who had some impairment of the kidney function. Preliminary to work on surgical patients, a series of nonsurgical patients with normal kidneys (as shown by the excretion of phenolsulphonphthalein and the estimation of nonprotein nitrogen of the blood) was studied for the purpose of determining the effect on the normal kidney of morphine in large doses frequently repeated.

From the clinical material available in the Wisconsin General Hospital, we selected twenty-one patients for study. Ten of these were not operated on and had normal kidney function. Eleven were surgical patients. All of these surgical patients were over 36 years of age; the oldest was 72.

The nonsurgical patients were given morphine sulphate, 1/6 or 1/4 grain (11 or 16 mg.) every four to six hours until the point of tolerance was reached, as shown by such symptoms as extreme drowsiness, nausea and vomiting. Tests of the kidney function were made every twenty-four hours for three days; the tests used were the estimation of the nonprotein nitrogen of the blood and the intramuscular injection of phenolsulphonphthalein, the urine being collected in two specimens over a period of two hours and fifteen minutes.

Table 1 shows the total amount of morphine given, the period over which it was given and the results of the studies of the kidney function, both before and after the administration of the drug.

### Table 2.—Effect of Morphine on Kidney Function in Surgical Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Operation</th>
<th>Preoperative Nitrogen</th>
<th>Nonprotein Nitrogen</th>
<th>Phenolsulphonphthalein</th>
<th>Postoperative Nitrogen</th>
<th>Nonprotein Nitrogen</th>
<th>Phenolsulphonphthalein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>Hypertrophied prostate</td>
<td>Suprapubic cystotomy</td>
<td>39.4</td>
<td>49%</td>
<td>1/3 grain in 21 hours</td>
<td>31 hrs. 25.5</td>
<td>29%</td>
<td>31 hrs. 25.5</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>Epididymitis</td>
<td>Epididymectomy</td>
<td>37.5</td>
<td>49%</td>
<td>1 grain in 72 hours</td>
<td>24 hrs. 60.5</td>
<td>30%</td>
<td>24 hrs. 60.5</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>Hypertrophied prostate</td>
<td>Prostatectomy</td>
<td>36.8</td>
<td>39%</td>
<td>1/10 grains in 72 hours</td>
<td>24 hrs. 24.6</td>
<td>30%</td>
<td>24 hrs. 24.6</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Diverticulum of bladder</td>
<td>Suprapubic cystotomy</td>
<td>42.5</td>
<td>25%</td>
<td>1/3 grain in 72 hours</td>
<td>24 hrs. 42.3</td>
<td>30%</td>
<td>24 hrs. 42.3</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>Undescended testis and epididymitis</td>
<td>Epididymectomy</td>
<td>35.7</td>
<td>30%</td>
<td>1/3 grain in 72 hours</td>
<td>24 hrs. 33.0</td>
<td>40%</td>
<td>24 hrs. 33.0</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>Hypertrophied prostate; malignant</td>
<td>Suprapubic cystotomy</td>
<td>36.8</td>
<td>39%</td>
<td>1/3 grain in 72 hours</td>
<td>24 hrs. 41.0</td>
<td>30%</td>
<td>24 hrs. 41.0</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>Hydromephrosis and functionless kidney</td>
<td>Nephrectomy</td>
<td>37.5</td>
<td>49%</td>
<td>1/4 grains in 72 hours</td>
<td>24 hrs. 41.0</td>
<td>15%</td>
<td>24 hrs. 41.0</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>Hypertrophied prostate</td>
<td>Prostatectomy</td>
<td>28.3</td>
<td>49%</td>
<td>1/3 grains in 72 hours</td>
<td>24 hrs. 37.7</td>
<td>30%</td>
<td>24 hrs. 37.7</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>Diverticulum of bladder</td>
<td>Resection of diverticulum</td>
<td>38.7</td>
<td>43%</td>
<td>1/3 grain in 72 hours</td>
<td>24 hrs. 40.0</td>
<td>30%</td>
<td>24 hrs. 40.0</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>Hypertrophied prostate</td>
<td>Suprapubic cystotomy</td>
<td>42</td>
<td>49%</td>
<td>1/3 grain in 72 hours</td>
<td>24 hrs. 42.5</td>
<td>40%</td>
<td>24 hrs. 42.5</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>Hypertrophied prostate</td>
<td>Prostatectomy</td>
<td>33.9</td>
<td>44%</td>
<td>1/10 grain in 69 hours</td>
<td>24 hrs. 60.2</td>
<td>40%</td>
<td>24 hrs. 60.2</td>
</tr>
</tbody>
</table>

In studying the surgical patients, the nurses were instructed to give morphine sulphate, in doses of 1/4 grain (16 mg.), as often as necessary to keep the patients comfortable. Studies were made daily for three days, as in the nonsurgical patients; the results are shown in table 2.

In the nonoperative patients, the amount of morphine given varied from 1 1/2 to 3 grains (0.08 to 0.2 Grn.) in seventy-two hours. In the surgical patients, the amount varied from 1/3 grain to 2 1/4 grains (0.03 to 0.14 Grm.) in seventy-two hours. All of these patients recovered from the operations.

The results were sufficiently constant to justify the following conclusions:

1. Morphine sulphate, given in the usual therapeutic dose and repeated every four to six hours until the patient develops toxic symptoms does not impair the function of the normal kidney.

2. Urologic surgical patients may be given morphine sulphate in the usual therapeutic doses without fear of impairment of renal function.

BERIBERI ("MALADIE DES JAMBES") IN LOUISIANA

WITH ESPECIAL REFERENCE TO CARDIAC MANIFESTATIONS*

LEONARD C. SCOTT, M.D.

and

GEORGE R. HERRMANN, M.D.

