CREATINE METABOLISM IN A CASE OF GENERALIZED MYOSITIS FIBROSA.*

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Myositis fibrosa has been defined by Steiner (1) as "a single or multiple inflammation of the muscles, mostly subacute or chronic, which generally begins in the lower extremities, and presents but slight constitutional symptoms. Eventually the muscle tissue concerned is largely or wholly replaced by connective tissue, and quite pronounced muscle atrophy may then be observed." A sand-bag feel or a wood-like hardness of the muscles is said to be characteristic of the disease.

The generalized form of myositis fibrosa is exceedingly rare, as may be judged by the fact that despite the relative certainty with which it may be diagnosed, only a few cases are to be found in the literature. Since the first authentic description by Gies in 1879 (2), single cases have been reported by each of the following clinicians: Kreiss (3), Janicke (4), Gowers (5), and Batten (6). A more recently reported case is that of Burton, Gowan, and Miller (7). To these may perhaps be added the case briefly described by Hoover (8), the diagnosis for which must remain somewhat unsettled, since it was not confirmed by histological study of the tissues nor by postmortem examination. Finally, under "dermatomyositis," Hoover describes three cases, one of which (Case 3), presents many features which are not altogether typical of dermatomyositis, but which resemble more nearly the symptoms associated with myositis fibrosa.

Relatively little is known of the pathology of this rare condition, and as to its etiology no definite opinion has yet been advanced. A search of the literature has failed to reveal a single reference to a biochemical study of this obscure disease.

A detailed account of the clinical observations and pathological findings will be reported elsewhere. The present paper will be limited principally to a consideration of the creatine metabolism,

* Part of the data contained in this communication was presented before The Thirteenth International Physiological Congress at Boston.
and only such portions of the history will be given as may have a
direct bearing on the questions involved.

The patient, a negro boy nearly 15 years of age, was admitted
to the hospital complaining of stiffness of the whole body and pain
in the chest. About 1 year previously, his mother had noticed
that he was not as active as formerly and that he seemed to move
about slowly and deliberately. However, he continued to go to
school and to do odd jobs around the house. A few weeks later,
the patient noticed a peculiar stiffness in his hands which made it
somewhat difficult for him to perform the finer movements. This
stiffness became slowly but progressively worse. 4 or 5 weeks
after the recognition of the stiffness of his hands, he noticed a
similar condition beginning in his legs, which seemed largely to
involve the knees, and which interfered to some extent with walk-
ing. In September, 7 months after the beginning of his trouble, he
started to school as usual, but was unable to play with other boys
as he had previously done. While doing calisthenics at school, he
noticed that he was not able to bend over as far as the other pupils
and that his back seemed to be getting stiff and rigid. During
this period of his illness his appetite remained good. As far as
he could tell, he had lost no weight. At no time during his illness
did the patient complain of any pain in his muscles or joints, a
feature which is said to be characteristic of all but the initial
stages of generalized myositis fibrosa.

On physical examination of the muscular system, all the muscles
of the body, some more than others, seemed to be indurated and
hard, and to have lost their normal elasticity, resulting in limita-
tion of movement. To the palpating hand, they imparted the
sensation of being firmer and stiffer than normal, and not unlike
a sand-bag. The volumes of the muscles were fairly well pre-
served with the exception of the deltoid and pectoral muscles
which showed considerable atrophy. None of the muscles was
painful, either on palpation or movement.

A few days after admission to the hospital, the patient began to
show an occasional slight afternoon rise in temperature. This
disappeared during the month of February, but in March the
afternoon temperature became more or less continuous, reaching
on one occasion as high as 102°F. Examination of the chest
showed signs of infiltration in both apices. x-Ray studies con-
firmed the clinical findings and suggested that the process was in all probability tuberculous in nature. There was no cough or expectoration and sufficient sputum for examination could not be obtained.

From the standpoint of creatine metabolism, several points which have been brought out in the foregoing excerpts from the patient's history, such as the age, the occasional afternoon rise in temperature, and, possibly, the complicating tuberculosis, will require special consideration.

