A COMPARISON BETWEEN SOME PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS.

THE OLIVER-SHARPEY LECTURES, DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON.

BY JOSEPH BARCROFT, M.A., F.R.S.,
FELLOW OF KING'S COLLEGE, CAMBRIDGE.

LECTURE I. (Abstract.)

AFTER expressing his sense of the honour conferred upon him and of the responsibility which he had incurred, Mr. Barcroft said:

The lecturer on physiology whose classes consist largely of medical students necessarily and inevitably spends a large part of his time in pointing out antitheses between the normal and the abnormal—contrasts between the physiological and the pathological.

A simple example of what is in my mind may be furnished by the constituents of urine. One of the most notorious items in a physiological education is the fact that sugar is absent from normal urine. This is not emphasized because of the interesting philosophical problem which it involves, but because of the practical issue which the presence of sugar under abnormal conditions presents. Yet no one of a reflective turn of mind can be satisfied with a physiology which consists of such antitheses, for they are essentially superficial, and if in lecturing to students I have to enforce and even exaggerate them, I may to-day perhaps claim the luxury of turning the medal over and discoursing for a little on the essential similarity of the normal and the abnormal rather than of the difference between them.

A cell in the animal body is from one point of view a chemical complex, it is capable of certain reactions and these reactions are limited by the properties of the molecular groupings of which it is composed. How comes it, then, that these reactions are at one time of one description and at another time of another description? Usually, or as we say "normally," the reactions are of one character, but sometimes, that is "abnormally," they are of another. Does the leopard really change his spots? or is there underneath this apparent contrast some principle of unity which we can discern?

Let me return to the sugar in the urine. I do not know from what substance the kidney derives its energy, but this I do know, that if this substance were sugar the kidneys of the rabbit would require about a quarter of a gram of sugar daily. Now, the rabbit secretes about 100-200 c.cm. of urine in the twenty-four hours. This fluid by some means parts with about half that quantity of sugar, or rather more, before the kidney has turned it out as urine. It seems to me eminently probable that as this fluid traverses the kidney the sugar is utilized. But if the percentage of sugar in the blood were to rise considerably, the amount traversing the kidney cells might easily exceed what suffices for the needs of the organ and the balance would then appear in the urine. Such a condition would occur if excessive quantities of carbohydrate were eaten. If these be the facts there is no real antithesis between the kidney that is not secreting sugar and the kidney which is secreting small quantities of that substance. The difference is in essence one of degree, not of kind.

This very simple example has been chosen to indicate the direction in which my mind is running, but the topics of which I am about to treat are much more complex. For when we speak of the normal metabolism of the cell, or of the organism, we are speaking of something which presents a considerable range of variety in different directions.

Alterations in the circumstances under which the organism finds itself are of constant occurrence. The organism is not merely a "passive resister" of these changes, but ages of evolution have endowed it with the power of producing some efficient adaptation to each alteration of circumstance. It can adapt itself to rest, it can adapt itself to activity, it can adapt itself to oxygen want, and so on. It is of these adaptations which I wish to treat, and in the treatment it will appear that every one has its reflection in some pathological condition of common occurrence.

I. THE PYREXIA OF EXERCISE.

On the ordinary clinical thermometer there is a little mark pointing to 98.4° F. This mark is the outward and visible sign of one of those antitheses of which I have already spoken—the antithesis between the normal and the abnormal body temperature. The whole of recent research has tended to limit the use of the word "normal" with regard to this temperature and to emphasize the physiological variations which the body temperature undergoes.

Of these the most noteworthy is the rise of temperature which takes place during physical exercise. Much information on this subject has been collected by Pembrey¹ and others; this I will not rehearse. Let it be clear, however, that the pyrexia of exercise is a true physiological phenomenon. It is not, as might at first sight appear, a breakdown of the heat-regulating mechanism—a sort of physico-chemical lesion. It is to the benefit of the body, and this in more than one way. It is a response to the circumstance of muscular exercise, just as a pathological pyrexia is a beneficent response to bacterial invasion. The pyrexia induced by the same piece of work is very different in different individuals, but rather constant in any one person. In support of this statement are some data which I obtained from one of the boats² of my own college (King's) at Cambridge. The rectal temperatures of the men were taken on successive evenings, before and after practice. The data from "bow" are typical of most of the men.