NEW ORLEANS

The occurrence of beriberi in association with an exclusive use of rice as a staple diet in the Louisiana rice producing parishes, far removed from the accepted endemic regions of the disease, is both significant and interesting. Coincident with a recent outbreak in the

* From the Louisiana State Board of Health, the New Orleans Charity Hospital Heart Station, and the Tulane University of Louisiana School of Medicine.
The elucidation of the cause of oriental beriberi is correlated with the development of our knowledge of vitamin deficiencies without the epoch-making work of the Japanese Takaki,1 the Hollander Eijkman2 and Grijns,3 the Englishmen Fraser and Stanton,4 Bradon5 and Fletcher,6 and the German Schaumann,7 Funk8 would perhaps not have investigated the matter so exhaustively.

An enormous amount of literature has accumulated on the subject and much of it, in the light of present knowledge, appears to have been hair splitting controversy, as a large number of the investigators wandered around blindly even after Fraser and Stanton and Eijkman offered reasonable proof that the relation between beriberi and polished rice appeared to be perfectly clear. At present we find it difficult to accept any other interpretation, such as that of McCarron9 and of Sprawson,10 that the disease may have a bacterial as well as a vitamin deficiency etiology. Manson-Bahr11 also reflects some doubt on the theory of anavitaminosis as the sole cause.

Vaughan12 gives an excellent summary of the investigation on beriberi and points out that at one time or another twenty-two different theories were advanced to account for it. He rejects all of them except the theory of vitamin B deficiency. Vaughan also draws attention to the fact that this deficiency may exist not only in polished rice but in any food product from which the water-soluble vitamin B has been removed.

Beriberi is essentially a disease of the tropics and subtropics. Although endemic in the orient, where it is known as kakke, the symptom complex is well known in the West Indies and in South America. Apparently, the disease has not occurred to any striking degree in the United States; at any rate, few reports have appeared in the literature.13 Nevertheless, the mortality statistics of the United States Bureau of the Census show seventy-eight deaths between the years 1911 and 1919. In 1918 there were five deaths in California, four in Washington, and two in New York. So far as we are aware, no cases prior to 1921 were reported from Louisiana. In fact, only five have ever been recorded at the state bureau of vital statistics, and these in the years 1922, 1923 and 1926. In 1927 there were two cases at the Charity Hospital, New Orleans, and one in the Parish Prison, though they seem not to have been reported as beriberi.

So far as we are aware, Young14 was the first to report the occurrence of beriberi in Louisiana. We assume that the rice industry was then only in its infancy, presumably having begun late in the eighties of the last century. Young reported that he had seen forty cases between 1898 and 1903 but knew of a large number of others coming under the observation of a colleague in Abbeville, the parish seat of Vermilion Parish.

In the last twenty-five years, rice production in these parts has increased enormously. According to the best available statistics of the United States Department of Commerce, 351,594 acres was under cultivation and 12,289,000 bushels produced in 1924. Rice culture is essentially confined to those parishes having a surface configuration suitable for extensive irrigation. In 1924, ten out of twenty-four parishes produced 54.6 per cent of the yield on 54.9 per cent of the acreage. These parishes, in the order of their yields, are Vermilion, Jefferson Davis, St. Landry, Lafayette, St. Martin, Evangeline, Iberville, Iberville, St. John the Baptist and St. James. It is certain that a large number of people are dependent on rice, not only as a means of livelihood but as a staple constituent of their diet. Moreover, the character of the population is such that they would have a tendency to restrict themselves as much as possible to their home product. The result of this one-sided diet is a recurring series of seasonal epidemics of a disease the symptoms of which are identical in all respects with those of true oriental beriberi.

"MALADIE DES JAMBES" IN THE LOUISIANA RICE REGIONS

In 1921, Dr. C. W. Lewis of Eunice, La., in Evangeline Parish, directed the attention of the state board of health to a large number of cases of beriberi in his district. An investigation was carried out by one of us,15 and a condensed report was published.

Two years later, in 1923, Lewis again drew our attention to an outbreak and this, also, was investigated thoroughly. Since this time beriberi has been reported from a number of other parishes. Beriberi does not belong in the category of officially reportable diseases, which accounts for the fact that we know little about the epidemiology in Louisiana and must depend mainly on the statements of physicians, who at one time or another have communicated their observations to the board.

In the rice belt, which includes Evangeline and St. Landry parishes, the disease is well known to the population under the colloquial appellation of "maladie des jambes." This is a very apt expression and corresponds well with the Japanese term kakke, also said to mean "disease of the legs." It has prevailed in the rice belt for many years, and while apparently showing predilection for males, women have occasionally suffered attacks. Children are also known to have acquired the disease. Prior to 1921 physicians, aside from Lewis, seem not to have made an attempt to arrive at a true diagnosis, though they were apparently familiar with the syndrome. They knew that the overwhelming majority of cases occurred after the rice had been harvested, and reports were received with requests for medical assistance principally during the months of September, October and November.

At certain periods of the year, especially in the autumn during those months of the greatest prevalence of the disease, the people are said to live on an exclu-
sive diet of polished rice. They eat a mixture of rice and bacon grease which they call “riz et sauce” or “riz sauce” with undiminished relish three times a day, virtually excluding all other foodstuffs. The samples observed at the time of the first epidemic showed that the rice was perfectly white without a vestige of the pericarp layer or embryo remaining. It was clear that the vital portions of the rice grain, those known to contain the antineuritic vitamin B, had been removed completely. The rice farmers seem to prefer to sell their entire crop and buy polished rice rather than thresh out and use their own rice without having it polished, as was done formerly.

When winter comes the diet materially changes. Rice is replaced by fresh meat after the butchering is finished, and potatoes and bread are also added. It is stated that during the winter no new cases of “maladie des jambes” occur.