Relation of Meat Intake to the Elimination of Creatine and Creatinine.—On the routine hospital diet which included a small amount of meat once a day, the patient eliminated, in the course of 24 hours, 1.146 gm. of creatine and creatinine, of which 0.672 gm. was present as creatinine and 0.474 gm. as creatine. For the next 3 days meat was excluded from the diet, which consisted of eggs, oatmeal, cream, butter, bread, cabbage, and other vegetables. On this diet there was little change in the elimination of creatine and creatinine. When the amount of meat was somewhat increased, as on February 13, the creatine output was also increased. The effect of a higher intake of meat was determined on analyzing the urine of February 26. For several days previously, as well as on the day of the urine collection, the patient was given liberal amounts of meat. Although the total nitrogen amounted to only 17.07 gm., an increase of 7.07 gm. over the preceding period, the output of creatine and creatinine was doubled, the increase in creatine being 0.99 gm. (expressed as creatinine) or 78 per cent of the extra "total creatinine" elimination.

As is indicated by the data in Table I, the patient exhibited a marked creatinuria even on a meat-free diet, and the ingestion of a moderate amount of meat produced a very marked increase in the creatine output. That the patient had not lost the ability to convert a portion of the exogenous creatine to creatinine is manifested by the fact that after being on the high meat diet for several days, the creatinine output was considerably higher than on previous experimental days.

During this period of observation the patient was afebrile and his weight remained fairly constant at 49 ± 1 kilo.

The question to be considered in this connection is whether to attribute the creatinuria entirely to the muscular condition, or
TABLE I.
/Data Showing Effect of Meat Intake on Nitrogenous Constituents of Urine of Patient with Myositis Fibrosa.

<table>
<thead>
<tr>
<th>Date</th>
<th>Date</th>
<th>Maximum and Minimum Temperature</th>
<th>Volume of Urine in 24 Hrs.</th>
<th>pH</th>
<th>Total N.</th>
<th>Urea N.</th>
<th>Uric Acid N.</th>
<th>Unusual Nitrogen</th>
<th>Total Creatinine</th>
<th>Per cent of Total Creatinine, Excreted as Creatinine</th>
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<td>1850</td>
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<tr>
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<td>2120</td>
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<td>8.82</td>
<td>7.45</td>
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<td>1890</td>
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<td>0.157</td>
<td>0.80</td>
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<td>2200</td>
<td>6.3</td>
<td>10.00</td>
<td>8.40</td>
<td>0.47</td>
<td>0.120</td>
<td>0.53</td>
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<td>0.73</td>
</tr>
<tr>
<td>&quot; 26</td>
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<td>0.230</td>
<td>1.30</td>
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</table>
whether the age of the patient is a factor to be taken into account. Unfortunately, the data for the creatine elimination of normal boys for the age period of the patient are both meager and conflicting. In his recent monograph, Hunter (9) has tabulated the results of a number of investigators for the purpose of providing information of the quantities of creatine which children of different ages may be expected to excrete on varying intakes of protein, but on what are usually considered creatine-free diets. Not a single analysis is given for boys older than 9 to 9½ years, the analyses for this age being based on the work of Harding and Gaebler (10) who found the creatine elimination, on a nitrogen intake of approximately 15 gm., to be 14.7 per cent of the "total creatinine" in one of the boys, and 6.1 per cent in the other.

In his important paper which established the presence of creatinuria in normal children, Rose (11) gives analyses of specimens of urine of two boys, aged, respectively, 14 and 15 years. The diets were not controlled and it was impractical in these cases to collect 24 hour specimens. The creatine elimination of the younger boy was 27.9 per cent of the total, and of the older boy, 25.3 per cent. Rose observed no creatinuria in boys above this age. Folin and Denis (12) examined a specimen of urine of a 17 year old boy, who was a vegetarian, and found 18 mg. of creatine in 100 cc. On the other hand, Krause (13) was unable to find creatine in the urine of boys after the age of 7, his data including analyses of the urine of male subjects up to the age of 16. More recently, Cameron and Gibson (14) observed no creatinuria in two boys, aged 9 and 12 years. Obviously, there is need for more information regarding the creatine metabolism of boys at the age of puberty and during adolescence.

In this connection it is to be stated that the patient was very well developed sexually, giving the appearance of a much older boy.

Although this evidence was taken into account, it is felt, nevertheless, that it would be safer not to exclude the factor of age as possibly contributing to the creatinuria in the case under discussion.

