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SOME ASPECTS OF THE PROBLEM OF FATIGUE

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Ludwig Aschoff pointed out in his lectures on pathology that it is impossible to distinguish histologically between infections and regenerative and reparative inflammation. This means that the organism has few ways, or probably one essential way to act or react in its struggle for life and health. This is true not only for the above mentioned reactions but also for the causes which produce some of them.

In this short article an effort has been made to show that processes such as fatigue, trauma, poisoning, old age and inflammation are all due to the same type of changes in the mineral metabolism. The different clinical and pathological pictures vary according to the degree of change and the damage caused. We may begin by saying that abnormal biological processes start with changes in the mineral metabolism, and the return to normal begins with the reestablishment of a normal mineral metabolism. This points to a uniformity in nature, as the same law can be applied to plants, animals and human beings. The problem of fatigue will first be dealt with from this viewpoint. Fatigue is generally explained as a disturbance of metabolism and particularly as an excess of acids, especially of lactic acid after exercise, while various authors bring one or another component into the foreground.

In short, though the symptoms seem to be essentially different, they arise from the same source.

Fatigue and weakness are often the first symptoms of diverse chronic diseases, such as mental disturbances, myasthenia, tuberculosis, old age, cancer, etc. I have described in several articles that the underlying cause of some of these diseases is, in the beginning, an increase in the cells of water, sodium chloride, and other minerals belonging to the sodium or Na group and a decrease in potassium, calcium, phosphorus, and other minerals belonging to the potassium or K group. Margeria (1) defines fatigue as follows: It is a sense of general discomfort and a lessened readiness of the muscular system to perform work. He finds that in fatigue the period of contraction of muscle fiber is prolonged and that, as a result, the frequency of contraction is slowed down. He holds the general view that this is caused by the creation of the acid products of metabolism which at first stimulate more rapid contraction, but later impede contraction by accumulation. In periods of rest these waste products are removed by means of oxidation and the former ability to work is restored.

Although he emphasizes that the essential physiological process of glycogen division in the muscle fiber takes place anaerobically, he still thinks that the function of the O_2 supply is decisive in fatigue. Several other authors, including Helmuth Boehme (2), Isac and Matthes (3), and Isac, Matthes and Yamanaka (4), share this view and even go a step further.

The last named investigators find that the damage is done, not so much by a deterioration of the above described composition of the arterial blood, as by a poor O2 supply at the periphery, resulting from the slowdown in circulation; that is, the O2 supply is less, the farther the tissue is removed from the center.

According to Margeria, in prolonged anaerobic activity the pH content of blood is reduced by some “0.4 to 0.5 units”. This signifies a high degree of acidosis, which would lead to coma if it were not checked by all available protective mechanisms for the neutralization of acids. He thinks that the appearance of nervous disturbances is due to the insufficient functioning of this protective mechanism, which also explains the temporary improvement following the use of sodium bicarbonate.

The decrease of pH in the blood is of course due to increased lactic acid and carbon dioxide, because breathing cannot remove the latter promptly enough. The accumulation of carbon dioxide produces still more unfavorable consequences in that it liberates additional quantities of lactic acid from sodium combinations, thus overburdening the liver.

Christensen's observations regarding the metabolism of muscular functions show two important results: 1. In great physical exertion the blood sugar sinks. If the sugar level of blood rises as a result of an additional sugar supply, the ability to perform work is considerably improved. 2. Three persons who were trained for these experiments were able to work up to three times as much with a predominant carbohydrate diet as with a fatty diet. Accordingly, he defines fatigue as a "hypoglycogen symptom of cerebral origin".

The facts cited up to this point explain the symptoms of fatigue somewhat as follows:

Fatigue sets in, and must set in, because the organs of metabolism, circulation and elimination are, in their daily, normal functions, incapable of functioning longer than for a limited period of time without rest. The more intense the activity, the more limited the period of uninterrupted functioning.