One of the peculiar characteristics of these people is that, although they raise chickens and vegetables and have eggs and milk in sufficient quantities to supply their needs, they prefer to sell these products and restrict themselves to a rice diet. Another point which, at least in 1921, may have contributed to the incidence of beriberi in that region was the circumstance that the previous season’s rice crop was a failure, and one physician informed us that spoiled or moldy rice was eaten in greater quantities than usual. Besides crop failure, it is worth remembering that the people who plant rice are compelled to spend long hours in the field in muddied water which is frequently cold; that they are often exposed to the inclemency of the weather, and finally that they live in houses very faulty from the sanitary standpoint. It is conceivable that these conditions are in line with McCarrison’s and Spreawson’s ideas on the multiple etiology of beriberi, at least so far as lowered resistance affords an opportunity for the degenerative process to develop. Certainly, not every individual exposed to the dietary deficiency develops the disease, which indicates that other factors may be at work.

The symptomatology of “maladie des jambes” is the same in general wherever it is encountered; Young’s description in 1903 agrees very well with our observations among the patients in central Louisiana. Information to the effect that there is but little variation in the symptom complex except in degree is available. Severe cases may run a relatively short course, beginning and ending fatally within a few weeks. These must be regarded as the exception rather than the rule. In general, however, it appears that the disease process progresses slowly; the onset is insidious, and the symptoms become gradually worse, and if no dietary changes are made and the deficiency is continued for a sufficiently long time, the patient eventually dies of heart failure or of an intercurrent infection. If for one reason or another the diet is altered so as to include foodstuffs containing vitamin B, the patient will gradually recover, though the convalescence may be prolonged.

When no specific dietetic therapy has been employed, and recovery has occurred in the usual course of events, the convalescent patient presents pronounced weakness for many months. Since in recovery there is necessarily an extensive regeneration of nerve elements, it is easily understood how defects in muscular innervation may persist for a long time.

One attack does not seem to predispose to another, though apparently the disease has occasionally developed in some persons in succeeding years.

CHARACTERISTICS OF BERIBERI

The symptom complex known as “maladie des jambes” is made up of disturbances that may be roughly grouped under three principal headings, namely: (1) cardiac manifestations; (2) neuritic phenomena, and (3) gastro-intestinal symptoms. The symptoms do not always appear in this order. Each case, however, usually presents one or more of each of the groups of symptoms.

1. Cardiac Manifestations.—These may appear early or late in the disease. As a rule they just precede or are accompanied by the appearance of edema of the lower extremities. Palpitation is an early and constant symptom, with an accompanying noticeably increased heart rate. It is quite likely that the cause of these symptoms lies in the fact that the fibers of the vagus nerves are uniformly affected. At any rate, one finds very marked disturbance in the continuity of the myelin sheaths of these nerves in the experimental polynoeritis of fowls.

Dyspnea, though at first barely noticeable, may suddenly become extremely severe, as a result, perhaps, of the accumulation of fluid in the pericardium. That the degenerative changes are by no means confined to the cardiac nervous mechanism is a well known fact in the oriental type of beriberi. That the heart muscle suffers as well as the nerve fibers is evident from the microscopic picture of myocardial degeneration. This would account for the initial palpitation and dyspnea, which become pronounced soon after the onset. Later there is enlargement of the heart area and cardiac dilatation with valvular incompetence; and these signs, together with a feeble, rapid, soft and irregular pulse and often also an enlarged, tender liver, accumulating edema, ascites, hydrothorax and hydropericardium, complete the picture of acute congestive heart failure.

Edema at first may not necessarily be an expression of heart failure; the general anasarca and serous cavity effusions are, however, to a marked degree the expression of cardiac failure in the late stages of the disease. It is an early, constant and the most prominent symptom in the wet type of beriberi.

Edema appears as a rule first over the tibia, and then spreads downward to the foot and upward to the subcutaneous tissue of the abdomen. It must be regarded as a trophneurosis, a nervous phenomenon which by disturbing the vitality of the capillary endothelium increases its permeability to fluids. Or perhaps it may be regarded in the light of a shift in the proportion between the intracellular mineral constituents which alters the osmotic pressure. The venous stasis of later myocardial insufficiency may further exaggerate the imbalance and conspicuously increase the edema.

Cardiac injury of some degree was suspected in the majority of the cases seen during the epidemics in 1921 and 1923 but could not be as carefully studied or as definitely established as in our present series. The patients seen during these outbreaks were, thanks to the attention of Lewis, well on the road to recovery, and some, too, had begun to appreciate their danger and had taken precautions before our examinations were made.

2. The Neuritic Phenomena.—Frequently the first sign of the disease is noticed in a feeling of weakness of the limbs. The patients say that the legs actually give way and double up under them, apparently just as in intermittent claudication. Sometimes the weakness is preceded by localized pains in the calf muscles.
The latter remain painful to the touch for a long time after the onset of the disease.

Weakness of the lower extremities, particularly of the knee and ankle joints, was a constant symptom. Efforts to extend the foot against opposition were distinctly weak. The strength of the grip was diminished. This weakness of the hand was a source of much annoyance to the patients and persisted after they had apparently recovered.

Paresthesias, such as the sensation of pins being driven into the skin or the crawling of ants, were not noted in the patients examined in either 1921 or 1923.

