XXXIII. THE INFLUENCE OF THE NERVOUS SYSTEM ON THE EXCRETION OF CREATININE.

EXPERIMENTS ON NERVOUS AND MENTAL PATIENTS.

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SINCE Folin's [1904, 1] method for estimating creatinine in urine became known numerous experiments have been conducted to determine the factors, which influence the excretion of this substance. Folin [1905, 1906] found that its amount in the urine stands in relation to the body-weight, and in such a manner that fat persons excrete a little less than others per kilogram of body-weight; he also found that creatinine is a product of endogenous metabolism. These results were verified by Van Hoogenhuyze and Verploegh [1905, 1908]; later Shaffer [1907, 1909] expressed the view that the degree of muscular development and more particularly muscular tonus has a bearing on the urinary creatinine. He found, however, that rapid muscular movements and fatigue have no influence on the excretion, and this has been confirmed by many observers. By a series of very interesting experiments Pekelharing and his colleagues [1910, 1911, 1913, 1916] observed an increased production of creatinine with increased muscular tonus and a decreased production with decreased tonus, and also a corresponding greater or smaller excretion of creatinine in the urine. Their view, namely, that muscular tonus is the most important factor in the excretion of creatinine, is shared by far the greatest number of observers.

The original object of my research was to determine the amount of creatinine in the urine of nervous patients. In connexion with this generally accepted tonus theory, it appeared to me to be of importance to make a systematic inquiry into the question, whether there is a smaller excretion of creatinine per kilo. of body-weight in the case of diseases with hypotonic muscles, than there is when the diseases are accompanied by an increased tonus of the muscles.

Earlier researches on the excretion of creatine and creatinine in nervous diseases have been performed by Spriggs [1908], Levene and Kristeller [1909], Skutetzky [1911] and others. These observers concluded that the excretion of creatinine in tabes dorsalis, spastic paralysis and paralysis agitans is more or less normal, whilst there is a decrease in the urinary creatinine in diseases

where much of the muscular tissue is destroyed, as for instance in the case of progressive muscular atrophy. Folin [1903, 1904, 2], Benedict and Myers [1907] and to a less degree Van Hoogenhuyze and Verploegh are responsible for a large number of experiments on psychical patients.

The first observers found normal or lowered values for the amount of excreted creatinine, but Van Hoogenhuyze and Verploegh found variations in this amount. They could not, however, say whether these variations went parallel with the frame of mind or not; but in general there was an increased excretion of creatinine with abnormal cheerfulness.

Experimental Method.

The patients were put on a creatine- and creatinine-free diet and this was continued for six days. In the cases where the patients were not necessarily confined to bed they were carefully guarded from tiring themselves. The amounts of urine of the last three days of the experiment were used to determine the average excretion of creatinine. The nurses took care that no urine was lost, and in all cases where the loss of urine was considered to be of such a nature as would influence the results, the experiment was looked upon as a failure. The amount of creatinine was usually ascertained as soon as possible; but when this could not be done, as happened on some days, small quantities of the experimental urine were preserved in the ice-chest until the next day.

The creatinine was determined according to Folin's method as applied by Autenrieth and Müller [1911] with the colorimeter of Autenrieth and Königsberger.

Observations.

As it would take me too long, I do not propose to give a detailed account of the 73 patients, who were employed in the experiments. I wish, however, to state that the cases, of which I do not treat, produced nothing that is contrary to the issues cited.

Values with normal persons.

It appeared to me to be undesirable to compare the values obtained with those that have up to now been considered normal.

Except in a few cases, the excretion of creatinine in pathological conditions has, so far, not been compared with that of normal persons under circumstances exactly similar to those of the patients experimented on. I have therefore to get a measure of comparison examined the urine of seven persons, who were in the university hospital at Groningen. The other patients were also in this hospital. The doctor in charge and myself carefully selected these people, and only those were taken, who had no nervous or mental disorder. In addition to this they were free from fever and the choice was limited to patients whose diseases were considered to be of no influence on the metabolism; and further to patients who willingly and without aversion took the creatine- and creatinine-free diets. This last point holds good for all the patients

examined. Of the seven, who were chosen, four were women and three men. The diagnoses were as follows:

A person cured from amentia (acute hallucinatory perplexity).

Four persons with ulcus ventriculi.

A person almost cured from tuberculous peritonitis.

A person with a fractura colli femoris subcapitalis.

The daily quantity of excreted creatinine per kilo. of body-weight was respectively: 5.5, 5.8, 5.9, 6.2, 6.4, 6.6, 7.9 milligrams, and this gives a daily average of 6.3 mg. per kilo. of body-weight. These values are extremely low for normal persons.

Shaffer observed, as early as 1907, that there usually was a very small excretion of creatinine present in the urine of patients who were in bed, irrespective of the cause of their disease. According to Shaffer this small excretion is found with a considerable number of pathological persons under very varying circumstances. Further it was found that abnormally small excretion of creatinine is not at all specific for any disease whatever.

Shaffer fails to explain this phenomenon, because absence of muscular work cannot be of influence; and besides this the only other possible causes, that can be of any importance, are intoxication and a change of tonus in consequence of the disease.

There are objections, however, also against the two last mentioned factors, because it can hardly be possible that the persons, whose excretion of creatinine I have given, were so enormously intoxicated as to excrete only ± 6.5 mg. of creatinine instead of the usual ± 20 mg., whilst they showed no other obvious symptoms of intoxication. The muscular tonus of these patients was normal so that this factor could not be of much weight.