The Body's Reactions to Avoid Fatigue

For the purpose of increasing the rate of activity it is possible for the organism to accelerate certain individual functions, and to add others. The supply of O_2 is increased by means of blood rich in erythrocytes from the reservoirs, and this increase in hemoglobin facilitates the absorption of O_2in the lungs. Simultaneously, more and more capillaries are being unfolded, thus bringing more O_2 to the active organs in the periphery. Maegeria, Atzler (6) and others, therefore, see in a deficient O_2 supply the main factor of the fatigue symptoms. In this manner Christensen's result of increased efficiency with a carbohydrate diet becomes understandable, because the carbohydrates need much less O_2 for combustion than fats and proteins.

In another article Christensen (8) states that the respiratory quotient during work shows only slowly increasing combustion of fats. Even if the blood sugar temporarily falls to fifty-two milligrams percent, forty percent of the energy is still furnished by carbohydrates.

F. Bruman made interesting observations on O_2 consumption. He introduced the assumption of an "O_2 debt" in the tissues which appears in connection with a certain exertion of the body. He describes how this "O_2 debt" is influenced by the addition of potassium chloride. The O_2 consumption is reduced to one half despite sufficient ventilation. The production of carbon dioxide is reduced. The elimination of ammonia falls. Potassium is partly retained … Accordingly the yield of the muscle rises to the highest possible level.

Fatigue and Mineral Metabolism (Experiments with the K Group)

During these experiments, the subject feels very uncomfortable; he can work only painfully, and is quickly exhausted. The advantages of such maximum performance of the muscle are therefore questionable; they are very limited in duration, and are accompanied by injurious nervous symptoms.

However, the fact that potassium supply seems to be a factor in the fatigue problem was evidenced by various other experiments. Thus, Winkler (10) found that there is an increase of potassium in the muscle of the pregnant uterus in preparation for the great task ahead. The dry weight of the potassium content is increased from 1.030 percent in the second month of pregnancy to 2.58 percent in the ninth. The potassium-sodium quotient is increased from 1,601 to 4,961. On the other hand, according to Gerard (11a), all tissues, whether muscle, gland or nerves, with maximum function have the greatest potassium-sodium quotient. This accumulation of potassium seems to be a precaution of the body to prepare these tissues for the inevitable increase in the amounts of acids which result from the increased activity during maximum function and these acids must be alkalized.

Eppinger's (22) animal experiments have contributed fundamental evidence of this fact. He measured a loss of potassium in muscle (from 439 mg. percent to 414), in the heart (from 411 to 394) and especially in the liver (from 428 to 350) resulting from increased activity.

As a consequence of my studies (7a) I introduced a potassium rich diet as treatment for cardiorenal diseases in order to eliminate sodium chloride and water from the edematous tissues. (The enrichment of the minerals of the potassium group and the diminishing of those of the sodium group provides the chief physiological basis for the absorption of the products of inflammations of an acute or a chronic nature, as they are found, especially in tuberculosis.)

The *changes of the mineral contents in fatigue* are shown in the following table[1]:

Normal

MG. PERCENT

	Number of Animals	K	Na	Ca	CI	K:Na
Muscles	29	439	109	11	40	2.39
Heart	29	411	125	11		1.94
Liver	29	428	99	8	69	2.55

After Eighteen Hours Running

MG. PERCENT

	Number of animals	K	Ka	Ca	CI	K:Na
Muscles	31	414	117	12	35	2.09
Heart	31	394	142	10		1.64
Liver	31	350	117	9	60	1.76

As regards the production of ammonia, the animal experiments of Heinz Wagner (12) have demonstrated that following radiation with x-rays and during heavy protein feeding ammonia is required for alkalizing. If four to five days before radiation, the alkali content of the blood serum is increased fourfold by means of an abundant diet of turnips, then the average loss resulting from radiation is sixteen percent for calcium and nineteen percent for potassium. In other words, with such an abundant supply of mineral salts from vegetables, the body uses these first to neutralize the acids, and only after their supply has been exhausted is ammonia produced for this purpose.

