period only results of a negative nature could be obtained. It was indeed somewhat late in the investigations that I obtained the least light on the nature of the lesion of the Heat Regulating Mechanism.

In the first part of the work I was much at a loss to account for the fact that I was never able to obtain the rise of temperature which has been observed in animals suffering from

from the great muscular twitching which occurs in the acute stage of the Cachexia. It seemed to me that I could scarcely have induced in any animal symptoms more severe than those which I have described. There was therefore no other explanation than that in this respect cats differed from dogs. That this is after all a difference in degree I found when I examined Cat No IX for in it, when it died after extremely marked twitchings I found a rise of temperature of 2°C; but that a rise in temperature is much rarer in cats than in dogs is quite certain, and apparently when it does occur it is never so great.

When I was making observations on Cat No II, I was much surprised to find that even when the animal was just about to die, and when its temperature was so low that it

it failed to raise the mercury in the thermometer at all, it had still the power of varying its heat production. That it was extremely far gone is apparent from the fact that the CO_2 given off by it then had decreased to about one third of what it formerly had been. Apart from its bearing on the investigations before us, this observation is of interest as showing the hold which the function of temperature regulation has on the metabolism in the warm blooded animal, and proves that in this respect it is extremely difficult to alter the character of the metabolism. The possibility of alteration that one naturally thinks of is that we might find a change more or less in the direction of the condition of the cold blooded animal where it is the direct influence of temperature and not

Temperature

temperature regulation that is the dominating factor in the metabolism. There was as we have seen no such change. Still it was by taking up the suggestion given by this observation that I arrived at a working hypothesis by which to explain the results I had obtained. The from conclusion from these observations is that in the Cachexia Strumipriva we have a lesion of the heat regulating mechanism by reason of which the cachectic animal suffers from cold greatly out of proportion to the degree of cold to which it is exposed.

The meaning of a heat regulating system for the animal is, if we may speak of it in a semi-teleological fashion, to give its life a wider range. Its normal temperature is also its optimum temperature and by

by means of its regulating mechanism it is able to preserve this through the range of external temperatures in which life is possible. By contrast to this, in the cold blooded animal where regulation of this sort is absent, the same range of external temperatures causes correspondingly large variations in the animal's vitality.

From what I have said in regard to Cat No II it is evident that any lesion of the heat regulating mechanism, though it may not make itself apparent by any striking change must have the most profound effect on the animal's metabolism.

The organism disabled in this way makes a ceaseless attempt to recover itself till it dies in the effort, and possibly even because of the exhaustion which this causes.

By establishing in the animal's atmosphere

atmosphere temperatures which brought into prominent use its heat regulating mechanism. I was able to make out in each case on which I had the opportunity of making an observation that the animal relied on its heat production for sustaining its temperature in the cold much more than it does in the normal condition. This I infer from the fact that its minimum metabolism which is that occurring when the air is at a temperature of 30° C was so much less than that occurring in cold air (under 10° C). This large difference in the amounts of Carbonic Acid for hot and for cold air I have never been able to obtain in the normal animal. The normal animal seems to rely primarily on its regulation of heat loss, and I interpreted the observations I made by concluding that

that the operation of removing the thyroid gland had somehow or other paralysed this function and compelled the animal to rely on its power of modifying its heat production. It is easy to see how by reason of this a condition of wasting must eventually set in, the drain on the resources being greater and greater as the lesion becomes more pronounced. The animal sinks lower and lower in its temperature, for with the exhaustion which supervenes it gradually becomes less and less able to reach the height of the normal temperature.

If the progress of the affection be slow, the fall of temperature will be slow also, or it may even in some cases become permanently subnormal to a definite number of degrees.

The progress of the Cachexia in the acute stage is so rapid that it

Why then were not a warning note produced?

it quickly brings down the temperature even as much as 4°, and the sign of exhaustion is seen in the fact that then only as much Carbonic Acid is produced as was formerly given off when the temperature was normal. This shows that the fall in temperature is due to the ~~heat~~ lack of ability on the part of the animal to go on producing an abnormally large quantity of heat.

It has been observed that when the fur is clipped from rabbits and their heat loss thereby permanently increased, the body temperature falls below normal and keeps permanently at this lower point while the increased heat loss continues. The results of the present investigations point to a similar factor in the lowering of the body temperature of animals in Cachexia Strumipriva and

presumably

presumably also of patients in myxoedema.

The conclusion that there is a specific lesion of this sort is not however entirely free from difficulties, and to these I must now refer.

From observations which Rübner has made on guinea pigs, it is known that an animal which is starving reacts much more readily to changes of external temperature, than one which is fully fed and especially if it have proteid food. This suggests that the results which I have obtained are due to starvation. There are however several reasons against this. I tried a moderate starvation of 4 days' duration, and found that the reaction to changes of temperature was not essentially modified as compared with that in the normally well

fed

fed animal. Doubtless the periods of nine hours I used for observations were exceedingly short for cats; but I wished to take advantage of this fact, because being amply sufficient for the cachectic cats, it brings into relief the difference between normal and abnormal animals. On this ground I do not bring forward this observation on starvation as in any way contradicting what Rübner obtained in the case of guinea pigs.

Another difference between the Cachexia and starvation is the fact that in the acute stage when the animal could not possibly be in a condition of starvation the reaction was readily obtained.