**COMPARISON OF THE SYMPTOMS OF ORIENTAL BERIBERI AND “MALADIE DES JAMBES” OF EVANGELINE AND ST. LANDRY PARISHES**

**BERIBERI**

**“MALADIE DES JAMBES”**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Onset insidious with malaise and asthenia</td>
<td>1. Not entirely confirmed</td>
</tr>
<tr>
<td>2. Swelling of feet and tibial edema</td>
<td>2. Edema always present; not clear whether beginning over skin, but highly probable view of the appearance of the skin</td>
</tr>
<tr>
<td>3. Difficult breathing, palpitation</td>
<td>3. Increased respiration and heart rate on the least exertion</td>
</tr>
<tr>
<td>4. Cramps in calves of legs; difficulty walking; inability to walk on &quot;something soft&quot;; numbness and paresthesia</td>
<td>4. Pains in calf muscles; paresthesias not clearly defined; walking difficult; “walking on felt”; “feet glued to floor”</td>
</tr>
<tr>
<td>5. Dull pain in lower joints, loss of appetite; diarrhea; large meal increases distress</td>
<td>5. Pain in epigastrum a fairly constant symptom; it seems to have been generally the case with these patients that a larger meal increased distress</td>
</tr>
<tr>
<td>6. Bowels constipated</td>
<td>6. Chronic constipation is the rule in recent cases</td>
</tr>
<tr>
<td></td>
<td>Signs</td>
</tr>
<tr>
<td></td>
<td>7. Carotid and epigastric pulsation not noted</td>
</tr>
<tr>
<td></td>
<td>8. Palor; increased rate and low tension</td>
</tr>
<tr>
<td></td>
<td>9. Heart enlarged; dilated on right side</td>
</tr>
<tr>
<td></td>
<td>10. Pleuritic and peritoneal effusion</td>
</tr>
<tr>
<td></td>
<td>11. Tenderness of calf muscles; tenderness on pressure over pylorus</td>
</tr>
<tr>
<td></td>
<td>12. Anesthesia begins in feet, extending upward and in patches</td>
</tr>
<tr>
<td></td>
<td>13. Ring of anesthesia around mouth</td>
</tr>
<tr>
<td></td>
<td>14. Wrist drop and ankle drop</td>
</tr>
<tr>
<td></td>
<td>15. Loss of grip power</td>
</tr>
<tr>
<td></td>
<td>16. Loss of sense of heat and cold</td>
</tr>
<tr>
<td></td>
<td>17. Reflex changes in patellar and achilles tendons; at first definitely increased and later decreased and absent</td>
</tr>
<tr>
<td></td>
<td>18. Tactile gait</td>
</tr>
<tr>
<td></td>
<td>19. Diminished output of urine</td>
</tr>
<tr>
<td></td>
<td>20. Condition may last for weeks and months</td>
</tr>
</tbody>
</table>

The tactile, pain and temperature senses showed disturbances of one sort or another in every case. Invariably sharply defined areas of anesthesia and analgesia were to be found on the legs. In some of the analgesic areas encountered on several of the patients, pins could be driven into the skin without provoking any complaint of pain from the patient. The areas of numbness were usually over the tibia, though sometimes they occurred over the calf. One patient showed an anesthetic area in the shape of a belt around the abdomen. One also presented an area near or around the navel where sensation was diminished. Circumoral analgesia was present in all cases in which it was looked for.

Subjective sensations, such as feeling as though “walking on felt” or being touched by “gloved fingers” or “through cloth” when a patient was actually touched by objects or fingers, were frequently complained of. Numminess of the fingers, especially in the area of the distribution of the ulnar nerve, was noted. It is worthy of remark that one of the early symptoms that the disease has begun is the peculiar sensation which the patient experiences when he puts his feet to the floor on arising in the morning. It seems to be a feeling of “goneess,” as though the floor had ceased to be solid.

Changes in the reflexes were invariably present and thus constituted an important nervous symptom. Only in one instance was hyperactivity of the knee jerks noted. This was in a man whose brother had suffered from the disease and who, apparently learning from observation, had made a change in his diet as soon as the symptoms appeared. In all the patients examined not a single one preserved a trace of either the patellar or the achilles reflex. Lewis stated that, according to his observations, the knee jerk was at first exaggerated and then gradually diminished, until it completely disappeared. Sensitivity to deep pressure seemed to be maintained for a longer time, and ataxia was demonstrated only once in the 1921 and 1923 outbreaks, though Lewis asserted that he had repeatedly been able to demonstrate it. Ataxia was noted once in the 1927 series (case 2).

The gait of a person with “maladie des jambes” is a constant and rather characteristic symptom. A patient is said to walk as though his feet were “glued to the floor.” Others have an ankle drop and throw out their feet in the manner characteristic of ataxic tabs. Only a few were observed with anything approaching this gait. The patients themselves described their way of walking as “shuffling,” which is probably correct, and there is no doubt that they were greatly inconvenienced by it.

3. The Gastro-Intestinal Symptoms.—Patients do not uniformly complain of symptoms referable to the stomach. It may be that the reason for this discrepancy lies in the fact that the average person neglects or fails to notice or to think much about minor gastric disturbances. A story, however, is frequently elicited of nausea and vomiting as well. Patients who suffer from constipation mention the occurrence of diarrhea, though neither constipation nor diarrhea occurs with sufficient regularity to be regarded as in any way characteristic. An important sign, however, is the pain on pressure in the epigastrum. This is a regular and constant symptom of which every patient complains. Lewis stated in 1921 that in his experience pain was most frequently localized in the region over what would correspond to the pylorus. A painful sensation or what is described as a feeling of fulness and oppression of the heart after meals seems to be a relatively constant symptom. Though the gastro-intestinal symptoms are vague and inconstant, they may possibly be related to the degenerative changes in the vagus nerves, which, however, are most constant and striking features.

**THE SIMULTANEOUS OUTBREAKS OF MALADIE DES JAMBES AND PRISON BERIBERI**

Another epidemic of what the rice belt natives called “maladie des jambes” was reported to the Louisiana State Board of Health from one of the south central parishes. A personal investigation of the outbreak could not be conducted owing to the pressure of other work. However, four white patients were brought to the Charity Hospital in August and September, 1927,
from these regions. These patients related a fairly typical story of a moderately severe epidemic of between twenty and forty cases, with two very acutely fatal terminations in young men.