Spastic cases. Eight patients with increased muscular tonus were examined, and these had the following varying diseases: post-apoplectic paralysis, tuberculous spondylitis, operated benign tumor myeli, cerebro-spinal syphilis, trauma of the spinal column, spastic spinal paralysis and multiple sclerosis. In all the cases mentioned an increased amount of creatinine was found in comparison with the normal values given above. The figures obtained varied between 8.8 and 13.2 mg. per diem per kilo. of body-weight, and this gives an average of 11.5 mg. per kilo.

Hypotonic cases. On the strength of the tonus theory a lowering of the creatinine value could be expected; but on the contrary it was found that two patients with tabes dorsalis, one with multiple sclerosis, and one with hereditary ataxia (Friedreich) with hypotonic muscles, showed distinctly increased excretions, namely 9.7–14 mg. per kilo. of body-weight with a mean value of 11.4 mg.

How can all this be interpreted? It is plain that muscular tonus cannot be the only factor that is bearing on the excretion of creatinine, because not only do we find an increased excretion of creatinine with increased tonus, but also with decreased tonus.

It is possible that some other additional factor is involved. When the cases examined are mutually compared, it is striking to find that they all show one common feature, and that is that the conduction of impulses from the cerebrum to the muscles or *vice versa* is interrupted or in any case badly hampered through an injury to one or more of the long tracts.

An increased excretion of creatinine is therefore also to be expected in those nervous disorders in which the connexions between brain and muscles are damaged without appreciable changes in the tonus. I have, in fact, found in two cases of multiple sclerosis with increased reflexes, Babinski's reflex and ataxis, but without changes in the tonus, the values 10 and 15·4.

It appeared to me to be interesting to investigate whether a functional interruption of the tracts between the motor and sensory areas of the cortex and the muscles would influence the creatinine metabolism.

For this purpose the following two series of patients were examined:

- (1) Patients with preoccupied consciousness.
- (2) Patients with diffused consciousness.

Both in cases of intense preoccupation and diffused consciousness the normal peripheral innervation is inhibited. In illustration of this last point I wish to mention: obstipation with melancholia; catalepsy in cases of dementia praecox; disappearance of the arrhythmia in the pulse with preoccupation and an increase of these differences with patients of diffused consciousness, according to Wiersma [1913].

Preoccupied consciousness. The urine of seven cases of hysteria, of one patient with traumatic neurosis, and of five cases of melancholia, was examined, and the average excretions were 11·8, 15·6 and 12·1 respectively.

One case of psychasthenia gave an average of at least 15. Two cases of mania gave averages of 12·3 and 14·3 respectively. None of these patients showed any signs of increased muscular tonus. As a matter of fact in some of the cases of melancholia a *lowered tonus* was present and moreover this did not influence the excretion of creatinine.

Diffused consciousness. With two patients with cerebral tumours, who were dull and had hemipareses, the excretions of creatinine were 11·6 and 15·2; in two cases of dementia epileptica, 13·2 and 18·5; in two cases of dementia praecox, 15·7 and 16·9; in two cases of dementia paralytica, 18·2 and 14·5; in one case of dementia senilis, 12·7.

CONCLUSIONS.

In comparison with normal persons, who were under external circumstances similar to those of the patients experimented on, an increased excretion of creatinine was found with patients suffering from nervous disorders. The disorders were of such a nature that the normal connexions between muscles and brain were damaged and further that the patients were preoccupied and diffusely conscious.

In contradistinction to Pekelharing and Van Hoogenhuyze an increased creatinine excretion was found also with lowered muscular tonus. The question now arises how this high excretion, that is generally accepted as the normal value, is to be explained? By far the greatest number of persons examined in the past were physiologists and students. These people naturally lived under very different psychical circumstances from those of the patients with whom they were compared. It is questionable whether, in the light of the above experiments, the higher values obtained with the students are not to be accounted for by the fact that these people are continuously preoccupied; whilst the patients in a hospital have a calm and regular life and do no or very little mental work.

To answer this question, I have, after the completion of the foregoing experiments, examined the urine of some other patients in the local hospital. The investigations included: a soldier with practically cured otitis media; a case of ischias; one of compensated mitral insufficiency; one of ulcer ventriculi; one of almost cured pleuritis tuberculosa and one of chronic bronchitis. All these cases can be considered more or less normal as far as their metabolism is concerned.

To my great astonishment they all gave high excretions, which correspond to the normal values given by former investigators. Unluckily I cannot as yet explain this phenomenon. It is however of importance, in connexion with the foregoing, to state that some of these last patients gave a distinctly high excretion of creatinine on a certain day, when they were in an emotional state of mind. This also points to the fact that the mind is of influence on the excretion of creatinine. I hope to investigate more closely the different nervous and psychical factors, that bear on the formation and excretion of creatine and creatinine, at an early date.

In any case we can accept, and this is in keeping also with what other observers found in cases of nervous disorders, that the muscular tonus is not the most important factor in the excretion of creatinine.

When the generally accepted normal values are used as standards of comparison, it is seen that there is, in cases of nervous diseases with both increased and lowered tonus, an equal or slightly less quantity of urinary creatinine. If we are justified, however, in taking as normal the values that I have found for normal persons in the first experiments, then it is clear that both increased and decreased tonus is accompanied by increased excretion. In this case it can also be stated that the functional interruption of the nervous connexions between cerebral cortex and muscles, in preoccupied and diffused consciousness, causes an increased excretion.

SUMMARY.

In summing up the above mentioned observations, the following conclusions are legitimate:

- (1) The muscular tonus cannot be the preponderating factor in the excretion of creatinine.
- (2) It is probable that the condition of the tracts between the cerebrum and the muscles influences the excretion of creatinine in the urine.
- (3) An important influence on the excretion of creatinine in the urine should be assigned to the mind.

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