Finally in the chronic condition in which some of the cats continued for months, they had a perfectly good appetite and ate food freely. In two of these

there

there was a gradual loss of weight in spite of their having taken food, and they invariably showed the abnormal reaction. There is a distinction between the wasting of a chronic Cachexia when plenty of food is being taken and the wasting of starvation. It would be more just to say that the wasting and the abnormal reaction to heat and cold were equally symptoms of the same condition.

The consideration of the reaction accordingly makes it possible to apply the conclusions of this research to the explanation of the subnormal temperature which it is well known is one of the prominent symptoms of Myxoedema.

To complete the application of the results to the explanation of Myxoedema, what is necessary is that a direct observation of a patient should be made; but

I may in the mean time point out one or two resemblances between the two cases, which justify the comparison.

In a case of Myxoedema in the ordinary chronic condition we have a patient who, ~~is~~ not in a condition of starvation from lack of food, suffers from an abnormally low temperature and from the feelings which accompany a too rapid loss of heat from the surface of the body. In addition to this it is known that equally for patients and for cachectic animals, to establish a moderately high temperature in the surrounding atmosphere is of great value in relieving acute symptoms, and in the case of animals of prolonging life. My own experience with animals was that the symptoms of those in the acute as well as of those in the chronic stage were affected

affected by Temperature. Cat No II continued almost free from symp. toms, though it lost in weight, through the warm weather of summer 1892. When the cold weather of winter set in, it became exceedingly ill and died in a few days. A similar, though not fatal change happened in the case of Cat No VI. We must remember also the interesting fact observed in the cases of Cats IX and X, that a rise in temperature seemed almost more disturbing than than the cold. In Cat IX especially a Temperature of 30° C caused intense distress, as I have already explained in giving the details of the observations. To a less degree the same thing happened in the case of Cat X. Cat VI in the chronic condition suffered very much from the heat if the temperature rose over 32.° C. This confirms an observation

which

which Parson made on dogs when he was examining them for the effect of thyroidectomy on nitrogenous metabolism. What exactly such a phenomenon means however, is not clear. The animal in the cold evidently loses heat too quickly. In the hot atmosphere the change seems more to concern the giving off of Carbonic Acid than the giving off of heat. Yet if the animal suffer from a condition corresponding to the dry skin of myxoedematous patients, one would expect that its heat losing function must be seriously disabled, as far as its function of regulating for high temperatures is concerned.

Again it is possible that a lesion which affected the loss of heat, or the physical side of regulation, might give rise to the phenomena we have under consideration. If, for example, the skin had

ceased

ceased to act in the normal way of preventing the flow of heat outwards when the animal was exposed to external cold, then when the temperature of the surrounding medium was raised it would probably be from the same cause equally unable to prevent the flow of heat in the opposite direction. For example if the vascular element in heat regulation were rendered functionless there would be a disturbance which in all probability would tell both ways.

The apparently contradictory phenomena may therefore spring from the same cause.

This however scarcely seemed the explanation of the whole case, for the relief due to the cold was far too sudden to be caused by a lowering of the animal's body temperature.

We are introduced in this way to

to the general question of what might be called the Physiological Sequence in the complex train of Symptoms before us. If we possessed the answer to this question, we could proceed with confidence to a comparison of Myxoedema with the Cachexia Strumipriva.

In the first place what requires to be explained is how far the phenomena to which I have referred as characteristic of this particular form of Cachexia, and how far they are to be found in other forms of Cachexia, or conditions of tissue wasting. To do this it will be essential to contrast the present observations with a similar examination of such forms of Cachexia as are seen in Phthisis and other febrile diseases.

Experimental investigations so far have shown that the chief symptom which is present in

patients

patients who suffer from Myxoedema, as well as in all forms of the Cachexia Strumipriva, is the fall in temperature which comes on sooner or later. In small animals such as cats, dogs, and rabbits, true Myxoedema has not been obtained, but in them temperature changes are on the whole much more acute than those seen in larger animals. In sheep, and monkeys, and some other large animals, Myxoedema has been obtained by Professor Horsley, and there show slowly developing changes in temperature.

Any explanation of Myxoedema must include in it the reason for this difference between large and small animals.

Further, for the solution of this problem there is required a much more careful study of the various symptoms of the Cachexia than has hitherto been bestowed

bestowed on them. The symptoms I refer to are such as the difficulty in breathing which is invariably the first phenomenon to appear, and which exists altogether in the earlier part of the Cachexia and never beyond the acute stage. Various other symptoms which I have described as occurring in the acute stage fall into the same group. Generally speaking, the condition of the vaso-motor system requires study. This system naturally suggests itself as that in which we may probably find the explanation of the changes in heat regulation.

What is required however before proceeding further on the lines indicated is a thorough investigation of the changes in nitrogenous metabolism which occur in the Cachexia in the acute and chronic stages.

This

This I have already so far carried out.

Closely connected with the foregoing research and those which I have suggested as arising out of it, is the problem of the treatment of Myxoedema and allied conditions by the administration of the Thyroid Gland taken from healthy animals. The success of this method of treatment leads one to hope that by means of it we may be able to discover the best possible method for studying the disease experimentally. For if we have in our hands the means of restoring the animal approximately to its normal condition, we can hope to isolate the essential changes of the disease in a way that would be impossible on any other method.

Tables of Observations.