Two of the hospital patients presented conclusive evidence of an edematous polyneuritic syndrome of beriberi. The other two showed conspicuous edema and shortness of breath, and complained of weakness and tightness in the legs which in their opinion was "maladie des jambes," without, however, presenting any evidences of neuritic disturbances, anemia, paresthesia or rombergism except sluggish tendon reflexes. On the other hand, chemical and microscopic studies of the urine and the blood, and renal function tests gave evidence of disturbances of sufficient grade to indicate serious and predominant kidney lesions. It is interesting to note here that our clinical studies in these and subsequent cases of what apparently is a true beriberi revealed evidences of constitutional more renal irritation and actual kidney injury than is generally reported to be present in beriberi.

By a happy coincidence, just as our interest was aroused in this outbreak we were accorded the privilege of studying a group of patients with prison beriberi. The latter outbreak appeared in the Parish Prison in September and October, 1927, and was attributed to a definitely faulty diet in which, however, rice did not play any part whatever. Eight of the patients were referred to the Charity Hospital; of these, one died on the way, another died in the hospital, and six recovered. Only four of these could be considered as having unquestionable beriberi. The opportunity was offered in these cases of making complete cardiac examinations, including electrocardiographic studies in the heart station at Charity Hospital.

There were many more prisoners with similar but milder symptoms, including edema and tenderness of the leg muscles, for whom transfer to the Charity Hospital was not deemed necessary after the nature of the outbreak was determined and the specific dietary treatment was outlined. Two patients were transferred to Baton Rouge and eight patients with apparently mild attacks recovered promptly when the prison diet was modified by the addition of fresh vegetables.

The previous prison fare, according to the prisoners, had consisted of a stew of salt pork or beef and boiled hard cowpeas or beans or carrots and soup and white bread, molasses and water. Milk or fresh vegetables or fruits were not served. The prison fare was sufficient in amount, but monotonous and definitely without vitamins, since the legumes were so hard that they were not eaten. This diet did not produce typical beriberi even in many who had been on it for almost four months; but in some of those brought into the hospital it had apparently precipitated more or less latent heart and kidney disease or had contributed in some way or other to the physical incapacitation of the prisoner.

Not a single case of beriberi developed among those prisoners who received food from relatives and friends on the outside. Constitutional resistance and other factors, such as chronic infections and exposure, determined the production or suppression of manifestations of the disease. Nothing approaching a definite incubation time could be determined. The patients had been on the abnormal diets for variable periods of from three to four months. Symptoms had been present for as long as six to eight weeks, but the average period of trouble before admission was three weeks.

The symptoms and signs presented in these two series of cases

The cardiovascular symptoms were outstanding in both these series. Edema of the lower extremities, gradually becoming generalized, and a feeling of weakness in the swollen legs were among the first symptoms to attract attention. Shortness of breath and palpitation were common symptoms. Pains in the leg muscles, paresthesias, and a feeling of numbness in the extremities were complained of in every instance.

Nausea and vomiting occurred in only two of the cases, and then only after eating the none too inviting prison fare. Constipation was the rule.

The physical signs presented in these series were enlargement of the heart of moderate degree in only two patients, each of whom also presented apical systolic murmurs. A presystolic gallop rhythm was noted occasionally, especially conspicuous in the fatal case.

Electrocardiograms were taken in every case. These presented fairly consistently small complexes which may have resulted from the subcutaneous edema, negative T waves in less than 20 per cent. Two patients, and 111, slight to moderate left ventricular predominance, and some slurring and slight aberrations in the ventricular complexes. While there were no characteristic or pathognomonic electrocardiographic observations, these suggest that even in the milder cases very definite myocardial changes may occasionally be present.

Generalized edema in all these cases classified them as of the "wet" type. The urinary and renal function tests showed considerable evidence of kidney irritation and injury.

Some one of the characteristic neurologic manifestations of tenderness of the gastrocnemius muscles, changed reflexes, areas of anesthesia, wrist drop or foot drop, weakness, ataxia, loss of motion and position, or rombergism were considered prerequisite to the diagnosis of beriberi.

Diagnostic Diagnosis

As pointed out in the present series, the differentiation of beriberi from primary myocardial insufficiency is of paramount importance and at times difficult. There is evidence suggesting heart muscle injury in many of the chronic cases, while in the acute pernicious cases death is generally considered the result of acute heart disease, though this may possibly be the result of bilateral vagus degeneration.

The generalization of the edema, the absence of pulmonary edema and liver engorgement, and the presence of muscle tenderness, reflex changes and anesthetic areas are signs not present in the general run of cardiac cases.

We were at times perplexed in the matter of estimating the part played by the renal injury. Apparently in an outbreak there are cases in which the clinical picture if studied carefully, as it was in two of our cases, would be called acute nephritis. It may be that in these cases the metabolic upset has at times concentrated its effects on the kidney tissue or shown a predilection for it. In the true cases of beriberi, contrary to the general opinion, we found evidence suggestive of severe renal irritation and injury. The criteria here again are the neuritic phenomena, the presence of which permit the diagnosis and the absence of which militate against the diagnosis of beriberi.

Hookworm infestation not infrequently presents a generalized edema, a waxy pallor, some breathlessness and weakness. It is common in the parishes from which
our cases of "maladie des jambes" come, and it may occasionally be mistaken for nephritis or beriberi, as Castellani has pointed out, or it may be a contributory factor. The absence of the characteristic neurologic signs, however, rules out the possibility of beriberi.

Syphils of the central nervous system may cause pains in the legs but not tenderness, and may show absent reflexes and rombergism, but not so often anesthetic areas. There is never any edema in tabes dorsalis, but there is also a "dry" type of beriberi. The pupillary changes are not present in beriberi, nor are the characteristic spinal fluid and serologic reactions. Syphils may be a constitutional, contributory factor or it may be coincidental. The epidemicity of the "maladie des jambes" symptom complex is not simulated by central nervous system syphils.