In considering the data in Table I, the effect of the tuberculosis may probably be ruled out. During the period of these observations, the patient's temperature was normal and not subject to
wide fluctuations. The symptoms of the disease were not sufficiently marked in order to make a positive diagnosis. Nevertheless, the complication is not to be ignored even at this stage of the disease if the various factors are to be brought in relation to each other. For this reason, the effect of tuberculosis on creatine metabolism may be briefly considered. In so far as the disease is associated with periodic elevation of temperature, an increased creatinine elimination and even some creatinuria may be expected. Meyer (15) studied the metabolism of two female patients (ages not stated) with advanced tuberculosis and found creatinuria in both. Van Hoogenhuyze and Verploegh (16) found creatinuria in a case of chronic pulmonary tuberculosis (male, age 72), but in this case the patient exhibited a high temperature. Of much greater value in appraising the data obtained in the present study is the information furnished by McClure (17). In a case of pulmonary tuberculosis (male, age 19), creatinuria was absent as a rule. Of twenty-nine 24 hour specimens of urine analyzed, creatine in very small amounts was found in only three. This patient exhibited approximately the same fluctuations in temperature as those observed in our patient during March. McClure's patient, though maintained on a modified Shaffer-Coleman (18) diet, showed considerable variation in the daily output of creatinine, whereas in our case the "total creatinine" elimination was fairly constant, both on the house diet and the meat-free diet.

In a second case of pulmonary tuberculosis reported by McClure (male, age 27), small amounts of creatine were present in only four 24 hour specimens and absent in twenty-seven, in spite of the fact that the patient was febrile, the temperature frequently rising above 102°F.

Effect of Feeding Creatine.—On March 8, the patient received 1 gm. of creatine hydrate (0.758 gm. of creatinine), all of which was recovered in the urine collected during that 24 hour period, 92.1 per cent being excreted as creatine and the remainder as creatinine. It should be mentioned that the creatine preparation itself was practically free from creatinine.

On the following day 2 gm. of creatine hydrate were administered, of which 64 per cent was recovered that day. Of the amount thus recovered, 91.8 per cent was present as creatine and 8.2 per cent as creatinine. The urine collected during the subsequent
24 hour period contained extra creatine and creatinine to account for an additional 27 per cent, but in this case, 54.9 per cent was present as creatine and 45.1 per cent as creatinine. All the calculations in this, as well as in the preceding experiment, are based on the analyses of March 3, which have been taken for control.

On March 11, 5 gm. of creatine hydrate were given in 1 gm. doses at half hourly intervals. The extra "total creatinine" the 1st day was 2.657 gm., or 70.1 per cent, nearly all of which (94.05 per cent) was present as creatine. The extra elimination on the 2nd day accounted for 14.5 per cent and on the 3rd day, 7.13 per cent, making a total recovery of 91.73 per cent. The proportion present as preformed creatinine was 5.95 per cent on the 1st day, 18.2 per cent on the 2nd day, and 48.2 per cent on the 3rd day. The significance of these results will be discussed presently. In the next 24 hour period the creatine and creatinine elimination returned to approximately the normal values for this individual, as shown by the data in Table II.

The preceding experiments were controlled by giving the patient 2 gm. of creatinine. Of this amount, 90.5 per cent was recovered the 1st day (i.e., actually within 15 1/2 hours), and an additional 6 per cent was present in the urine of the following day.

For the next few days the patient was given the usual house diet, without the meat. To provide the usual amount of protein, two eggs were given at each meal. While on this diet, the patient was given 1 gm. of creatine hydrate at 9.30 a.m., on March 20. On the basis of the calculations on the control analyses of March 17 to 18, 77.85 per cent of this was recovered within the next 20 1/2 hours. Sufficient extra creatine and creatinine was found in the urine of the subsequent 24 hours to account for an additional 10.55 per cent. Thus, 88.4 per cent of the creatine was recovered. If the calculations were based on the analysis of the 24 hour specimen of March 19, an even higher value for the total recovery would be obtained.

Powis and Raper (19) have observed that on giving creatine to a normal child in the morning, most of it was excreted during the ensuing 12 hours, but if the same amount was given before going to bed, a large proportion was retained. To determine whether creatine retention could be obtained by administering it at night, 1 gm. was given at 8.30 p.m., shortly before the patient's
### TABLE II.

**Fate of Creatine and Creatinine.**

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House diet.  
"1 gm. creatine hydrate (0.758 gm. creatinine). Total recovered, 100%; 7.9% was creatinine, 92.1% creatine."

House diet; 2 gm. creatine hydrate (1.516 gm. creatinine). Recovered 64%; of which 8.2% was creatinine, 91.8% creatine.