Cat No I

(1)

Note - The CO_2 & O are given in grammes, and along with the actual amount for the period observed, the amounts per hour are given, for the sake of comparison. The periods in this table are chiefly of two hours' duration.

Date	Temp. of Cat	Temp. of Chamber	CO_2 for period observed	CO_2 per hour	O for period observed	O per hour	Quotient	
8·6·92	39·3°C	22°C	4·94	2·47	4·09	2·04	·88	Normal Cat
			4·57	2·28	3·90	1·95	·84	
10·6·92		22°C	5·29	2·64	4·65	2·32	·82	
20·6·92	Experiment of Thyroidectomy -							
21·6·92	39·3°C	17·5°C	4·66	2·33	4·03	2·01	·81	During the whole
		"	5·73	2·86	5·13	2·56	·80	day the cat
		18·0°C	6·04	3·02	5·50	2·75	·79	slept quietly.
		18·3°	5·20	2·60	4·99	2·49	·75	There were no signs
		18·8°	4·79	2·39	4·40	2·20	·79	of discomfort apart
	38·6°	18·5°	4·84	2·42	4·65	2·32	·75	from a little difficulty in breathing. On coming out took 20 grms. flesh & 140 c.c. milk.
22·6·92	39·2°C	18·2°	4·56	2·28	4·25	2·12	·77	Cat still very
		19·5°	4·12	2·06	3·97	1·98	·73	quiet. It has
		19·5°	4·24	2·12	4·17	2·08	·74	slight difficulty
		19·3°	3·91	1·95	3·64	1·82	·78	in breathing. No
	39·5°	"	4·33	2·16	4·12	2·06	·76	evidence that it is suffering pain. Took at night 82 grms flesh 230 c.c. milk
23·6·92	39·3°C	16·0°C	4·44	2·22	4·35	2·17	·74	Tremors appearing
		18·5	5·06	2·53	4·80	2·40	·76	when Cat is
		39·5°	"	3·63	1·81	3·43	1·71	·77	lifted. These disappear when it lies down to rest in the chamber. Wheezing in breathing. Took 62 grms. flesh 40 c.c. milk.

Cat No. I continued — (2)

Date	Temp. of Cat	Temp of Chamber	CO_2 for period observed	CO_2 per hour	O for period observed	O per hour	Quotient	
24·6·92	39·1°C	18·0°C	4·27	2·83	3·81	1·90	·81	
25·6·92	38·4°C	19·0°C	3·90	1·95	3·88	1·94	·73	Cat shows very marked twitching when it attempts voluntary movements.
27·6·92	Below 35°C		3·26	1·63	2·85	1·42	·83	Observation extending over 1 hour 40 minutes at the end of which Cat died in the Respiration Chamber — Immediately after death its temperature was 35·1°C

Cat No. II

(1.)

Note. The CO_2 and O are given in Grammes, and along with the actual amount for the period observed the amounts per hour are given for the sake of comparison. The periods in this table are chiefly of two hours' duration.

Date	Temp of Cat	Temp. of Chamber	CO_2 for period observed	CO_2 per hour	O for period observed	O per hour	Quotient	
28·6·92	38·4°C	22°C	5·47	2·73	5·57	2·78	·71	Cat very restless at first till it became accustomed to the chamber.
		22·5	4·73	2·36	4·83	2·41	·71	
		22·8	5·05	2·52	5·06	2·53	·72	
		21·8	4·08	2·04	4·18	2·09	·71	
		22·8	4·96	2·48	4·74	2·37	·76	
29·6·92	38·9°C	19·5	6·26	3·13	6·21	3·10	·73	
		17·8	5·09	2·54	4·93	2·86	·77	
			6·01	3·00	6·07	3·03	·72	
30·6·92		Operation –						
	39·1°C	17·8°C	5·03	2·51	4·86	2·43	·71	
1·7·92	38·5°C	18·5	6·21	3·1	5·21	2·6	·86	
2·7·92	38·7°C	20·0	3·99	1·99	4·14	2·07	·70	Tremors distinctly marked. They came occasionally in small Epileptiform attacks. Between the attacks there were occasional single tremors in different parts of the body. Appetite gone & no food taken.
3·7·92	38·3°C	22·4	3·42	1·71	3·37	1·68	·73	Tremors marked, no food taken.
	38·6	21·5	3·04	1·52	3·06	1·53	·72	
4·7·92	38·6°C	23	2·96	1·48	2·99	1·49	·72	Tremors practically continuous.
		23–17	3·62	1·81	3·46	1·73	·73	

Cat No. II continued – (2)

Date	Temp of Cat	Temp of Chamber	CO_2 for period observed	CO_2 per hour	O for period observed	O per hour	Quotient	
5. 7. 92	38·7°C	19·5°C	2·78	1·39	2·58	1·29	·78	Tremors marked but no convulsions. A little water taken, but no food. Cat getting very sleepy.
7. 7. 92	38·6°C 38·2°C		Effect of cold tried. Chamber reduced to 16°C but this only increased the tremors. No convulsions though this cold was continued for two hours.					
8. 7. 92	38·7°C 38·7°C		Cat seemed better today, but had taken nothing during the night.					
9. 7. 92	38·6°C							
11. 7. 92	38·0°C	19·5°C	3·76	1·88	3·68	1·84	·74	
		19·0	3·82	1·91	3·61	1·80	·74	
		18·3	4·13	2·06	4·08	2·04	·73	
	38·2°C	"	3·69	1·84	3·82	1·91	·70	
12. 7. 92	38·3°C	17·5	2·75	1·37	2·65	1·32	·78	
13. 7. 92	37·9°C	16·0	3·99	1·99	4·01	2·00	·72	

14. 7. 92 An experiment was now performed to test the effect of air at different temperatures on the Carbonic acid.
37·8°C – in the morning.
38·0 – at night.