Rise in Rectal Temperature as the Result of Rowing Practice lasting for about One and a Quarter Hours (in Degrees F.)

	May 29.	May 30.	June 1.	June 2.	June 3.	Mean.
Bow ...	0.8	0.6	—	0.6	0.9	= 0.7
No. 5 ...	1.1	1.6	2.1	1.7	1.1	= 1.5
Stroke ...	-1.6	-1.1	-0.5	0.0	-0.4	= -0.7

Whilst this case of "bow" may be regarded as an average one, the extreme cases are those of stroke and five. The case of stroke is of considerable interest, for be the explanation of the thermometer readings what it may, the readings go to show that the exercise was not such as would have strained the power of the thermotaxic centres in the other individuals to keep the temperature normal had such a consummation been desirable.

The benefit which the muscular economy derives from the rise of temperature is at least twofold.

1. A. V. Hill³ has shown that the efficiency of frog's muscle is increased about 100 per cent. for every rise of temperature of 25° C. By efficiency in this connexion is meant the tension set up for a given output of heat in the muscle. More recently Weizsäcker⁴ has come to the same conclusion. "The efficiency," he says, "of muscle in developing tension rises as the temperature rises, and at the higher temperature the rise may be quite obvious." This rise of efficiency does not seem to mean a reduction in oxidation. Unfortunately Weizsäcker's experiments on muscle had not been extended to the investigation of this point when he left Cambridge shortly before the war; but we may fill in the gap from similar experiments on the metabolism of cardiac muscle which he performed at Heidelberg.⁵ Following the conception of the Cambridge school of myologists based on the work of Fletcher and Hopkins,⁶ he would classify the processes involved in contraction in the following way:

Processes involved in contraction.

At the higher temperature a greater proportion of the energy liberated—(1) supra—is converted into mechanical work (2). Though both (1) and (2) may be increased absolutely, involving a corresponding increase in the subsequent oxidative process (3).

2. The second benefit conferred upon the muscle by the

rise in the body temperature has to do with a subject upon which I can speak with greater authority—namely, the opportunity presented to the muscle for the acquisition of the oxygen necessary to maintain this exaltation of the oxidative processes.

The oxygen comes, of course, from the blood, and the readiness with which the blood adheres to its oxygen is a function of its temperature. This matter has in recent years formed the subject of researches by Loewy and Caspari⁷ and of several workers in Cambridge. Let me quote the figures of Oinuma⁸ in this connexion; they show that a rise of temperature scarcely affects the rate at which oxygen is taken up by the blood, whilst it greatly facilitates the ease with which it is given off. A stream of gas free from oxygen was passed through blood, reducing it from the arterial to the venous conditions. The same degree of reduction was effected as follows:

Temperature.	Time taken for Reduction from 90 to 40 per cent. Saturation.
37° C.	8 minutes
27° C.	16 "
17° C.	32 "

A rise of 10° makes a difference of about 100 per cent. in the rate at which blood parts with its oxygen.

II. INFLAMMATION AND FUNCTIONAL ACTIVITY.

Leaving the body as a whole, I wish now to draw your attention to another comparison—one which is connected with localized areas or particular organs. This comparison is between the effects following upon functional activity and those which are associated with the earliest stages of local inflammation.

Bearing in mind that the cardinal symptoms of inflammation are "rubor, calor, tumor, and dolor," I wish to put before you the condition of two organs—a condition which I think is typical of others—after they have been subjected to considerable degrees of functional activity. The figures which are at my disposal were those obtained on dogs by my colleague, Dr. Toyojiro Kato,⁹ Professor of Medicine in Sendai University, and myself. In all cases the dogs were anaesthetized with A.C.E. mixture and urethane.

1. The Submaxillary Gland.

The submaxillary gland is the first organ of which I propose to treat.