[1] From Eppinger: *Arch. F. exper. Path. U. Pharmakol* 133:509-524

The significance of potassium for the function of the muscle fiber was the subject of researches by Murray (13). By means of a potassium-free solution he made the hearts of chicken embryos poor in potassium. When these hearts were then immersed in a potassium-containing solution, there was a distinct fibrillation, more pronounced even than that of the normal heart.

W. R. Hess (14) also found that normal contractions are restored to heart muscle fibers poor in potassium after adsorption of potassium. He also found that the parasympathetic nervous system has a "histiotropic function", by which he means the removal of waste material from the tissues as well as their replacement. This function is stimulated and accelerated by the addition of potassium. This confirms the views held by Kraus and Zondek.

Tatyaeva (15) irritated the sympathetic nerve fibers: of an isolated frog muscle which was immersed in Ringer's solution. He found that only the fatigued muscle yielded potassium and lactic acid to the surrounding liquid; there was no such outflow of potassium and lactic acid from the resting muscle. Wallace O. Fenn (16) found that among others the fatigued muscle showed evidence of a phosphorus loss.

The loss of potassium by the actively functioning muscle—and especially by the heart muscle—has further been established under many various experimental conditions. Dennis and Moore (17) found that after artificial locking of the coronary arteries the potassium content of the coronary veins rises; this signifies loss of potassium by the muscles. Marenzi and Fustinoni (18a) determined the potassium and sodium distribution in the bodies of toads after removal of the adrenals. As soon as insufficiency symptoms appeared, usually forty-eight to seventy-two hours after the operation, these investigators found that in the blood plasma sodium falls and potassium rises; while in the liver and heart muscle the contrary happens. That is, in the liver and heart potassium is lost and sodium is taken up. This process is less pronounced in the other muscles.

There is, therefore, increasing evidence that fatigue is a problem of metabolism, the basis of which is a loss of potassium, phosphorus and other minerals, and penetration into the cell of sodium and other elements. To avoid these pathological changes as far as possible I worked out the fundamental principle of salt free diets and found that some fruit juices are especially helpful for sodium elimination (18b).

Different Conditions for the Change in Mineral Metabolism

However, it must not be forgotten that before this exchange of minerals can take place, the capillaries must first have been damaged. Kaunitz and Schober (19b) furnished experimental proof of this fact with eight salamanders which had been poisoned with allylformiat. They found that the lowering of the normal potential difference occurred in the vena cava after some five to thirty minutes, but in the liver only after some twenty to sixty minutes. This so-called "salamander experiment" has meanwhile been confirmed by many other investigators, so that the fact has become generally accepted that the damaging of the capillaries must precede any change in the parenchyma cells.

Fenn (20) observed the same phenomenon, and while studying the potassium and chlorine ions of the muscles he found that various conditions influenced these ions in the opposite sense. In hard and prolonged work the fibrilla loses potassium and absorbs instead an equ1valent quantity of sodium. This change is reversible during a rest period. This result led to the assumption that, following the accumulation of the acid waste products of metabolism the cell membranes become permeable for both potassium and sodium but traveling in the opposite direction.

The chief result of these studies is that as a biological law, the following process is always repeated: If the cells have been damaged, sodium enters and potassium, together with phosphorus, calcium and magnesium, leaves. This process remains fundamentally always about the same, irrespective of the type of cell damage, which preceded it.

The only variable feature in fact is the degree of damage suffered and the momentary condition of the cell. The following may be mentioned as causing such varying degrees of cell damage: fatigue, trauma, operation, poisons, anesthesia, alcohol, toxins (from infectious diseases), tumor, atrophy of the organs, loss of organs, and old age, R. Keller (21).