Time of Observation	Temp. of air in Chamber	CO_2
12.12 — 1.12	18 — 18·5	2·05
1.12 — 3.12	18·5 — 17	4·37 = 2·18 per hour.

This amount of cold was not satisfactory as a test. It was in the hot weather of June and it was practically impossible to bring down the temperature sufficiently by ice. This experiment works well only when the cold of the water supply is sufficient to give a low temperature say below 10°C. Heat was then applied as follows —

over

Cat No. II continued — (3)

Date

14·7·92 continued —

Time	Temp. of steam entering jacket	Temp. of air leaving chamber
4·39	26°C	26
4·5	27	26
5·10	27·5	26
5·45	28·3	26·9
6	28·5	27·1
6·11	29·1	27·2

At 6·12 the CO_2 for the three hours was weighed

~~3·12–6~~	Temp. of Chamber	CO_2
	About 26	6·26 = 2·08 per hour.

As the heating up was somewhat slow and the temperature of 26°C was not obtained till 4·30 or so, I continued about one hour more at a high temperature.

6·21	23·8	26
6·27	25·8	26·1
6·40	28	25
6·57	44·9	25·8
7·12	41·8	29·

Time	Temp. of Chamber	CO_2
6·12–7·12	27·5	1·90

It was then allowed to cool down for two hours. In this time it reached the ordinary temperature of the room of about 18°C. In this time the CO_2 amounted to 1·83

Afterwards when this apparatus worked well both cold + heat were more perfectly under command and much more satisfactory observations were taken but this one is given because later observations confirm it.

After this observations of this cat were stopped for a while. The temperature was occasionally taken.

	Temp. of Cat	
15·7·92	38·6	Tremors becoming distinctly less marked.
	38·3	
16·7·92	38·2	
17·7·92	38·0	
18·7·92	39·0	Tremors now indistinct + appetite returning. Cat taken from observation room.
21·7·92	38·4	Tremors still. Cat shakes its head and its forefeet with great frequency. This was frequently observed in the cats. It was simply the exaggeration of an action often seen in perfectly normal animals.

Dale

Cat No. II continued — (4)

Date	Temp. of Cat	
28·7·92	38·0	Cat eats & sleeps well. Can walk & leap without difficulty. It goes sniffing about the room in the ordinary inquisitive way of a normal cat. Tremors now gone, 4 weeks after the operation.

On returning to Oxford at the end of the Autumn vacation I took some more observations of the metabolism of this cat, which was now apparently very much degenerated. It was now stiff & walked with difficulty. Its appetite was still good. It was however very stupid and had ceased to take any interest in its surroundings. It had lost 25% of its body weight.

Date	Time	Temp. of Cat	Temp. Chamber	CO_2	CO_2 per hour	O	O per hour	Quotient
10·10·92	4–6		18°C	3·65	1·82	3·28	1·64	·80
	6–8			3·50	1·75	3·11	1·55	·81
	8–10			3·59	1·78	3·28	1·64	·79
19·10·92	2·15–6·15	Below 36°	18·5°C	5·88	1·47	5·13	1·47	·83
	6·15–10·15	36·6		5·23	1·30	4·69	1·30	·82

20·10·92 The weather had by this time become cold, 14·5°C, & the cat suffered from this. Next day it was much worse. I then took advantage of the cold to make an observation on its heat regulating system.

21·10·92	3·20–6·20	Too low	16°C	1·20	This shows that the heat regulating system was still in functional activity.
	6·20–9·20	to register	28°C	·99	
	9·20–12·20		16°C	1·01	

22·10·92 Cat found dead this morning — 4 months after the operations.

Cat No. 111

Note - The CO_2 & O are given in Grammes -

Date	Temp of Cat	Temp of Chamber	CO_2 per hour, ~~for 4 hours average.~~	
28·6·92	39·3°C			
29·6·92	38·8°			
17·7·92	38·8°	16·5°C	2·93	
			3·09	
18·7·92	38·8°		2·79	
			2·60	
			2·99	
			2·81	
			2·26	
20·7·92	38·4°	Operation -	(12 — 1·30)	
	38·5°		2·86	(evening)
21·7·92	38·2°		2·83	
			2·77	Tremors beginning today -
22·7·92	38·2°	20°C	2·94	Tremors distinct. Difficulty of breathing - Salivation - Rapid breathing.
23·7·92	37·3°		2·74	General convulsions extremely marked
	37·4°		2·29	in character - Fits -
24·7·92	36·9°	20°C	2·44	
	37·3°		2·58	
25·7·92				Cat dead -

Cat No IV.

Note - The CO_2 & O are given in grammes.

