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THE PRESENT-DAY PHYSIOLOGICAL BASIS OF THE CLINICAL STUDY OF FATIGUE.

BY R. D. GILLESPIE,* BALTIMORE.

CONCERNING 'fatigue,' no final conclusion has been reached in the laboratory. Yet it is a phenomenon which is repeatedly encountered in clinical cases, in the absence of any gross disease, both in general and in neuropsychiatric practice. Thus it may occur in states of depression, or it may replace depression as a symptom (Adolf Meyer). The occurrence of fatigue in the so-called neurasthenias is well known. Fatigue-symptoms may be referred especially to one system, as, for example, in 'D.A.H.' (disordered action of the heart). Bleuler makes a classification into neurasthenias and pseudo-neurasthenias, depending largely on the etiology. Apart from general statements as to the existence of low blood-pressure, for example, in the clinical picture, and from mere surmises as to the etiology of the condition, there does not seem to be a connected conception of fatigue as it occurs clinically, based on physiological as well as clinical considerations. The following pages contain a survey of some of the known physiological facts which have a bearing on clinical fatigue.

DEFINITION.

Definition is advisable, as there is much use of the word 'fatigue' in a vague way. Fatigue is most satisfactorily defined as a diminished capacity for work, other conditions remaining constant. (See, however,

* McCunn Scholar in Physiology, Glasgow University. From the Department of Psychiatry, Johns Hopkins Hospital, Baltimore.

Muscio.¹) This definition applies more particularly to muscle, but possibly it will some day be shown to have a strict application to nerve also. That the conditions shall remain constant is an important proviso. It is only necessary to cite, for example, the possibility of obtaining, after work to exhaustion at a higher load or rate, further ergographic work by diminishing the load (Treves²), or the rate (Hough³). The definition has the disadvantage of being *à posteriori*. Not the work that has gone before, but the work that can still be done, determines the degree of fatigue. This distinction is important, because too often it is tacitly assumed in using the word that 'fatigue' is synonymous with having done work; which it is not—except in a special sense, as we shall see. Work may be done, and yet the capacity for work remain as great as before, *provided restitution be complete*. This conception of fatigue may be put simply as follows: Let the organism be capable of an amount of work, A . If a small amount of work be done *and no restitution occur*, then the remaining capacity for work $= A - da$, and $\frac{A - da}{A}$ is a proportionate measure of the remaining capacity and of the intensity of the fatigue, i.e., $\frac{A - da}{A} = \frac{K}{\text{fatigue}}$, or $\text{fatigue} = \frac{KA}{A - da}$. Successive performances of such an amount of work reduce the capacity by Σda . When $A = \Sigma da$, the organism is exhausted. Any intermediate stage represented by $A - \Sigma da$ is a state of fatigue. This formula also expresses the fact that fatigue begins with the beginning of each performance of work, and is not merely an end-product. This is contrary to the conception of Muscio,¹ who seems to regard fatigue as a state reached at some period after work has begun, but seldom or never synchronous with its commencement. It is, on the other hand, in perfect accord with the statement of Verworn⁴ that "fatigue is perceptible to a slight degree even after the first excitation." This assertion is founded on physiological experiments establishing the conditions of the 'Treppe' phenomenon in muscle.

The practical conception, outlined above, of fatigue as a diminished capacity for work, which begins always with the beginning of work and persists to the extent to which restitution is incomplete, is supported by the experimental observations of Verworn,⁴ which led him to formulate the following generalization: "Every living system possessing irritability (in our pragmatic terms 'capacity for work') undergoes a period of reduced irritability at the time of and subsequent to every excitation, for every excitation momentarily decreases the amount of products capable of disintegration and increases the disintegration products in the unit of space. As restitution involves time, a stimulus occurring in the phase preceding complete restitution cannot break down the same quantity of molecules as would be the case after the establishment of

complete restitution; that is, the response is weaker; the irritability is decreased." For Verworn this period of lessened potentiality of disintegration, of lessened irritability (diminished capacity for work) is the refractory period and is identical with 'fatigue.'

RHYTHM.