Redness.—The gland was thrown into activity by intravenous injection of 10 mg. of pilocarpine. The flow of saliva was at first rapid, and gradually became more slow, and at the end of three hours it had almost ceased; but the flow of blood through the vessels was about three times as great as at the commencement of the experiment, and, indeed, at the end of four and a half hours there was still a marked hyperaemia. The flushing of the submaxillary gland during secretion is a very old observation; it is only in part, however, to be accounted for by the increased quantity of blood in the gland, but the nature of the blood has a share in producing the red appearance of the gland. In this experiment the blood which emerged from the gland during its activity contained considerably more oxygen, and was therefore much redder than during rest.

Heat.—Not only was the blood flow through the gland greatly increased, but there was profound chemical activity which persisted when the salivary flow had ceased (or nearly so), and which must have had its expression largely in the formation of heat. The difficulty of measuring this has a literature of its own, to which Professor Bayliss and Professor Leonard Hill have been the principal English contributors. But whether one interprets "calor" in the sense of a rise of temperature due to increased blood flow through the gland, or in the more literal and scientific sense of heat production measurable in calories, there can be no doubt of its existence.

Swelling.—The phenomenon which underlies swelling is that of the increased exudation from the blood vessels. In the case of the salivary glands this fluid, which traverses the vessel walls, forms the basis of the saliva. More fluid, however, is lost from the blood than appears as saliva, and the balance either flows away from the gland as lymph or remains in it as "swelling." The following table gives the blood flow, the degree of oxidation, and the exudation and the saliva during the course of the experiment.

Before Injection.			After Injection of 10 mg. Pilocarpine.						
Time after injection (minutes)	—	—	6	27	56	80	140	181	—
Blood flow (c.cm. per minute)	1.4	—	8.9	4.6	6.8	5.1	4.3	3.9	—
Saliva flow (c.cm. per minute)	0	—	1.04	0.63	0.54	0.28	0.21	0.13	—
Exudation (c.cm. per minute)	0	—	0.37	0.15	0.26	0.21	0.28	0.27	—
Oxidation (c.cm. of oxygen per gram per minute)	0.19	—	0.68	0.52	0.52	0.52	0.48	0.36	—

2. Striated Muscle.

The measurements of muscle differ essentially from those given above in one important respect, namely, that the whole of the fluid which traverses the capillary walls finds its expression either as lymph or swelling. With this preface let me pass to a description of the experiments which we performed. They were either on the gastrocnemius or the anterior belly of the digastric in the dog. The exercise, rhythmic in character, was a short tetanic contraction each second for fifteen minutes; the results were as follows:

Redness.—The blood flow reached a maximal value six times the flow through the resting muscle. For six hours after the exercise ceased the blood never dropped below a threefold increase of its "resting" value, and even after seven hours and three-quarters the blood flow was still twice what it had been to start with. Moreover the venous blood was quite arterial in its brightness, being at times about 90 per cent. saturated with oxygen.

Heat.—The increased oxidation in the muscle was sustained for three and a half hours after the exercise. It was then over twice the resting value. Here again the oxidation represents heat formation with some storage of potential energy.

Swelling.—The increased exudation from the capillaries lasted for three and a half hours and probably longer, and about 50 c.cm. of lymph were secreted as the direct result of the exercise. Of this about 7 c.cm. appear to have remained in the muscle, swelling it out, for the muscle which had been exercised weighed 38 grams, whilst that of the other side weighed but 31 grams. The counterpart of this change in weight was to be found in the specific gravities of the two muscles, the heavier muscle having the lesser specific gravity, and thus showing that its gain in weight was due to the imbibition of water. Their specific gravities were 1061 and 1070 respectively. These phenomena, which may easily be repeated in the frog,¹⁰ recalled an old observation of Ranke on this subject.