Date	Temp. of Cat	Temp. of Chamber	CO_2 for period observed	CO_2 per hour	
28.6.92	39.5°C				
29.6.92	38.9°C				
25.7.92	38°C	19°C	3.00	3.00	This is Copy from the restlessness
			2.82	2.82	of the cat during the first hour.
			2.48	2.48	
26.7.92	39.2°	20°C	1.35		a series of half hourly observations -
			1.58		
			1.46		Cat has learnt to be quiet
			1.34		still today.
			1.44		Sitting quietly.
		20.1°	1.44		
			1.4		
			1.70		Disturbed a little.
			1.46		
		19°	1.26		sleeping.
			1.39		Asleep the whole time.
			1.32		"
			1.30		"
		19.1°	1.38		"
			1.39		"
		18.4°	1.32		"
			1.25		"
		18°	1.19		"
			1.05		"
27.7.92	39.2°	Operation -			
28.7.92	39.1°		2.65	2.65	} hourly observations -
			2.31	2.31	
			2.41	2.41	
			2.65	2.65	
			1.09		half hourly observations.
			1.19		
			1.18		
			1.05		Sitting quietly -
			1.02		
			1.42		Restless, moving about & cleaning its fur.
		38.8°	1.03		Quiet the whole time.

Cat No IV continued — (2)

Date	Temp of Cat	Temp of Chamber	CO_2 for period observed	CO_2 per hour	
29·7·92	39·7°C		1·53		Half hourly observations —
			1·49		½ lb. beef eaten ~~during~~ the night.
			1·50		Tremors possibly but not very distinct.
			1·60		
30·7·92	39·1°C		7·94	2·29	
31·7·92	39·1°C		10·64	2·66	
			7·18	2·39	
1·8·92	39·7°		3·18	3·18	No symptoms of any sort.
			3·23	3·23	Cat moves about in a perfectly
	39·6°		2·55	2·55	natural manner.
2·8·92	39·5°		3·06	1·53	No abnormality.
	38·8°		2·97	1·48	
3·8·92	38·6°			2·82	average of 4 hours
				2·92	average of 6 hours
4·8·92	39·0		Observations stopped.		
29·9·92	37·3°		Cat busily engaged in hunting for mice in the Laboratory.		

On returning to Oxford in Autumn I found this animal practically unchanged. It was a little more wasted. It still consumed large quantities of food — It had occasionally attacks of vomiting.
I made a few observations on its metabolism, and in the cold weather I tested its heat regulating mechanism.

Date	Temp. of Cat	Temp of Chamber	CO_2 for period observed	CO_2 per hour	O for period observed	O per hour	Quotient	
11·10·92	37°C	16°C	6·48	3·24	5·40	2·70	·88	Two hours periods
			5·22	2·61	4·44	2·22	·85	
			6·22	3·11	5·49	2·74	·82	
12·10·92	37·3°	15·8°	5·71	2·85	4·27	2·13	·97	Two hour periods
			5·93	2·96	5·09	2·54	·93	
			6·08	3·04	5·09	2·54	·93	
			5·28	2·64	4·65	2·32	·83	
			4·76	2·38	4·01	2·00	·84	

Cat No IV continued — (3)

Date	Temp of Cat	Temp of Chamber	CO_2 for period observed	CO_2 per hour	O for period observed	O per hour	Quotient	
29.10.92	38.2°C	19°C	7.49	2.49	6.76	2.25	.80	These hour periods.
			7.61	2.53	6.89	2.29	.80	
			8.20	2.73	7.41	2.47	.80	
			7.09	2.36	6.39	2.13	.80	
31.10.92	39.1°C	16.8°	9.17	3.05	8.52	2.84	.78	" "
			8.23	2.74	7.96	2.65	.75	
2.11.92	38.6°		8.89	2.96	7.61	2.53	.85	" "

On November 3? I made an observation of the reaction to change of temperature in the surrounding air.

Date	Temp. of Cat	Temp of Room	Temp of stream of water in Jacket	Temp of air in Chamber	CO_2 in 3 hours 11.36–2.36	CO_2 per hour
3.11.92	39.1°	17.5°	9.5°	14.5°	7.44	2.46

Heating began at 2.36.

Time	Ingoing stream of Jacket	Outgoing stream of air
2.55	20.5°	16.3°
3.15	26.5°	20.8°
3.55	29.5°	25.5°
4.55	32.0°	29.0°
5.30	30.0°	28.5°

Time = 2.36 — 5.36 CO_2 = 6.70 = 2.23 grms per hour.

Cold Period Ingoing Stream 9.5°C Air of Chamber 15°C Time 5.36–8.36 CO_2 8.09 = 2.69 grms per hour

Cat was fed with Liebig's Extract of Meat to test the effect of the presumed Extractives in its food. It did not however show any symptoms. It was fed also with food in every variety — lean lungs, raw beef, boiled beef, raw rabbit-flesh, boiled rabbit's flesh, Cat's flesh from the body of one that had died in the acute stage of the Cachexia. This variety of food excited no disturbance, provided it was in sufficient quantity to appease its hunger.
The observation which follows was, the day after, after a large meal of bread saturated with strong Liebig's Extract Soup, which it took but not greedily.

over

Cat No IX continued. (4)

Date	Temp of Cat	Temp of Chamber	CO_2 for period observed	CO_2 per hour	O for period observed	O per hour	Quotient	
4.11.92	39.8°C		8.55	2.85	7.51	2.50	.82	for 3 hours
			11.87	2.96	10.75	2.68	.80	for 4 hours
5.11.92	39.5°C		7.19	2.39	7.01	2.33	.74	for 3 hours
			6.14	2.04	5.77	1.92	.77	" "

Later towards the end of December, I made a careful observation of the reaction to change of temperature in the surrounding air.