Another source of confusion occurs in connection with *rhythm*. Frequent search is made, especially in industrial work, for a measure of diurnal fatigue. No unequivocal evidence of diurnal fatigue has been found (Lee and Vanderbuck ⁵). It is possible that under normal conditions diurnal fatigue may not occur, and that rhythm, about which so little is known, and not fatigue, is the basis of the diurnal variation of the human organism. Thus the idea of sleep being a fatigue phenomenon has long been abandoned. The 'Law of Fluctuation' recently propounded by Hering ⁶ is an attempt to make rhythmic alternation in function of constituent parts of an organ a basis for the relative indefatigability of, for example, the heart. Graham Brown ⁷ believes that rhythmic action is one of the most fundamental properties of the nervous system.

Catheart, ⁸ under the influence of Pawlow's teaching, considers that the rhythm of work adopted alike by a laboratory subject and by a factory operative is simply a general example of a conditioned reflex. Vernon ⁹ states that "experienced industrial workers unconsciously adopt habits of work which tend to the production of a maximum output with the minimum of effort." "This capacity of the organism to build up a series of conditioned work-reflexes is one of the potent factors in the prevention of fatigue" (Catheart ⁸).

Rhythm must not be confused with simple time-relations. Some authors, e.g., Charles Féré ¹⁰, are repeatedly guilty of using 'rhythm' when they mean simply 'rate of working.' Time relations are very important. The body replenishes itself automatically as work proceeds, but for replenishment to be complete the rate of work must not be too great (Verworn) on time for restitution, and this optimal rate probably varies for different muscles and organs. It follows that theoretically an organ may go on doing work indefinitely and without fatigue. This receives a practical illustration in the heart muscle. But even the heart muscle may be fatigued if the rate is excessive. Thus, cardiac overstrain is recognized by clinicians (Price ¹¹) even in the normal heart. The practical indefatigability at optimal rates explains also the results obtained by Nicholson ³⁹ in hypnosis. The fatigue which occurred in his waking experiments must have been a complex affair of attention-weariness and sensory discomfort, plus perhaps some suggestion. The rate of working in these experiments is not mentioned, but must have been such as to produce *no* appreciable local fatigue at the given loads.

Thus, Laulanié,¹² assuming that fatigue had a purely physical origin, went the length of maintaining that muscles spontaneously find the optimal rate of work where the intervals of repose exactly suffice for sufficient recuperation, so that long spells of work may be done.

SEAT OF FATIGUE.

These experiments with hypnosis bring us to a question which has been much discussed (with sometimes a blindly assumptive attitude). Ioteyko¹³ arrives at the conclusion that fatigue is peripheral, in opposition to those who have supposed it to be central. This opposition of 'peripheral' and 'central' is the outcome of the older muscle-nerve physiology. It is Adolf Meyer's aim, in his psychobiological approach, to treat the organism as a whole, and it is interesting to find that physiology has lately been passing more and more to the same viewpoint. Sherrington²⁰ took the initiative with his classical *Integrative Action of the Nervous System*. Haldane has followed this with his philosophical as well as physiological outlook in his work entitled *Respiration*,¹⁴ and in various addresses.¹⁵ Cathcart,⁸ in his address to the British Association at Hull, in 1922, on the Physical Efficiency of Man, has given more explicit emphasis to this method of approach, and has shown how the old muscle-nerve physiology has been placed on a broader, more scientific, and at the same time more practical basis. Most of Benedict's¹⁹ work has been done with the human organism as a whole. To look on fatigue as being definitely localizable somewhere, as a monosystematic or mon-organic phenomenon, is a very narrow view. It is a commonplace that in the working of the organism there are many processes, simultaneous and successive, and only after considering the position and the fatigability of each in turn, instead of dividing them arbitrarily into two groups, peripheral and central, will it be possible even to begin to approach the question of the seat of fatigue.

Regarding the organism, then, as a whole, it is to be held in mind that the chain of processes includes digestion, absorption, assimilation (anabolic processes), initiation and transmission of impulses, and contraction (dissociation of physicochemical complexes—katabolism). Moreover, the organism is integrated and is for work. A failure of even one of these processes means a diminished capacity for work, *i.e.*, according to definition, a certain degree of fatigue, and that fatigue may be anywhere. A mere slowing of process is probably not sufficient. Bayliss,¹⁶ following Hopkins,¹⁷ has pointed out that "the metabolism of the cell undoubtedly takes place in such a series of reactions that the products of one form the starting point of the next following. The various component reactions of this chain will almost certainly not progress at the same rate. Suppose, then, that the first component is kept constant in concentration by continuous supply, as will usually be

the case. Then the amount of the products of each reaction at any given moment will be in inverse ratio to the rate at which they change into the next member of the chain. It is clear that in such a state of dynamic equilibrium the actual amount of chemical change taking place in each reaction must be the same: so that if the rate at which any particular step is decomposed into the succeeding one is less than that at which it is produced from the preceding one, there will be a heaping up until the large quantity reacting will compensate for the lesser rate of change. In symbolic form,