Pain.—Amongst the remarkable features of this exercised muscle was its "feel" to the fingers. Shorter, and of much greater circumference than its fellow, it felt distended somewhat after the fashion of a Rugby football—in fact, it felt stiff. What precise relationship there may be between this objective sensation of stiffness and the subjective sensation which bears the same name is not easy to determine, but that this distension is an important factor in muscular stiffness I have no doubt. Even with a minor degree of inflation I should fancy it would feel stiff, and by the time the swelling amounted, as in this case, to 20 per cent. of the size of the muscle, the stiffness likely enough drifted into something which might be as correctly described by the word "pain."

Further than this I have not been able to follow the analogy. In muscle, at all events, it appears that the symptoms never are pushed to the point of diapedesis taking place; with rest they go as they came.

CONCLUSION.

Now that I have finished the drawing of comparisons I wish to raise a question which you may think that I should have raised at the commencement, rather than at the end, of my lecture. Are such comparisons worth drawing? Does any scientific reality underlie them, or are they a mere ringing of the changes on familiar facts, and like other comparisons—essentially odious? To me they have had at least this value—having been founded on cruder observations which I had previously considered, they have elicited the much more striking data which I have put before you in the latter part of my lecture. But the real answer to my question depends upon factors as yet undetermined. The cause of the redness, the swelling, etc., which take place as the result of

activity is no doubt the presence of bodies which we call metabolic, which are shed into the tissue spaces by the active cells; the cause of the similar phenomena in the case of inflammation is the presence of bodies which we call toxic in these same spaces. Whether a scientific truth underlies the apparent similarity depends upon the, as yet unascertained, relation of these two classes of bodies. In the meantime so long as we have anything to learn from such comparisons they are worth drawing, and I hope in my next lecture to deal with a comparison which is at least something more than a coincidence.

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EPIDEMIC CEREBRO-SPINAL FEVER:

THE PLACE OF THE MENINGOCOCCUS IN ITS ETIOLOGY.

A BACTERIOLOGICAL STUDY.

(Interim Report.)

BY

EDWARD C. HORT, F.R.C.P. EDIN.,

DIRECTOR OF THE CONSTANCE TROTTER RESEARCHES, AND PHYSICIAN TO THE ADDINGTON PARK WAR FEVER HOSPITAL;

C. E. LAKIN, M.D., M.R.C.P.,

ASSISTANT PHYSICIAN TO THE MIDDLESEX HOSPITAL;

AND

T. H. C. BENIANS, F.R.C.S.,

PATHOLOGIST TO THE PRINCE OF WALES'S HOSPITAL.

(From the Bacteriological Laboratory of the Addington Park War Fever Hospital.)

In a preliminary note on the bacteriology of epidemic cerebro-spinal fever we recently recorded the following facts:¹

1. That from the blood, cerebro-spinal fluid, and urine of acute cases we had frequently isolated, and as far as possible identified, the so-called meningococcus of Jaeger.

2. That from the filtrate of a fresh catheter specimen of urine from a severe case we had obtained a slight growth, a single colony of which was composed of the following morphological types:

- The meningococcus of Jaeger.
- The meningococcus of Weichselbaum.
- A Gram-negative rod-shaped granulating organism, each granule consisting of a pair of cocci with flattened opposed surfaces. This organism for convenience of reference will be referred to as the "biscuit bacillus."
- Various Gram-positive forms.

3. That in stained preparations from deposits of fresh catheter urine from acute cases with fever we had sometimes found:

- Gram-negative cocci, lying free in pairs and tetrads, and morphologically indistinguishable from the meningococcus of Weichselbaum.
- Clusters of much smaller Gram-negative diplococci.
- Minute and large Gram-negative bacilli.
- Various Gram-positive forms.

In the same note we also discussed the unsatisfactory nature of the epidemiological and bacteriological evidence usually relied on by those who consider that the meningococcus of Weichselbaum is the primary infective agent in epidemic cerebro-spinal fever.

As a result of these observations, themselves suggested by recent bacteriological work in typhus fever, it was suggested by one of us (E. C. H.) that the *Meningococcus intracellularis* might prove to be merely a late non-infective phase in the life-history of the true infective agent, and that for reproduction of the disease this must be present in its earliest forms.