House diet. Recovered 27%; of which 45.1% was creatinine, 54.9% creatine. Total recovery within 48 hrs., 91%.
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House diet; 5 gm. creatine hydrate (3.79 gm. creatinine). Recovered 1st day, 70.1%; of which 94.05% was creatine, 5.95% creatinine.

House diet. Recovered 2nd day 11.5%; of which 18.2% was creatinine, 81.8% creatine.

House diet. Recovered 3rd day 7.13%; of which 51.8% was creatine, 48.2% creatinine. Total recovery of creatine in 3 days, 91.73%.

House diet. Recovered 1st day 90.5%.

House diet. Recovered 2nd day 6%. Total recovery of creatinine in 2 days, 96.5%.

Meat-free diet. Average analysis of 2 days urine.

Meat-free diet.
<table>
<thead>
<tr>
<th>Date</th>
<th>Maximum and minimum temperature</th>
<th>Volume of urine in 24 hrs.</th>
<th>pH</th>
<th>Total N.</th>
<th>Urea N.</th>
<th>NH₃</th>
<th>Urea N.</th>
<th>Total creatinine</th>
<th>Per cent of total creatinine excreted as creatinine</th>
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Meat-free diet; 1 gm. creatine hydrate (0.758 gm. creatinine) given at 9:30 a.m. Total recovered 1st day, 77.85%; of which 80.3% was creatine, 10.2% creatinine. Analyses of Mar. 17-18 taken for control.

Meat-free diet. Recovered 2nd day, 10.55%; of which 62.5% was creatinine, 37.5% creatine. Analyses of Mar. 17-18 taken for control. Total recovery, 88.4%.
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<td>0.68</td>
</tr>
<tr>
<td>27</td>
<td>98.4</td>
<td>705</td>
<td>6.2</td>
<td>8.87</td>
<td>6.00</td>
<td>0.47</td>
<td></td>
<td>2.016</td>
<td>0.601</td>
<td>1.415</td>
<td>70.0</td>
</tr>
<tr>
<td>28</td>
<td>97.4</td>
<td>850</td>
<td>6.0</td>
<td>8.65</td>
<td>6.12</td>
<td>0.61</td>
<td></td>
<td>1.78</td>
<td>0.45</td>
<td>1.33</td>
<td>74.7</td>
</tr>
</tbody>
</table>

Meat-free diet; 1 gm. creatine hydrate given at 8.30 p.m. Recovered 1st day, i.e., within 0.5 hrs., 37%; of which 3.6% was creatinine, 96.4% creatine.

Meat-free diet. Recovered 52.8% 2nd day; of which 5% was creatinine, 95% creatine. Total recovery for 2 days, 89.8%.

Meat-free diet.

Test for sugar in urine faintly positive.

High meat diet. Patient ate about 300 gm. of ground beef in morning, but was too ill to continue experiment. Analysis of Mar. 24 taken for control.

Meat-free diet. Patient ill.
bedtime. In the urine voided at 6 a.m. the following morning, sufficient extra creatine and creatinine were found to account for 37 per cent of that administered. Most of the remainder was recovered in the urine of the following day. The total recovery, in this experiment, was 89.8 per cent. Apparently, the retention was no better when the creatine was given at night than when given in the morning.

On the following day the composition of the urine returned to the normal for this patient. The creatine elimination was now 50 per cent of the "total creatinine." To determine whether carbohydrate ingestion might have some effect on the creatinuria, 400 gm. of pure glucose were given on March 26, in addition to the meat-free diet. Although by this time the condition of the patient had become worse, the sugar was exceedingly well tolerated, the urine for that day giving but a faint Benedict's test for reducing substance. Presumably, the metabolism of the carbohydrate had no effect on the creatine metabolism, unless the somewhat increased elimination of both creatine and creatinine may be taken to indicate a slight stimulation of tissue catabolism. It may be further stated that at no time during these observations did the patient exhibit any symptoms of acidosis.

On the following day it was intended to determine again the effect of a high meat intake. In the morning the patient slowly ate about 300 gm. of ground beef, but during the rest of the day he was too ill to continue the experiment. Although the total nitrogen elimination for that 24 hour period was only 8.87 gm., the "total creatinine" was 2.016 gm., an increase of 0.746 gm. over the control period of March 24. The creatinuria continued to be very marked on the following day.