$K_1(A) = K_2(B) = K_3(C) = K_4(D)$, etc., where K_1, K_2, K_3, K_4 , etc., are the respective velocity constants of the reaction, and (A) (B) (C) (D), etc., are the corresponding concentrations, in accordance with the law of mass action. It is plain that if K_1 is small and K_2 is large, (A) must be large and (B) small, and so on."

A mere slowing of a single process, then, will be compensated by the heaping up of a larger quantity of the reacting substance in question, provided the *previous component is supplied in sufficient amount*. But if the preceding component be not supplied sufficiently, the compensatory heaping up cannot occur. If $K_2(B) = K_3(C)$ represents, for example, the reaction occurring in muscular contraction, and if B (glycogen in this case) be deficient, the amount of energy liberated must also be less, unless the reaction $K_1(A) = K_2(B)$, which represents, say, the conversion of foodstuff into glycogen, can be speeded up, and this is only possible if the carbohydrate in the bloodstream and hence in the blood is ample. The succession of physicochemical changes which leads from the digestion of foodstuff to its utilization as external work can be only approximately represented by such a series of reactions as has been symbolized above. The matter is infinitely more complicated; but the dependence of the ultimate capacity for work on every preceding step in the series of physicochemical changes is well brought out.

The anabolic and katabolic processes involved may be classified in other ways. The classification of mental functions into receptive, elaborative and emissive (Meyer¹⁸) is well known. There is possible also at a lower physiological level a division into receptive and emissive or receptor and effector functions, as they are better known (Sherrington²⁰). In speaking of fatigue it has been customary to consider principally the effector side, and it has been too often forgotten that a 'receptor' (nutritive) deficiency, while not so immediately remarkable (partly because of the organism's power of storage), will lower the work-capacity and will, if the organ's performance be compared with its own performance in a previous (healthy) stage, cause a degree of fatigue (cf. Benedict's¹⁹ experiments on inanition and metabolism).

It is important to demonstrate this significance of the receptor side, since it has been much neglected, yet it cannot be passed over

clinically. The importance for a given chain of reactions of an adequate supply of the preceding components has been touched on above. It is unnecessary to do more than mention the influence of digestion and absorption disorders in diminishing the energy intake and the energy reserve of the body, but it is of more recent interest to notice Haldane's¹⁴ work on the intake and availability of oxygen and its effect on the organism.

It has been shown by Haldane that the influence transmitted through the vagi initiates inspiration or expiration, and the centre persists in the inspiratory or expiratory phase till the vagus gives the signal which terminates the phase and initiates the complementary phase. The centre behaves as if it always remembered the last signal, and the analogy between any act dependent on memory and the duration of the inspiratory and expiratory phases of breathing is evident. Haldane showed (along with Davies and Priestley²¹) that resistance to respiration causes quickening and shallowness (i.e., shortening of the 'memory' of the centre), and finally cessation of breathing. Even a slight deficiency of oxygen greatly favours the development of such symptoms, e.g., during any muscular exertion the oxygenation of the blood may diminish and the patient suffers from shortness of breath literally because the breath is short.

Meakins and Priestley²² found a marked deviation from normality in the breathing in cases designated 'D.A.H.,' neurasthenia, soldier's heart, etc. All the signs of fatigue of the centre were present in these cases, including an abnormal increase in the readiness with which the Hering-Breuer reflex is elicited, due to weakness of the centre, i.e., a diminished persistence of the individual inspiratory and expiratory discharges of the centre. If we apply the same general conception to the other exaggerated reflexes and general failure of nervous coordination in 'neurasthenia,' fatigue, and shock, we seem to render these conditions more intelligible. Thus the quite general nervous irritability, exaggeration of circulatory reflexes, tendency to sweating, and occasional instability of temperature observed in neurasthenia are probably analogous to the exaggerated reflex restriction in depth of breathing and the inability to hold a breath in anoxæmia. All these symptoms are due to what Hughlings Jackson calls 'release of control.'