Toxic neuritis from arsenic, alcohol or lead, especially with its edema, may be differentiated often only by the history with especial reference to occupational exposure, drug intake and diet; and rarer conditions, as malarial neuritis and trichinosis, require blood studies and tissue section at times to disprove the diagnosis.

Scurvy is excluded by the absence of spongy gums and hemorrhages, but it may coexist and will respond to high vitamin therapy.

Fever, war edema, ship kakke and asylum or prison bloat are apparently closely related to antineuritic vitamin B deficiencies or acute nephritis, if not identical with them.

REPORT OF CASES

Three rather typical clinical case records of the neuritic edema syndrome, two types of which we have had an opportunity to study, have been selected for presentation. The history, physical signs and autopsy observations in one fatal case will also be given. Cases 1 and 2 are examples of the rural "maladies des jambes," while case 3 is one of the four typical cases of urban prison beriberi.

We consider the two types to be identical in nature, the result of avitaminosis, however much they may vary in immediate cause and environmental conditions.

Case 1.—X. E., a white man, aged 41, a rice farmer from St. Mary Parish, came to the clinic, Aug. 31, 1927, because of weakness in the legs with swelling and pain below the knees. His symptoms had come on very insidiously and had been troublesome for only about one month. Within the month the symptoms had incapacitated him, principally because of the appearance of shortness of breath. Besides being painful and weak, the legs became numb and seemed heavy, dead and noncontrollable. His diet had been practically restricted to rice and salt pork for many months and, aside from unusually heavy work in the field, no significant change was noted in his routine life or health. He had not had any serious illnesses, but he had had some similar though milder disturbances during a previous summer.

He related the interesting news that there were twenty or more persons in his community suffering from a similar disease. A nephew of his had had a very acute fulminating pernicious type, which had proved fatal within a period of less than two weeks. From the description that he gave, his nephew had died of what was apparently acute heart failure.

On admission the skin appeared somewhat pasty. There was no drowsiness, pain or discomfort. The pupils reacted normally to light and in accommodation. The teeth were carious, and much alveolar suppurition was present. The lungs were normal.

The heart was very slightly enlarged. An apical systolic murmur and a presystolic gallop rhythm with some sharpening of the first sound were noted. The blood pressure was 120 mm. of mercury systolic and 94 diastolic.

The abdomen was distended. The subcutaneous panniculus was somewhat edematous, and there were some evidences of accumulation of fluid in the abdomen. No organs were palpable.

The lower extremities presented pretibial edema. Knee and ankle jerk reflexes were absent. There was bilateral foot drop and anesthesia in patches over the anterior surfaces of the legs. There was no triceps sign present. The gait was ataxic.

There was some tenderness of the gastrocneum. The patient was unable to rise from a squatting position because of weakness.

The urine showed a specific gravity of 1.025 and contained a slight trace of albumin and a few hyaline casts. The phenolsulfophthalein excretion was 45 per cent in two hours. Analysis of the blood showed: nonprotein nitrogen, 45 mg.; urea nitrogen, 25 mg.; creatinine, 1.5 mg.; uric acid, 3.5 mg., and blood sugar, 100 mg. per hundred cubic centimeters.

The Wassermann reaction was negative. The body temperature was normal.

The diagnosis was beriberi, myocardial injury and subacute renal irritation. The patient refused to be admitted, but improved after his visit to the clinic and his stay with city relatives, who lived on a simple but evidently vitamin containing diet. This was doubtless responsible for his improved condition.

Case 2.—A. C., a white youth, aged 18, a swamp worker from Assumption Parish, came to the clinic complaining of swelling and numbness in his legs. He was admitted to the hospital, Sept. 29, 1927. His trouble began with swelling of the feet and legs about two and a half months before admission and lasted for about a month, to be followed by occasional pains, tenderness, weakness and numbness, which symptoms not only persisted but gradually became so aggravated that he was unable to walk for several weeks. A persistent nonproductive cough was annoying. He had not had a previous similar attack, although he had "rheumatism" and the ordinary infectious diseases. His diet had been distinctly deficient and, other than exposure, there was no apparent precipitating factor.

The patient, who was awkward and rather ignorant, appeared not to be suffering from any gain but was quite alert. He was able to coordinate satisfactorily the muscles of the extremities. The pupils reacted to light and in accommodation. The tonsils were enlarged and septic. The oral hygiene was poor. The lungs presented evidences of moisture in the basal bronchi. A friction rub was heard at both bases.

The heart was apparently enlarged, and an evanescent, faint systolic murmur was audible at times. The heart sounds were of a more valvar character. The blood pressure was 100 systolic and 65 diastolic. The electrocardiogram showed a slight right ventricular predominance. The T waves were diphasic minus plus within themselves. T was negative.

The lowered myoglobinism presented many significant and characteristic abnormalities. There was weakness in both legs and feet. The patient could not rise from a squatting position nor could he stand alone. He walked with an ataxic, bilateral foot drop gait by holding on to some support, such as the bed. The Romberg sign was conspicuously positive. The reflexes, including the patellar, achilles and plantar, were all absent. Moving pictures were taken of these abnormal reactions.

The specific gravity of the urine was 1.024; it was acid in reaction, and contained a trace of albumin, with pus cells found only in the sediment. The phenolsulfophthalein excretion was 30 per cent in two hours.

On analysis of the blood showed: nonprotein nitrogen, 40 mg.; urea nitrogen, 24 mg.; creatinine, 1.25 mg.; uric acid, 2.9 mg., and blood sugar 91 mg. per hundred cubic centimeters.

The Wassermann reaction was negative. The temperature was frequently subnormal.

The diagnosis was beriberi, myocardial injury and renal irritation.