23.12.92	39.4°C	12°C	3.65	2.44	for 1½ hours.
			2.59	2.59	for 1 hour.
			1.30	2.60	for ½ hour.

The mean of these quantities gives for the cold period 2.54 grms. CO_2 per hour – The hot stream was turned on at 2.23 and the CO_2 was estimated for half hours period thenceforward.

Time	Temp of Chamber	Time of taking CO_2	CO_2 for period observed	CO_2 per hour
P.M. 2.37	14.5°C	2.23–2.53	1.29	2.58
2.47	17.8°			
3.2	23.0°	2.53–3.23	1.00	2.00
3.12	26.5°			
3.20	28°			
3.33	30°	3.23–3.53	.95	1.90
3.53	31°	3.53–4.23	1.08	2.16
4.15	31°	4.23–4.53	1.09	2.18
4.43	31°	4.53–5.23	.87	1.74

The mean of these values is 2.02 grms. CO_2 per hour.

5.27	24.5°	5.23–5.53	1.28	2.56
5.53	15.5°	5.53–6.23	1.12	2.24
6.0	13°			
6.20	12°	6.23–6.53	1.25	2.50
8.45	11	6.53–8.53	5.27	2.63

The mean of these values is 2.55 grms CO_2 per hour.

20 4 93 Cat Dead.

Cat No V.

Note. The CO_2 & O are given in grammes.

Date	Temp of Cat	Temp of Chamber	CO_2 for period observed	CO_2 per hour	Observations on first day are for half hours.
29.7.92	38.4°		2.44	4.88	Cat very restless.
			1.81	3.62	Rest.
			1.51	3.02	Sleep
			1.65	3.30	Sleep
			1.58	3.16	Sleep
			1.28	2.56	Sound sleep.
			1.07	2.14	Quite dark, every one away from Laboratory.
30.7.92	38.4°	Operation	—	3—4 p.m.	
31.7.92	38.9°	22.3°	2.01	4.02	Tremors appearing in the morning -
			1.88	3.76	markedly increased by afternoon. The
			1.81	3.62	whole body in spasm by 4.30. After
			1.61	3.22	a fit it could walk about much
			1.57	3.14	better. In fits quick shallow breathing, dilated nostrils, dilated pupils. No biting action, nor chafing of the head nor salivation. Respiration 50 per minute.
1.8.92	37.4°		1.32	2.64	Fits which seem rather less severe
			1.30	2.60	tonight. No dyspnoea. Respiration 50.
			1.51	3.02	Right fore leg seems most affected.
2.8.92	36.8°		8.09	2.69	(3 hour period.) Cat better tonight.
			4.30	2.15	(2 hour period.) no general spasms now. walk & sit comfortably. No dyspnoea.
3.8.92	37.1°		10.92	2.73	(4 hour period.) Fits again. No appetite. Thirst. Stupid.
4.8.92	36.6°		9.55	2.38	(4 hour period) Fits.
5.8.92	34.1°		5.51	2.75	2 hour period. Very bad fits.
			4.93	2.46	" " Temperature very low.
			6.80	2.26	3 hour period. The observation is
			4.56	2.28	2 hour period. not perfectly accurate as the mercury was below the scale.
6.8.92	Too low for the Thermometer		2.71	2.71	1 hour periods
			2.73	2.73	
			2.77	2.77	

Cat dead.

The CO_2 is given in Grammes. Cat No. VI. (1)

Date	Temp. of Cat	Temp. of Chamber	CO_2 for period observed	CO_2 per hour	
1·8·92	38·4°C		10·10	2·85	4 hours periods. Cat restless.
2·8·92	38·4°		7·06	2·53	3 hour period
5·8·92	38·4°	Operation -			
	39·1°	Evening temperature.			
6·8·92	39·0°		3·02	3·02	
7·8·92	38·4°		2·85	2·85	Tremors just beginning to
			2·78	2·78	appear. Cat restless.
			2·60	2·60	
8·8·92	38·4°		2·95	2·95	Salivating. Biting. Tremors,
			2·46	2·46	but none of these very pro-
			2·72	2·72	nounced as yet.
9·8·92	38·3°		5·99	1·99	3 hour period
			4·34	2·17	2 hour period
10·8·92	38·2°		8·29	2·76	3 hour period. Tremors well
			2·82	2·82	marked today.
					Appetite good.
12·8·92	38·8°		11·34	2·52	4½ hour period.
			2·44	2·44	
13·8·92	38·8°				A few tremors still.

Observations stopped as I then left Oxford for vacation.

The following observations were taken on my return!