According to this theory the earliest phases might lie outside the range of vision, in which case their morphology would be indeterminable, and it would be impossible to say whether the meningococcus of textbook fame is derived from a coccal ancestor or not. On the other hand, the earliest phases of the causal organism might lie within the range of vision, in which case it should be

possible to determine whether the meningococcus is always a coccus, or whether it is derived from bacillary ancestors. In the latter event only could true pleomorphism be proved, though as regards infectivity it would be immaterial whether the earliest phases were coccal or not, provided that the relatively large diplococcus of Weichselbaum were incapable of reproducing the disease. And this appears from animal experiments to be the case.

Since the publication of our first note we have repeated in other cases the observations there quoted, and have obtained the same essential results. We now, however, wish to record further experiments, with special reference to the question whether a filter-passing organism is or is not present in the blood, cerebro-spinal fluid, urine and naso-pharyngeal secretion of acute cases, leaving the question of its infectivity to animals to a later occasion.

The following observations are selected from a large number of experiments, and are admittedly incomplete owing to the absolute necessity for control microscopical examinations at every step, and the heavy expenditure of time and labour involved.

CEREBRO-SPINAL FLUID.

Case I (E. C. H.).

A specimen of cerebro-spinal fluid was obtained from an acute case, death ensuing forty-eight hours after lumbar puncture. A slope of inspissated serum was inoculated from the centrifuged deposit of the fresh fluid, and gave, after incubation for forty-eight hours, a good growth of Gram-negative meningococcal organisms. Further identification was not possible owing to pressure of work, but *post-mortem* examination by one of us (C. E. L.) proved the case to be one of sporadic cerebro-spinal fever with meningitis.

Post-mortem Notes.

An examination of the body was made twenty hours after death, and showed the characteristic appearances of a case of cerebro-spinal fever. A swab taken from the nasopharynx by West's method showed the presence of a Gram-negative coccus, but whether this was the meningococcus or *Micrococcus catarrhalis* was not determined. On removal of the calvaria the dura mater exhibited a slight degree of vascular injection, and when this membrane was stripped off creamy pus was found ascending to the vertex along the course of the cerebral vessels and extending between the convolutions of the brain. At the base the exudate was collected around the optic chiasma, the tuber cinereum, the crura, and the ventral aspect of the pons, while posteriorly it was found upon the upper surface of the cerebellum. The tympanum on each side and the ethmoidal sinuses were laid open, but no sign of disease was disclosed.

On cutting into the lumbar portion of the spinal dura mater a quantity of purulent fluid escaped, and a creamy purulent exudate was observed lying upon the posterior aspect of the cord in the dorsal and lumbar regions. No pus was found upon the cervical portion of the cord. It was noticed that while the consistence of the lumbar and dorsal segments of the cord was markedly diminished, that of the cervical portion was still firm.

Examination of the viscera afforded little indication of morbid change. There was slight cloudy swelling of the kidneys, and fatty change was commencing in the liver. The lungs were congested. The spleen was not enlarged; its cut surface was smeared over two nasagar plates, and from these a growth was obtained of *B. coli*, streptococci, and a Gram-negative coccus.

The remainder of the fluid not required for centrifuging was incubated for one night, and films made from loopfuls of the uncentrifuged incubated fluid showed a few Gram-negative cocci, both free and intracellular, a film from the deposit of the fresh unincubated fluid showing intracorpuseular organisms only. Three c.c.m. of the cerebro-spinal fluid which had been inoculated for one night were then diluted with twice the volume of autoclaved normal saline made with water previously filtered at low pressure through a new Chamberland bougie. After sterilization in the autoclave the saline was again thoroughly boiled. The diluted cerebro-spinal fluid was then passed, by the aid of a medium exhaust, through a new Berkefeld filter. (The methods employed for assembling, sterilizing, and testing all filters used in these experiments will be detailed in a separate note.) On the completion of filtration, which lasted twenty minutes, the filter was removed from the filter flask through a large spirit flame, and 2.0 c.c.m. of the filtrate were taken up, still through flame, in a sterile Pasteur pipette guarded with wool. The point of this was again flamed, and the contents of the pipette were slowly discharged under the lid of a