Fatigue—Rudiments of Inflammation

The following chart compiled by Eppinger has been chosen to show that there is only a difference of degree between fatigue and inflammation. It must be emphasized that of the ten symptoms of inflammation, the three first are also typical for fatigue:

X.	Invasion of leucocytes.
IX.	Formation of necrosis, equalization of chemical and physical tension.
VIII.	Tearing up of capillaries—formation of pudules of blood.
VII.	Thickening of epithelium.
VI.	Thickening of capillary wall—disturbance in cell nutrition.
IV.	Increase in sodium and loss of potassium—cloudy swelling.
III.	Potassium and sodium migration. \
II.	Change in potential difference. > Fatigue
I.	Change of the physical permeability. /
I. to III.	Histologically not identifiable fatigue.
IV. to X.	Histologically identifiable *serous inflammation,* etc.

The experiments of Fenn and Gosch (23), showed consistent results. They fed rats with two different one-sided diets until atrophy of the muscles had been produced. The one diet consisted of cereal-milk foods with the addition of cod liver oil; the other consisted solely of grains, thus exaggerating the usual faults of the human diet. The analysis of atrophied muscles showed that the loss of potassium was incomparably greater than that of creatin; and that the increase in sodium was almost double that of chlorine. That is, sodium entered not merely in combination with chlorine, but in addition by itself. These atrophy experiments therefore show in greatly exaggerated form the same process, namely, a loss of potassium by the cell and the penetration of sodium.

There is a close connection between fatigue and sleep during which, according to Waelsch (30), similar Changes in the metabolism of the cells occur after changes in their permeability have taken place. This problem, as well as the clinical symptoms of fatigue in various diseases, and the connection between fatigue and fear in psychiatry (Claudes) are not a part of our inquiry.

Up to this point we might summarize the facts cited above somewhat as follows: Fatigue is caused by a condition of slight general acid poisoning which changes the mineral contents of the cells by a loss of potassium, phosphorus and other minerals, and their replacement by sodium, chlorine, and water. This change is reversible during rest. Compared with inflammation, fatigue seems to be a reversible partial symptom of general inflammation.

Old age, on the other hand, seems to be a chronic, nonreversible form of fatigue. The following table, compiled by Peter W. Salit (24) of the Eye Clinic of the University of Iowa, shows clearly the shifts in the mineral contents of the cells from the eyes of oxen in old age.

EXAMINED ANIMALS	AGE	CAMERA FLUID MG. PERCENT POTASSIUM	CORPUS VITREUM MG. PERCENT POTASSIUM	SERUM MG PERCENT POTASSIUM
5	4 weeks	21.3	29.5	24.5
6	6 weeks	21.3	22.7	27.2
6	8 weeks	19.6	28.3	30.6
5	1 year	20.1	20.5	27.0
7	5-10 years	16.5	23.4	21.6
5	over 10 years	8.5	20.5	15.3

With its chief characteristics of reversibility, fatigue stands, in effect, outside the realm of pathological symptoms; for its general and local changes disappear again during rest, in contradistinction to the more lasting or permanent changes of inflammation, atrophy and other pathological processes.

The mechanism of changes occurring in the cell during fatigue and inflammation is further illuminated by the studies of Jacques Loeb (25) who seems to have been the first to discover a swelling of the living cell following the penetration of sodium. His essential discovery was that the proper distribution of the mineral salts as between the blood and tissues is linked up with t certain *"Schwellenwert",* the so-called "potential difference". He concluded that proper distribution of the mineral salts is the determining factor for the functions of the cells. And he also found that it is possible to influence the capillary membranes. The normal plant and animal cells have certain powers which counteract the forces of osmosis and diffusion so as to prevent an equalization of the potential difference. According to Szent-Gyorgi (26) vitamin P helps to maintain the potential difference.

The studies of Rudolf Keller (27, 28) and Hans Eppinger and his school have further advanced the understanding of these processes. Eppinger found that a number of vital forces are effective in the normal function of the cell mechanism: 1, hydrostatic pressure; 2, osmosis and diffusion; 3, oncotic pressure (with plasma protein as refulator); 4, viscosity of the plasma (for instance, more highly concentrated venous; 5, interstitial connective tissues (the connective tissues inserted between the cell and the capillaries take an active part in the exchange of fluids); 6, electrostatic forces.