Date	Temp. of Cat	CO_2 for period observed	CO_2 per hour	O for period observed	O per hour	Quotient	
14·10·92	38·6°	4·80	2·40	4·58	2·29	·76	Cat shows no par-
		4·63	2·31	4·30	2·15	·78	ticular symptoms
		4·27	2·13	3·88	1·94	·79	

9·11·92 Observation on the heat regulating mechanism. The same period of cold weather which presumably caused the death of Cat No II caused a recrudescence of the muscular twitching in this animal. The tremors were now continuous and

(2)

Cat No VI

and its appetite was gone. It seemed to suffer more when the cold air was turned on than during the period of warm air. The following are the details —

Date	Time	Temp of Cat	Temp of air	CO_2 for period	CO_2 per hour	
9·11·92	12·10–3·10	39·4°	14·5°	8·23	2·74	Respirations 48.
	3·10–6·10		30°	5·64	1·88	Respirations 30. Looks much better.
	6·10–11·40		14·5°	13·97	2·56	
10·11·92	2·26–5·26	38·4°	14·5°	6·58	2·19	Sparrs occasionally
	5·26–8·26		33°	4·10	1·03	
	8·26–11·26		13·5°	7·49	2·49	

11·11·92 Cat was fed with Liebigs' Extract of Meat but this did not cause any increase in the symptoms.

14·11·92 Warmer weather came on & cats tremors have disappeared.

7·12·92	12·10–3·10	38·1°C	11·5°C	7·84	2·61	Cold
	3·10–7·10		25°	8·25	2·06	Hot
	7·10–11·10		10·5°	10·12	2·53	Cold
21·12·92	10–11	38·4°	13°C	2·72	2·72	Cold
	11–12			2·48	2·48	Cold
	12–1		13°–27°	2·00	2·00	Hot
	1–2		29°–31°	1·53	1·53	Hot
	2–3		31°–32°	1·53	1·53	Hot

The cold air was now turned on and observed in half hour periods —

3·37–4·7		18°–13°	1·23	2·46	Cold
4·7–4·37		13°	1·22	2·44	"
4·37–5·7		13°	1·19	2·38	"
5·7–5·37		13°	1·34	2·68	"
5·37–6·7			1·00	2·00	"
6·7–6·37	38·4°		1·17	2·34	"

At the end of January 1893 the cat had quite recovered and seemed to be now all right. Another observation was taken on its heat regulating system —

(3)

Cat No 11

Date	Time	Temp of Cat	Temp of Air	CO_2 for period	CO_2 per hour	
26.1.93	11.52 — 12.52	38.3°	15°	2.58	2.58	Cold
	12.52 — 2.52		12°	4.75	2.35	"
The hot air was now turned on and the observations taken in half hours.						
	2.52 — 3.22		17°–22°	1.23	2.46	Hot
	3.22 — 3.52		25°–27°	1.19	2.36	"
	3.52 — 4.22		27°–29°	1.02	2.04	"
	4.22 — 5.22		29°	1.22	2.44	"
	5.22 — 5.52		29°	1.17	2.34	"
	5.52 — 6.22		29°–17°	1.29	2.58	Cold
	6.22 — 7.52		12°	2.38	2.38	"
	7.52 — 9.22		11°	4.81	2.40	"

Cat No VII.

The interest here is in the normal reactions to the amounts of heat and cold-~~heat~~ compare with the abnormal animals.

Date	Temp of Cat	Temp of Chamber	Time	CO_2 for period	CO_2 per hour
26.11.92	39.1°	14°C	12.34–5.34	14.78	2.95
		30°	5.34–7.4	4.01	2.68
		14°	7.4–1.4	15.89	2.66
28.11.92	38.7°	13°C	12.21–5.21	12.95	2.59
		30°	5.21–8.51	8.70	2.48
		13°	8.51–11.21	5.34	2.13
3.12.92	38°	10°C	11–2	8.19	2.73
		30°	2–5	6.43	2.14
		9.9°	5–8	5.74	1.91
		9°	8–9	2.25	2.25
		9°	9–10	1.80	1.80
		9°	10–11	2.02	2.02

Cat having been left ~~without~~ food for 3 days is examined on the 4th day to see the effect on it of the hunger.

16.12.92	37.3°	10°	1–4	7.95	2.65
		30°	4–7	6.13	2.04
		10°	7–11.30	8.23	1.83

No VIII Kitten

Date	Temp of Kitten	Temp of air	Time	CO_2 for period	CO_2 per hour
6.12.92	39.1°	9.8°	3–6.30	6.12	1.75
		30°	6.30–10	5.09	1.45
		9°	10–12	2.76	1.38
21.12.92	39°	10°	11–12	1.87	1.87
		10°	12–1	1.41	1.41
		10°	1–2	1.66	1.66

Hot air supplied and observations taken every half hour.

	10°–20°	2–2.30	.77	1.54
	20–27°	2.30–3	.70	1.40
	28°	3–3.30	.63	1.26
	30°	3.30–4	.64	1.28
	31°	4–4.30	.67	1.34
	31°	4.30–5	.60	1.20

Cold air turned on observations in ½ hours continued.

30°–17°	5–5.30	.64	1.28
17°–12°	5.30–6	.52	1.04
11°	6–6.30	.62	1.24
11°	6.30–7	.59	1.18
10°	7–10.30	4.78	1.36
10°	10.30–11	.64	1.28
10°	11–11.30	.68	1.36
	11.30–12	.70	1.40
	12–12.30	.78	1.56