The inability of the patient to store creatine is of fundamental significance, the results of our observations standing out in striking contrast to those that have been made in normal adults by Folin (20), Myers and Fine (21), Rose and Dimmitt (22), Chanutin (23), and others. Even in children, whose ability to retain exogenous creatine is much less than in adults, the administration of amounts of creatine, comparable to those taken by the patient, results in the recovery of much smaller quantities in the urine. It is only in very young children and in infants that complete recovery has been occasionally reported (Powis and Raper (19),
Beumer (24), and Gamble and Goldschmidt (25)). In the experiments of Gamble and Goldschmidt, of 88 mg. of creatine (anhydrous) fed to a 10 months old infant, weighing 7.2 kilos, 31 mg., or 35 per cent, were recovered in the urine of the next 2 days. When 0.264 gm. was given, 51 per cent was recovered in 2 days. In these experiments the infant was on a low protein diet. In a subsequent experiment, the infant was placed on a high protein diet, in the form of whole milk, and given 0.264 gm. of creatine. All of this was recovered in the urine of the ensuing 5 days. Apparently, even the 10 months old subject of these experiments was, as a rule, better able to retain creatine in his tissues than our 15 year old patient with generalized myositis.

 Practically complete recovery of exogenous creatine has been observed by Powis and Raper (19) in a case of amyotonia congenita in a child of 4, and by Gibson and Martin (26) in a case of pseudohypertrophic dystrophy in a woman.

 The deficiency of creatine retention in our patient seems to be very marked only when compared with the relatively prolonged type of creatine storage which may be assumed to occur on feeding creatine to normal adults. However from the standpoint of a transient type of storage, an appreciable retention of creatine in our subject seems to be indicated. The mere fact that all of the absorbed creatine was not at once excreted in the urine is in itself evidence that it was taken up to some extent by the tissues. Additional support for this idea is to be found in the fact that the administration of 5 gm. of creatine had no effect on the creatine content of the blood. This result, as indicated in Table III, differed from that obtained on feeding 2 gm. of creatinine, an excretory product, for a marked elevation of creatinine in the blood was promptly observed. But of more significance in supporting the idea of a transitory storage of some of the creatine are the deductions which may be drawn from the data in Table II. It will be observed that after feeding 2 gm. of creatine, nearly all of the extra "total creatinine" determined on the 1st day was in the form of creatine. However, on the 2nd day, the amount present as creatinine was appreciable, in fact, 45.1 per cent of the total. The results were similar when 5 gm. were given, the amount of extra creatinine being 5.95 per cent of the total on the 1st day, 18.2 per cent on the 2nd, and 48.2 per cent on the 3rd. There
can be little question of the origin of this extra creatinine, especially if one recalls Benedict and Osterberg's experiments with dogs (27), as well as those of Chanutin (23), and Rose, Ellis, and Helming (28) on man, which show (1) that an increase of creatinine does not immediately follow creatine feeding, but apparently occurs after the body has retained a proportion of the creatine fed, and (2) that whereas, on withholding creatine after periods of prolonged administration, the creatinuria markedly diminishes or disappears at once, the increased elimination of creatinine persists for some time.

### TABLE III.

**Summary of Blood Analyses.**

Figures are expressed in mg. per 100 cc. of blood.

<table>
<thead>
<tr>
<th></th>
<th>Non-protein N.</th>
<th>Uric acid.</th>
<th>Creatinine.</th>
<th>Crea-</th>
<th>Glu-</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb. 7</td>
<td>28.6</td>
<td>5.6</td>
<td>1.3</td>
<td>3.7</td>
<td>91</td>
<td>House diet.</td>
</tr>
<tr>
<td>“ 10</td>
<td>28.6</td>
<td>5.6</td>
<td>1.15</td>
<td>3.85</td>
<td></td>
<td>Meat-free diet.</td>
</tr>
<tr>
<td>“ 13</td>
<td>30</td>
<td>5.7</td>
<td>1.13</td>
<td>3.85</td>
<td>90</td>
<td>Moderate amount of meat.</td>
</tr>
<tr>
<td>“ 26</td>
<td>30</td>
<td>5.1</td>
<td>1.07</td>
<td>3.73</td>
<td></td>
<td>High meat diet.</td>
</tr>
<tr>
<td>Mar. 11</td>
<td>27</td>
<td>5.3</td>
<td>1.07</td>
<td>3.73</td>
<td></td>
<td>Blood taken at 4:30 p.m., 30 min. after last dose of creatine. Total given, 5 gm. creatine hydrate.</td>
</tr>
<tr>
<td>“ 15</td>
<td>28</td>
<td>5.4</td>
<td>2.5</td>
<td>4.00</td>
<td></td>
<td>Blood taken 30 min. after 2 gm. dose of creatinine.</td>
</tr>
</tbody>
</table>