Rudolph Keller shows in his studies that the parenchyma cells are positively charged, while the blood, the lymph and the connective tissues are negatively charged. The electrical tension between blood and parenchyma cells may at first seem insignificantly small—only sixty millivolts as measured in the high tension apparatus of Furth. Considering, however, the small distance involved it is very significant.

Keller and his school demonstrated in numerous papers that in plant as well as animal organisms salts, food elements, and vitamins are separated into two groups. In the highly concentrated biological milieu their electrical charge has been transformed; "they show a tendency to adhere to the protoplasma colloids, and to accept their traveling direction". In this manner, however, the normal movements of anions and cations in a diluted inorganic salt solution is reversed; in the latter, the acids travel to the anode, and the alkalis to the cathods. In the biological milieu it was shown by Waelsch by means of high tension apparatus that the negative chlorine and water travel to the negative cathods, while potassium, the most positive metal, goes to the positive anode. This means that within the living tissues, and especially in the living cells and membranes, the mineral salts are subordinated to the functions of these cells and tissues. They still retain their dominating power in the life of the cell as far as the equilibrium and exchange are concerned. They are the carriers of the electrical charge in cells, but have to adapt themselves to the prevalent laws of the colloidal proteins. The latter are themselves no pure electrical type, and have been called "zwitter-ions" or "in-between" ions.

The result of numerous experiments in this field permit us to say that in the living cell the minerals are grouped in such a way as "not to upset the very delicate equilibrium of the cell proteins". Gradually evidence has been accumulated that sodium, chlorine, disassociated calcium, H_2O, iodine and vitamin C are positively charged; and that potassium, PO_4, SO_4, calcium, magnesium, glucose, urea, insulin, some vitamins, etc., are negatively charged. Keller formulated the electrical *"Gruppenregel"* or "group-rule", and showed that the members of the positive group (the so-called Na group) cling to the negatively charged blood, lymph and connective tissues, while the members of the negative group (the so-called K group) are stored in the positively charged parenchyma cells. A description of the technique used in this research work can be found in an article by Edward Singer (33).

Now it becomes easier to understand the various forces which are active on the cell surface and which are also measured by the potential difference. Thus, in poisoning and inflammation the potential difference may fall considerably, even to zero, first in the capillaries and then in the cells themselves. Keller found that "fatigue, poisoning, illnesses, lack of oxygen, lack of food, reduce the normal electrical tensions in the tissues as well as in the blood serum and connective tissues".

Changes in the mineral contents of the cells produce different reactions as far as function is concerned. Sodium causes swelling of the cell and loss of glycogen in the liver cell: potassium has the contrary effect. I have not been able to find any data as to whether or not the glycogen loss of the working muscle increases with the penetration of sodium; it would be an interesting fact in comparison with analogous processes in the liver cells.

All these observations and studies may now give us certain indications regarding the biological processes underlying fatigue. 1, The membrane is damaged by the production of acids which make it more permeable. There follows, 2, lowering of the potential differences; 3, inflow of sodium, chlorine and water and outflow of potassium, calcium, phosphorus, magnesium, etc.; 4, regeneration towards the normal status in rest, or, 5, if rest is no longer able to restore the normal state then these changes become a permanent condition such as is found in atrophy or old age, etc. The theoretical conclusions of these fatigue studies seem now to point in the following direction: In order to attain greater capacity to work or increasing endurance, the human body requires an accumulation of minerals of the K group, so as to give the tissues a greater reserve for neutralizing the acids which are the inevitable waste products of body activity or metabolism. By means of this "K group reserve" the normal pH is strongly protected and the normal potential difference is maintained as long as possible.