Cat No IX

Date	Temp of Cat	Temp of chamber	Time	CO_2 for period	CO_2 per hour	
20·2·93	39·2°	17·5°	12–1	2·35	2·35	
		"	1–2	2·38	2·38	
		"	2–3	2·45	2·45	
		Hot air supplied				
		17°–27°	3–4	2·26	2·26	
		27°–32°	4–5	1·70	1·70	
		30°	5–6	1·51	1·51	
		Cold air supplied, the apparatus rapidly reading the temp of 17°C	6–9	3·91	1·30	
21·2·93	38·6	17°	1–2	2·95	2·95	
		"	2–3	2·88	2·88	
		Hot air supplied.				
		17°–28°	3–4	2·90	2·90	
		32°	4–5	2·61	2·61	
		31°	5–6	2·48	2·48	
		Cold air supplied				
		17·5°	6–9	5·29	1·76	
22·2·93		16°	12–1	2·36	2·36	
		"	1–2	2·37	2·37	
		Hot air supplied				
		16–30°	2–3·30	3·23	2·16	
		32°	3·30–4·30	1·95	1·95	
		32°	4·30–5·30	1·96	1·96	
		Cold air supplied				
		16°	5·30–7·30	2·93	1·46	
23·2·93		Operation				
25·2·93	38·4°	17°	12–1	2·75	2·75	Cat has tremors and difficulty in breathing salivation loss of appetite
		"	1–2	2·78	2·78	
		Hot air supplied –				
		17°–25°	2–3	2·79	2·79	Cat suffering extremely from heat dyspnoea so that cold air was turned on at once.
		27°–30°	3–4	1·57	1·57	
		Cold air supplied				
		30–17	4–5	4·45	4·45	27·2·93 Cat died today after severe muscular twitching. Temp. 40·6°C
			5–5·30	1·53	3·06	
			5·30–6	1·46	2·92	
			6–6·30	1·84	3·68	

Cat No X

Date	Temp of Cat	Temp of Chamber	Time	CO_2 for period	CO_2 per hour	
28·2·93	38·2°	15°	1·26–1·56	3·50	2·34	
			1·56–2·26	1·34	2·68	
	Hot air supplied					
		15°–30°	3·26–4·26	2·28	2·28	
		30°	4·26–5·26	2·10	2·10	
		30°	5·26–6·26	2·01	2·01	
1·3·93	38·4°	Operation –				
2·3·93	37·8°	16°	12·15–1·45	3·36	2·24	Tremors
			1·45–2·15	1·00	2·00	
	Hot air supplied					
		16°–28°	2·15–3·45	3·59	2·40	Cat does not suffer greatly from the heat.
		30°	3·45–4·45	1·99	1·99	
	Cold air supplied					
		30°–18°	3·45–4·45	3·45	3·45	
		17°	4·45–5·45	3·38	3·38	
	38·4°	17°	5·45–7·45	5·70	2·85	
3·3·93	37·8°	19°–16°	10–11	1·78	1·78	
		16°	11–1	3·77	1·88	
	Hot air supplied					
		16–29°	1–2	1·65	1·65	Cat in perfect comfort in the heat
		30°	2–4	1·55	·77	
	Cold air supplied					
		30°–23°	4–5	·90	·90	
		17·5°	5–6	1·06	1·06	
		16·5°	6–8	1·43	·71	
4·3·93	38·1°	17°	10–11	1·60	1·50	
		14·5°	11–12	2·07	2·07	
	Hot air supplied					
		14–25°	12–1	1·19	1·19	Tremors more marked in the heat
		25°–31°	1–2	1·65	1·65	
		31°	2–3	1·21	1·21	
	Cold air supplied					
		31°–18°	3–4	2·47	2·47	
		16°	4–6.30	2·37	1·38	
6.3.93	37.3°	18°–16°	10–11	1·40	1·40	
		15°	11–12	1·60	1·60	
	Hot air supplied					

Cat No X (2)

Date	Temp of Cat	Temp of Chamber	Time	CO_2 for period	CO_2 per hour
		Hot air supplied			
6.3.93	[illegible]	15°–28°	12–1	1·21	1·21
continued		32°	1–2	1·23	1·23
		32°	2–3	1·13	1·13
		Cold air supplied			
		32°–18°	3–4	1·45	1·45
		16°	4–5	1·45	1·45
		16°	5–6	1·00	1·00
		16°	6–8	1·12	1·12
7·3·93	37·7°	16·5°	11–12	1·45	1·46
		16°	12–1	1·59	1·59
		15·8°	1–2	1·64	1·64
		Hot air supplied			
		16°–28°	2–3	2·29	2·29
		30°	3–4	1·33	1·33
		[illegible]	4–5	1·14	1·14
		Cold air supplied			
		30°–20°	6–6	1·68	1·68
		17·5°	6–6.30	·57	1·14
	38·4°	16°	6.30–8.30	3·29	1·64
8·3·93	37·4°	17·5°	10–11	1·56	1·56
		15·3°	11–12	1·55	1·55
		15·5°	12–1	1·79	1·79
		Hot air supplied			
		15°–28°	1–2	1·73	1·73
		31°	2–3	1·41	1·41
			3–4	1·30	1·30
		Cold air supplied			
		31°–18°	4–5	1·38	1·38
	38·4°	15°	5–8	4·81	1·60
9.3.93	37·4°	16·5°	11–1	2·69	1·33
		16·5°	1–2	1·74	1·74
		16·5°	2–2.30	·86	1·72
		Hot air supplied			
		30°–18°	6.30–8.30	2·43	1·21
	37·4°		8.30–9.30	1·88	1·88
10.3.93	34·5°	17°	11.30–1	4·57	3·12
		17·2°	1–2.30	1·15	2·30
		17°	2.30–3	1·14	2·28

Cat died