On the other hand, fatigue in muscle increases the normal threshold stimulus (Gruber²⁹).

Irritability, in the pathological sense of lowered threshold of excitability, in which it is used above by Haldane, is to be distinguished from purely physiological irritability, in the sense of capacity for reaction to stimuli, in which it was used by Verworn. The two statements are entirely compatible if this difference in usage be kept in mind.

Haldane has thus shown that anoxæmia may produce an over-

excitability of the respiratory centre, or, as he prefers to put it, a fatigue of the respiratory centre, with consequent diminution of the threshold for the Hering-Breuer reflex. Bohr²³ and others have demonstrated the importance of the PH of the blood for adequate utilization of oxygen, and hence—since hæmoglobin is capable of acting as an acid—the importance of the latter not only as a carrier of oxygen but for its availability.

These considerations all refer to the receptive side, but anoxæmia means also a diminished store of oxygen on which the effector cells of nerve and muscle can draw; in other words, a lowered work-capacity. The evidence that oxygen is necessary for the functioning of nerve-fibres has been the subject of considerable discussion. Tashiro's evidence in favour of oxygen-consumption during the passage of a nerve-impulse is not generally accepted (Bayliss¹⁶), and the experimental results of Fröhlich, Thorner, and others demonstrate only that oxygen is probably necessary if the function is to remain unimpaired over a prolonged period. The case is different where nerve-cells are concerned. Here there is undoubted need of oxygen. The loss of consciousness which follows deprivation of oxygen to the brain is sufficient evidence of this (*v.* Haldane's experiments on himself and the animal experiments of Cushing and Macleod²⁴).

The personal experiences of Haldane¹⁴ in this connection are worth quoting. They present a picture of a kind of 'physiological psychosis.'

"As the slow course of anoxæmia advances, the senses and intellect become dulled without the person being aware of it; and if the anoxæmia is suddenly relieved by means of oxygen and ordinary air, the sudden increase in powers of vision, hearing, etc., is an intense surprise. The power of memory is affected early and is finally almost annulled, so that persons who have apparently never lost consciousness can nevertheless remember nothing of what has occurred. Powers of sane judgment are much impaired, and anoxæmic persons become subject to irrational, fixed ideas, and to uncontrolled emotional outbursts. Muscular coordination is also affected, so that a man cannot walk straight or write steadily. With further increase in the anoxæmia, power over the limbs is lost. The legs first become paralyzed, then the arms, and finally the head. The senses are lost one by one, hearing being apparently the last to go. A man suffering from anoxæmia cannot be held responsible for his actions—he may laugh, shout, or sing without reason, burst into tears, or become dangerously violent. He is, however, always quite confident that he himself is perfectly sane and reasonable, though he may notice that he cannot walk or write properly, cannot remember what has happened, and cannot properly interpret his visual impressions. When unable to stand I have always been quite confident of my own sanity, and it was only afterwards that I realized that I could not have been in a sane state of mind."

Further, Mott ⁴⁰ has drawn attention to the supposed importance of the oxidase granules of the cell-layers of the cortex, and has attributed much of the mental deterioration in dementia præcox to a diminution in their number and function.

That fatigue is not encountered in nerve-fibres is a belief discredited by Verworn ⁴ and his fellow-workers. Fröhlich, for example, found that the refractory period in a medullated nerve was prolonged by lack of oxygen. Thorner showed that the irritability of stimulated nerve sank with much greater velocity than that of non-stimulated nerve, in the absence of oxygen.

Bainbridge ³⁷ reaches the general conclusion that in ordinary muscular work it is the central nervous system that is fatigued. As to the elective site of fatigue within the latter, it is usually supposed that fatigue is evident first in the synapse, before it affects the cell (Sherrington ²⁰). Our knowledge of the physicochemical constitution of the synapse is largely conjectural, and the question is complicated by the demonstration of the continuity of nerve-fibrils from cell to cell. But this appearance has been attributed to post-mortem changes (Bayliss ¹⁶). It is, therefore, permissible to suppose that a diminution of difference in potential between the synaptic interfaces is the cause of synaptic fatigue. Such a condition of diminished potential is in accord with our general definition of fatigue.