Mineral Metabolism—a Unit in Soil, Plants (Food) and Animals

The studies of Dumont (34) show perhaps best the connection between fatigue and the larger problems of nutrition. He deals with the effects of a deficient mineral composition of the soil and the foodstuffs grown on it upon the working power and culture of the population. He demonstrates that the contents of such minerals as potassium, phosphorus, calcium, magnesium and others in soil and food become determining factors in the development of races and nations.

Dumont shows, for instance, that the staple diet in African Congo is exceptionally poor in calcium and phosphorus. The potato grown in that part of the world contains only three mg. percent of calcium oxide, as compared with nineteen mg. percent in Brazil and one hundred percent in Europe. Soil studies in the Congo have confirmed this almost complete lack of calcium. The very opposite conditions are found along the banks of the lower Nile, where the soil contents of calcium and phosphorus is exceptionally high. Now compare the beautiful bodies of the Arabs, their great strength, good teeth and their remarkable endurance, with the poor bodies, diminished strength and small endurance of the Congo negroes. Dumont explains their poor condition as caused by a disturbed mineral metabolism "a form of undernourishment with general asthenia, rapid fatigue, reduced immunity". The various medicaments against tropical diseases have hardly any effect in such demineralized bodies.

According to a study of the United States Department of Agriculture (35) phosphorus deficiency in the soil has been found in Minnesota, Wisconsin, Michigan, Florida, Kansas, Montana, Utah, Texas, Pennsylvania and California. "The deficiency may be localized in certain areas within the State or may become evident only during seasons of drought ... Animals suffering from a lack of this mineral may soon be lacking in other factors as well—such as calcium, protein, vitamin A, etc. … "Calcium deficiency has been established in Florida, Louisiana, Nebraska, Virginia and West Virginia.

The interesting fact about these findings is that deficiencies in certain important minerals cause the development of other deficiencies, such as of vitamins, hormones, ferments, etc. Much work needs still to be done in this field, especially as many studies point to the fact that the available tables regarding the mineral contents of plants constituting our main foods, are still entirely insufficient.

This brief review of the main components of fatigue shows that it is but a symptom indicating a disturbance in the entire metabolism: In the glycogen supply (hypoglycemia); in the oxygen supply (oxygen debt); in decreased oxidation power (not responsive to artificial vitamins); in heat radiation; in the adaptation of an increased blood supply; in the opening of the capillaries (avoiding capillary poison) ; in the transformation and elimination power of the waste product. All these are but parts of the entire metabolism. Neither one of them nor all of them together reveal the underlying cause. The nucleus of the problem lies in the neutralization of the acid waste products, (lactic acid, amino and fatty acids, carbon dioxide, etc.) and their elimination.

The logical therapy resulting from these facts must proceed in the following three directions[2]:

1. The mineral salts of the K group (potassium, phosphorus, calcium, magnesium, etc.), which are able to neutralize the waste products, must be so abundant in the food that the amounts taken in will always be in excess of those used up.

2. The prompt and unimpeded elimination of the waste products of the digestion of the food and the metabolism of the cells.

3. A minimum of fats and proteins in the food intake, so as to reduce both the burden on the oxygen economy and the accumulation of fatty and amino acids.

All these remedies are, however, able only to postpone fatigue, not to prevent it. For fatigue has to occur essentially because most of the organs are not adequately equipped to function without rest. The changes in the mineral content of the cells found in fatigue are, in themselves, only beginning disturbances, "functional and reversible" which with increasing severity are transformed into such permanent changes as we found in inflammation, atrophy, old age and other pathological processes.

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[2] See also "Feeding the German Army," by Max Gerson, *New York State Journal of Medicine* 41:14 (July 15) 1941, in which the practical results from the partial application of these principles are shown.

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[1]From Eppinger: *Arch. f. exper. Path. u. Pharmakal.* 133 :509-524.

[2]See also “Feeding the German Army,” by Max Gerson, *New York State Journal of Medicine* 41:14 (July 15) 1941, in which the practical results from the partial application of these principles are shown.