It may even be questioned, though, because of the complexity of the relations involved, not entirely on the basis of our own observations, whether the muscles in this case of myositis have actually lost much of their capacity to convert creatine into creatinine. The justification for this question, here, lies in the conclusions reached by Benedict and Osterberg (27) that the formation of creatinine from creatine is a definitely limited process, that the conversion is not a direct one, but that one or more intermediate reactions are probably involved, that the conversion occurs slowly, and that even on prolonged administration of creatine (to dogs) only about one-third of the retained creatine is converted to creatinine, the remainder following different metabolic paths. What-
ever these intermediate reactions may be, it seems likely that they depend on the retention of the creatine in the tissues in some form not easily liberated. We are therefore inclined to the view that even in this generalized muscular disease, if exogenous creatine is retained, a proportion, perhaps the physiologically normal proportion, is changed to creatinine. We believe that we are justified in assuming that the derangement of the creatine metabolism in this condition, and possibly in other diseases of the muscular system, is due not to failure to convert creatine into creatinine, per se,

**TABLE IV.**

**Creatine Content of Muscles and Its Relation to Anatomical Changes.**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Creatine in 100 gm.</th>
<th>Degeneration</th>
<th>Fibrosis</th>
<th>Inflammation</th>
<th>Creatine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soleus</td>
<td>324</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Quadriceps femoris</td>
<td>313</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Iliacus</td>
<td>160</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Intercostal</td>
<td>172</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>159</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Psoas</td>
<td>204</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Rectus abdominis</td>
<td>217</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Sartorius</td>
<td>229</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Deltoid</td>
<td>197</td>
<td>9</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

Least degeneration, fibrosis, or inflammation is denoted by a grade of 1. Most degeneration and inflammation are indicated by a grade of 9. Since several muscles showed approximately the same degree of fibrosis, the grade 5 signifies maximum fibrosis in this series. Intermediate degrees of anatomical change are graded accordingly. In the last column grade 1 denotes the most, and grade 9 the least, amount of creatine.

but primarily to an inability to "fix" the creatine in a form in which it would be retained in the tissues for more than just a very brief time.

**Muscle Creatine.** The only extensive series of determinations of creatine (and creatinine) in human muscle is that of Denis (29). In a group of five normal individuals, she obtained values ranging between 360 and 421 mg. Within this range fall the values obtained by Myers and Fine (30) and Shaffer (31). In autopsy material obtained from individuals dying of acute diseases, Denis found the creatine content of the muscle to be normal, although in
Creatine Metabolism in Myositis Fibrosa

a few instances low values were observed. The muscle creatine in
a proportion of the chronic diseases was found to be considerably
below the normal range, but in nearly all instances in which this
was the case, the clinical histories showed that the patients had
been ill for many months and were for some time before death in
an extremely cachectic and emaciated condition. To this class
belonged patients with Graves' disease, gastric and intestinal
carcinoma, etc. Since our patient definitely did not belong to this
category of chronic, cachectic diseases, the low creatine content of
his muscles (Table IV) must be associated with their diseased
condition.

Toward the end of March, the patient's condition became
rapidly worse. On March 29, a biopsy was performed to secure
muscle (quadriceps femoris) for histological study. A portion of
this was analyzed for creatine by the procedure of Ochoa and
Valdecasas (32) the determinations being made in triplicate,
and 100 mg. of muscle used for each analysis. Death occurred
on the morning of March 30. At autopsy, performed the same
morning, several specimens of muscle were obtained and analyzed
for creatinine. We have since had an opportunity of comparing
the method of Ochoa and Valdecasas with that of Rose, Helmer,
and Chanutin (33) and are assured of its reliability especially
when at least 100 mg. of tissue are used in each determination.

Owing to the limited number of analyses of normal human
muscle, comparison of the data in Table IV with the normal is
not entirely possible except in the case of the psoas, the muscle
which Denis selected for analysis in her series of determinations.
However, from the data for the creatine content of other human
muscles, that are to be found in the literature, it is clear that the
values for the various muscles, listed in Table IV, are very low,
the creatine content in some instances being less than one-half
that occurring normally.