The phenomena occurring in the isolated nerve-muscle are much better known (Hill, ²⁵ Fletcher and Hopkins ²⁶), so much so that the nerve-muscle preparation has been taken as a paradigma for fatigue of the organism as a whole. But here also the neuromuscular junction complicates and obscures the facts. As far as the muscle itself is concerned, there is an accumulated body of knowledge, which has lately been added to by Meyerhof ²⁷ and others, regarding the store of glycogen in muscle and its conversion into CO₂ and lactic acid, with the liberation of muscular energy which is manifest in muscular contraction. Diminution in the glycogen-reserve of muscle means diminished capacity for work and, to that extent, fatigue of the muscle. The matter is, however, more complicated, for fatigue is longer in occurring if the accumulated lactic acid be washed away as it is formed. This touches on the field of the influence of toxins on fatigue, to which we shall return.

THE INTERNAL SECRETIONS.

No account of the physiology of fatigue would be complete without reference to the internal secretions of the thyroid, pancreas, and adrenals, and to the vegetative nervous system.

First, as to the pancreas: It is now demonstrated that only in so far as the muscles by the aid of insulin are able to utilize the blood-sugar, is the latter available for the working of the organism. A lack

of insulin is equivalent in its effect to a lack of utilizable energy-reserve, and consequently a diminution of the organism's work-capacity.

The action of adrenalin is too well known to need recapitulation (Cannon²⁸ and his co-workers). Just how it acts is still unknown. Gruber⁴¹ has suggested that it mobilizes the glycogen of muscle, but Wilenco³⁰ declares that adrenalin diminishes the power of the tissues to burn sugar. The part played by adrenalin under normal circumstances, i.e., apart from emergencies, is still obscure. It is necessary to mention in passing, in order to question it, Spaeth's³¹ suggestion that 'nervous breakdown,' as he calls it (presumably 'exhaustion states,' 'neurasthenia'), may be due to 'adrenalin poisoning.' He bases this hypothesis partly on the hyperexcitability of the nervous system generally; but adrenalin acts principally on nerve-endings, and sympathetic endings at that. Moreover, Haldane has shown that anoxæmia may alone be sufficient to account for the nervous hyperirritability. Further, a state of adrenalin poisoning would reasonably be expected to show the symptoms of adrenalin excess, which neurasthenias, as usually understood, do not, but rather the reverse—a poor vasomotor tone, with low blood-pressure being not uncommon, while sweating (which probably is not a sympathetic phenomenon) is frequent.

Thyroid: The action of thyroxin in increasing oxidative processes, and therefore in producing a greater capacity for work, but also with a tendency to cause a more rapid utilization of energy-material, and therefore a profounder degree of fatigue in a shorter time if utilization be so accelerated as to exceed supply, is now fairly well established.

It is doubtless this effect which accounts in part for the fatigue complained of in patients with exophthalmic goitre. Another explanation is possible which would be more in accord with our conception of fatigue as present from the start. A relative oxygen-want may occur from the acceleration of the entire metabolism, which produces a corresponding increase in the requirement of oxygen (cf. Verworn⁴).

OTHER FACTORS BESIDE CHEMICAL ONES WHICH DETERMINE THE CAPACITY FOR WORK.

So far this discussion has dealt with chemical factors—storage of glycogen, oxygen-supply, adrenalin, thyroxin, and insulin. There are, however, other factors which determine the work-capacity of muscle, and since muscle is the chief effector, of the body generally. These factors are mechanical. Starling³² has enunciated the 'Law of the Heart,' in which he states that the work done by the heart muscle-fibres in a single contraction is a function of the original resting-length of the fibre. Up to a certain optimum point, the greater the initial length of the fibre, the greater the succeeding contractions. This involves the conceptions of tone and of optimum conditions. The resting-length of

a muscle fibre is an expression of its tone, and tone is dependent on certain factors (many of them being imperfectly known), not the least of which is probably oxygen supply. We are again reminded of the clinical importance of sufficient O_2 , and the influence of anoxæmia on the gastrointestinal condition, and, therefore, on nutrition and consequent fatigability.