Case 3.—J. C., a colored prisoner, aged 18, was brought to the service of Dr. S. Challie Jamison at Charity Hospital, Sept. 27, 1927, because of shortness of breath and inability to walk. His trouble had begun about September 1, after four months' confinement in the Parish Prison. Swelling was first noted, then weakness and tenderness in the right foot and leg. He was in a very few days. The swelling progressed and the abdomen became swollen. He was nauseated and vomited at times. Shortness of breath became so severe that he was unable to lie down, and the progress of
the disturbance in his legs made him unable to walk. The bowels had been obstinately constipated. He had had influenza in 1918, but stated that he had never had venereal disease.

Physical examination revealed orthopecty, with rapid respiration of 48 a minute and a pulse rate of 88. The pupils reacted to light and in accommodation. There was no circumsoral anesthsea.

The heart was at the upper limit and normal in size. The apex impulse was in the fifth interspace, 10 cm. to the left of the midline of the sternum. A systolic thrill and murmur and a questionable presystolic rumbling sound with a distinct presystolic gallop rhythm were heard over the apex beat. The second pulmonic sound was accentuated. The blood pressure was 112 systolic and 47 diastolic. The arteries were soft and pliable. The electrocardiogram showed a slight right ventricular predominance, a greatly prolonged R-T interval, small complexes, and a sinus tachycardia.

The lungs presented râles as evidence of moisture, and there were evidences of a slight accumulation of fluid in the pleural sacs.

The abdomen was distended, rigid and extremely tender, especially in the right lower quadrant. There was some subcutaneous edema.

The extremities presented hyperesthetic skin over the thighs and anesthetic areas over the tibias. The knee and ankle tendon reflexes were absent.

Laboratory Examinations.—The urine contained a trace of albumin and a few granular casts and pus cells and was concentrated. The blood examination showed a high grade secondary anemia, a strongly positive Wassermann reaction and chemically definite nitrogen retention, with a nonprotein nitrogen of 90 mg.; urea nitrogen, 55 mg.; creatinine, 2.4 mg.; uric acid, 7.14, and blood sugar 95 mg. per hundred cubic centimeters. Spinal fluid studies showed a normal tension, less than one cell per cubic millimeter, and a negative globulin colloidal gold curve and complement fixation test.

The edema decreased, but the patient became delirious and died three days after admission.

Autopsy was performed by Dr. M. P. H. Bowden, October 1.

Autopsy.—The body length was 170 cm. (64 inches) and the weight 66 Kg. (146 pounds), although the usual weight had been 62 Kg. (137 pounds). There was but slight subcutaneous edema. The peritoneal cavity contained much clear straw colored fluid (500 cc.). The mesenteric nodes were enlarged. The pleural cavities also contained large amounts of clear fluid. The pericardial cavity was distended with 75 cc. of clear pale yellowish fluid.

The heart was enlarged and greatly dilated. At autopsy it weighed 430 Gm. The fixed and cleaned weight was 312 Gm.; the ventricular weight, 250 Gm.; the auricular weight, 52 Gm.; the valve lengths, aortic, 6 cm.; mitral, 8 cm., and tricuspid, 9 cm. The ventricular walls were friable and measured left, 8 mm. and right, 6 mm. The microscopic sections showed evident granular degeneration of the heart muscle cells and intense engorgement of the vessels.

The lungs, spleen and liver showed intense congestion, and the latter also presented focal necrosis.

The kidneys weighed 150 Gm. each, and were hard with adherent capsules. The cortex was thin and prominent. Microscopically, there were interstitial and perivascular degeneration and fibrosis, hyaline degeneration of the renal epithelium and the glomeruli, intense engorgement of the blood vessels, and calcium deposits in the walls of some of the larger arteries.

Comment

There do not appear to be any reliable sources of information from which we can derive accurate data on the prevalence of "maladie des jambes" in the rural districts of Louisiana where rice is the staple crop and food. The statements of our informants that there were fifty to sixty cases in the two epidemics of 1921 and 1923 and from twenty to forty cases in 1927 have hardly to be regarded as approaching an accurate estimate.

The disease is not reportable, and even the deaths which we occasionally hear about are probably only a fraction of the number that occur and are not reported on death certificates. One gains the impression that the disease incapacitates a not inconsiderable percentage of the population in rice growing districts and at times becomes a scourge both in name and in fact.

The people engaged in planting rice are for the most part of very suspicious and conservative natures. They are probably descendants of the early French settlers intermingled and intermarried with those of the original Acadians, who are said to have migrated from Grand Préc, Acadia, Canada. They speak a French dialect, and a large proportion of them are illiterate. Few, if any of the older generation can speak, read or write English. Nevertheless, bitter experience has taught them that when afflicted with "maladie des jambes" a temporary change of residence will effect a cure. For this reason, it is stated that they often make a trip to the southern coast or to Hot Wells, a health resort a few miles north of Alexandria, La. If such is the case, the unavoidable change of diet with the pilgrimage and also perhaps more sunshine, rest, fresh air and better quarters as well as occasional baths are probably responsible for the cures.

The local physicians had not applied any specific methods of treatment to the cases, until Lewis pointed out the true nature of "maladie des jambes" and identified it as beriberi. He suggested radical changes in the diet together with tonics or heart stimulants as indicated. Eggs, milk, green vegetables, fruit and fresh meat were urged, and the results we understand justified in every way the therapy. An alcoholic extract of rice polishings was made and advocated in 1923. Unfortunately, we were never advised whether the administration proved efficacious.