Microscopic examination revealed as much as 30 per cent de-
generation of some of the muscles (deltoid, sartorius). By care-
ful comparison with each other the various muscles were graded
according to the amount of normal tissue still present. Arranged
according to the normal amount of muscle still present, the order
was: soleus, quadriceps femoris, iliacus, intercostal, diaphragm,
psoas, rectus abdominis, sartorius, and deltoid. The soleus
showed most normal muscle, the deltoid, least. Arranged according to the amount of fibrosis, the order was: deltoid, rectus abdominis, iliacus, and quadriceps femoris equally fibrosed; next in order the psoas, sartorius, intercostal, soleus, and diaphragm. The diaphragm showed least fibrosis. Arranged in the order of inflammation present, the order was: iliacus, deltoid, sartorius, intercostal, rectus abdominis, psoas, diaphragm, quadriceps femoris, and soleus, the last showing the least amount of inflammation. While these classifications are to be regarded only as fair approximations, they are nevertheless not without significance, especially when compared with the results of the creatine determinations. It is to be mentioned that these gradations were made without knowledge of the chemical findings.

In Table IV, a grade of 1 denotes either least degeneration (most normal muscle), fibrosis, or inflammation. Most degeneration, as well as most marked inflammation, is represented by 9. Since several muscles showed approximately the same amount of fibrosis, the grade 5 indicates maximum fibrosis in this series (deltoid, rectus abdominis, iliacus, and quadriceps femoris). The parallelism between the amount of anatomical change, particularly between the degree of the inflammatory process, and the creatine content, while in no sense absolute, is nevertheless very striking. Thus, the soleus, which appeared most normal and showed least inflammation, contained more creatine than any of the muscles. The quadriceps femoris (obtained at biopsy), while it exhibited a considerable amount of fibrosis, showed relatively little of other degenerative changes, and in harmony with this, the creatine content was also relatively high. On the other hand, the iliacus and deltoid which showed a great deal of inflammation and other pathological changes, were very low as regards creatine content.

The myocardium contained 159 mg. per 100 gm., a value slightly below that given by Constabel (34) for heart muscle. Histological examination revealed a slight enlargement of the fibers, apparently a hypertrophic change. The muscle cytoplasm was more granular than normal and there was a slight increase of fibrous tissue, as well as a few scattered mononuclear inflammatory cells. The data for the diaphragm show most departure from this parallelism. Whether this may be due to a low creatine content of this muscle, normally, remains to be determined.
Purine Metabolism.—The uric acid content of the blood was consistently above normal and seemed to be uninfluenced by the increased white blood cell count which occurred in March (the white blood cell count in February was 10,000; in March, 15,000). However, the uric acid elimination increased appreciably during March. These changes may have been wholly a manifestation of the tuberculous involvement, an inference which seems warranted from Wells' discussion (35) of purine metabolism in tuberculosis.

SUMMARY.

The results are presented of a metabolism study of a case of generalized myositis fibrosa, in the earlier stages, in a 15 year old boy.

Marked creatinuria was a constant feature, even on a creatine-free diet, the amount of creatine eliminated being more than 40 per cent of the "total creatinine."

The patient manifested an almost complete inability to retain, for more than very short periods, exogenous creatine. However, of the fraction which found transitory storage in the tissues, a portion was apparently converted into creatinine.

Analyses of the muscles revealed the fact that they were abnormally low in creatine content.

A relationship of the creatine content of the various muscles to the severity of the anatomical changes particularly to the degree of inflammation, has been demonstrated. It appears that an inflammatory condition of the muscles interferes with the normal storage of creatine.

We wish to acknowledge the cooperation of Dr. Titus H. Harris of the Department of Neurology and Psychiatry, who made the original diagnosis, and of Dr. Henry C. Hartman of the Department of Pathology, who confirmed the pathological findings.

BIBLIOGRAPHY.

2. Gies, T., Deutsch. Z. Chir., 11, 167 (1879).
8. Hoover, C. F., in Tice, F., Practice of medicine, Hagerstown, 6, 538, 544 (1924).
12. Folin, O., and Denis, W., J. Biol. Chem., 11, 253 (1912).
34. Constabel, F., Biochem. Z., 122, 152 (1921).
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