As to optimum conditions, Starling found that there was an optimum fibre-length for maximal efficiency. Spaeth,³¹ possibly forgetting this, has remarked that so far as he knows the physiologists have never answered the question as to the optimal conditions for muscular work, i.e., the conditions which will enable a muscle to furnish the greatest amount of work in a given time with least fatigue. In Cathcart's laboratory Gibson and myself tried to obtain some further data on this question with regard to the heart, and we found, over a range of load varying in the ratio of 3 : 1 at rates of work varying in the ratio 1 : 3, that the maximum pulse-rate and blood-pressure attained were very nearly constant; i.e., within the limits of our experiments the work done by the heart was almost exactly proportional to the external work done per unit time, and relatively independent of the actual rate or load.

EMOTIONAL FACTORS.

Such are the chemical and mechanical factors concerned in capacity for work and in fatigue. The emotional factors are not less important. It is significant that of late years it has become increasingly possible to place these also on a physicochemical basis. The increased output of adrenalin which apparently occurs in various emotions and its speeding up of physicochemical effector reactions, often to a level which exceeds what is advantageous to the organism (as in muscle tremor, acceleration of the heart beyond what is likely to be required for practical purposes by the muscles, and so on), must lead to a prolongation of the recovery period when the crisis is over, and enables us to understand why repeated emotional disturbances must be followed by fatigue, or even by actual exhaustion.

In close relation to these phenomena stand the now easily demonstrable changes in the blood-sugar concentration, with its possibilities of relative oxygen-want.

That prolonged emotional stress may lead to a permanent glycosuria has long been believed. Our conception of the chemistry of this phenomenon has been extended by the establishing of the importance of insulin in the utilization of the blood-sugar.

VAGO-SYMPATHETIC SYSTEM.

The relations of the vago-sympathetic system to fatigue are obscure. Three broad principles are fairly well established :—

1. The vagus was long ago given by Gaskell the designation of the 'anabolic nerve of the heart.'

2. The sympathetic comes into play when an extra output of energy is demanded (in conjunction with an increased secretion of adrenalin and increase of sugar in the blood).

3. The vagus and sympathetic are in a sense antagonists.

From these principles the general statement may be made that the tendency to fatigue of the organism will be greater or less according as the sympathetic or the vagus depresses the balance on one side or the other—on the side of increased or decreased metabolism.

TOXINS.

On the basis of our definition, the occurrence of a toxin is unnecessary to account for fatigue. But there remain to be accounted for:—

1. Sensations of fatigue.

2. The biological value of their occurrence.

Myers³⁸ has remarked that a subjective feeling of fatigue probably indicates a lessened capacity for work; but as Bainbridge³⁷ pointed out, an almost normal capacity for work may coexist with marked subjective fatigue. Fatigue is one of the factors of safety in the human organism (Pembrey³³, Cathcart⁸). Regarding the chemical changes in work as a reversible reaction, and as obeying the law of mass action, a slowing-up of the action as it nears the end-point would be expected. In other words, the rate of diminution of capacity for doing work would itself diminish as the capacity diminished (i.e., as fatigue increased). But there is nothing here to prevent the reaction ultimately reaching practically an end-point, i.e., complete exhaustion. The sensation of fatigue, however, intervenes long before this point is reached, and tends to cause a cessation of activity; the sensation is a 'factor of safety.' What causes this sensation of fatigue? Some of it is a feeling of heaviness in the limbs and chest due to loss of vascular tone and diminution in rate of blood-flow, but the more specific sensation of fatigue is probably due to the presence of lactic acid, and perhaps occasionally indol, skatol and phenol, and their derivatives (Hastings³⁴). That a definite fatigue 'kinetoxin' exists was asserted by Weichert,³⁵ but disproved by various authors, including Lee.³⁶ It is incorrect, however, to regard lactic acid as a fatigue 'toxin' in the strict sense of the term, since the reaction is a reversible one and the lactic acid can in part at least be rebuilt into the muscle molecule in the presence of oxygen, and because the retardation is simply an expression of the law of mass action, and not a specific action of the acid on the muscle fibre.

Such, briefly, are the fundamental physiological conditions, so far as at present known, underlying the condition known as 'fatigue' of

the human organism. In the investigation of fatigue as it occurs clinically only a study which takes as many of these factors into account as the available apparatus will allow—a study which, in other words, contemplates the organism as a whole from an examination of as many of its working parts as possible—will throw more than an equivocal light on the problem of clinical fatigue.

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