Four patients from the rice belt presented themselves at the Charity Hospital in the late summer of 1927 with what they termed "maladies des jambes." Of these, two had definite beriberi, while in the other two the picture of an acute nephritis predominated. There were ten cases in the parish prison besides the four true cases of beriberi received at the charity hospital. One prisoner died on the way to the hospital from the ailment and two were sent to Baton Rouge. Eight of those detained are said to have been relatively mildly affected and recovered when the diet was changed. Altogether eight prisoners were admitted to the hospital with edema and questionable cardiac lesions, but three were undoubtedly not to be classed as having true beriberi. It may, however, be assumed that preexisting heart disease was adversely influenced by the nutrition.

Conclusions

In our opinion the following conclusions are justified:

1. "Maladie des jambes," the nutritional disturbance frequently encountered among the rice farmers of Louisiana, is identical with the neurodegenerative syndrome classed as the "wet" type of beriberi in oriental countries or the sporadic outbreaks of neuritic edema in prisons, asylums, on shipboard, or in war. The outbreak of jail beriberi and aggravated heart lesions in the parish prison was provoked by a monotonous diet, which, though plentiful enough, was deficient in essential vitamin constituents.

2. Though authorities may still be divided on the true etiology, we must consider a deficiency of vitamin B in the diet as the principal cause. That polished rice is not specifically the cause evidenced from the prison cases, in which rice did not play any part in the diet. Nevertheless, the clinical picture was practically indis-
tistinguishable from that presented by the rice farmers in the original series.

3. Insanitary living conditions and exposure may act indirectly as contributory factors only so far as they tend in some way to lower bodily resistance.

4. Symptoms attributable to peripheral nerve degeneration with secondary myocardial dysfunction sometimes complicated by kidney injury are the salient features of the disease.

5. Death in the acute cases is probably due to bilateral vagus degeneration and possibly to failure of the right ventricle and general myocardial injury.

6. Electrocardiographic studies did not reveal any characteristic sign, but usually were suggestive of myocardial changes.

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PARENTERAL DENATURIZATION OF ANTIGENS

ITS BEARING ON THE CURRENT IMMUNOLOGIC THEORIES

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The development of a rational theory as to the origin, nature and physiologic role of specific antibodies that will be a reliable and permanent guide to clinical diagnosis and biologic therapy can come only from detailed knowledge of the fate of antigens in the animal body. One must know, for example, the topographic distribution of different antigens in normal organs, tissues and body fluids, the modifications in distribution as influenced by dosage and portals of entry, and the modifications due to pathologic conditions and to previous and concurrent sensitization and immunization. Above all, it is necessary to know the successive chemical changes in each antigen in immunologically important organs, tissues and body fluids until its final destruction, elimination or incorporation in the body.

Thus far, few attempts have been made to supply the necessary data. I have thought that it might be of value, therefore, to study the initial chemical changes in some typical antigen when injected intravenously into normal animals.

LOSS OF SPECIFICITY

If 2 cc. of horse serum per kilogram of body weight is injected intravenously into a normal dog, and if at various intervals after this injection blood samples are withdrawn from this dog and the serums from these samples are titrated with a specific horse protein-precipitating rabbit antiserum, the titrations show, within the limits of the experimental error, no qualitative or quantitative changes in the injected horse proteins for at least seven days. Nevertheless, other biologic tests show that the injected horse proteins are distinctly altered within that time.

For example, if within the first twenty-four hours after the injection of horse serum the blood of the injected dog is transfused into a partially exsanguinated horse serum-hypersensitive recipient, the recipient is thrown into a typical anaphylactic shock. The shock in this recipient is apparently identical, both qualitatively and quantitatively, with the shock in a control hypersensitive dog injected intravenously with the calculated transfusion dose of unaltered horse serum. If, however, the transfusion is delayed till the end of forty-eight hours, the severity of the transfusion shock is reduced one half. By the end of three days, it is reduced three fourths. By the end of four days, no anaphylactic reaction is demonstrable in the recipient, which means that by the end of four days at least 85 per cent of the injected horse proteins have been so altered in their chemical properties or relationships as to be anaphylactically inert.

An even more complete denaturation of the injected horse proteins is shown by sensitization tests. If, within the first three days after the injection, the blood of the injected dog is transfused into a normal dog, the transfused dog will develop a typical hypersensitive response to horse proteins after the usual incubation period. This sensitization is apparently identical with the sensitization of a control normal dog injected intravenously with the calculated transfusion dose of unaltered horse proteins. If the transfusion is delayed till the end of the fifth day, however, a distinct reduction in the sensitizing power is demonstrable. By the end of six days only half of the dogs given transfusions develop demonstrable hypersensitiveness. On and after the seventh day, only an occasional dog becomes actively hypersensitive. This means that by the end of seven days at least 97 per cent of the injected horse proteins have been so altered as to lose their original specific sensitizing power.

The possibility of such a loss of specificity by injected antigens has been usually overlooked by previous investigators.

RETENTION OF DENATURIZATION PRODUCTS

In order to follow the subsequent history of these partially denatured horse proteins, blood samples were withdrawn from the injected dogs about the thirtieth day. Without exception, the thirty-day blood samples gave little or no demonstrable precipitate with rabbit antiserum, when tested in low dilutions; e.g., from 1:2 to 1:16. Control tests with unaltered horse proteins gave ++ precipitates.

Such negative reactions are usually interpreted as conclusive evidence of the absence of a specific foreign protein. That this is not the true interpretation under the conditions of this experiment, however, is shown by continuing the tests to higher dilutions. When the dilution reaches 1:64, a distinct though faint precipitate is usually formed, increasing in strength with higher dilutions. With dilutions of 1:128 and over, the precipitates and turbidities are practically identical with those in the control tubes with unaltered horse proteins. With our present knowledge of precipitin reactions this can only mean that the partially denatured horse proteins are retained quantitatively in the canine circulation for at least thirty days, their detection being complicated by some inhibiting factor operative in low dilutions.

Titrations of blood samples withdrawn at later dates show practically no further changes in the horse proteins for at least four months (latest titrations thus


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