THE CAUSE, COURSE, PREVENTION, AND TREATMENT OF BERIBERI.

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I shall not attempt more than to outline the results of my researches into the cause, course, and treatment of beriberi. Full details have already been published.[1]

The cause of beriberi appears to be a bacillus which gains entrance to the alimentary canal in contaminated food and drink. It chooses for the site of its activity the contents of the stomach and small intestine, but chiefly the pylorus of the former and the duodenum. The bacillus, after causing a necrosis of the mucosa of these parts, with congestion and small-celled infiltration, invades the unhealthy mucosa and continues its work. At the site of its activity it appears to elaborate an extracellular toxin, which being absorbed into the circulation, poisons the peripheral terminations of the fibers in the different systems of neurons, and thus induces symmetric, bilateral, sensorimotor, cardiac, and vasomotor paralyses.

After a few weeks' activity, the bacillus and its toxin are eliminated, the paralyses which the toxin has induced either subside, or they resolve into narrower limits, and continue for months or years, until the subjects are carried off by an intercurrent disease or cardiac failure.

The causal bacillus of beriberi seems also to be able to accomplish its effects by invasion of an open wound. Therefore, we not infrequently see beriberi after surgical operation, in chronic ulcer cases, and in parturient women. In all classes of acute beriberi, the specific bacillus appears to induce its remote effects, paralysis, by means of an extracellular toxin carried to the neuronal terminations in the circulation. There is as yet no evidence that the bacillus extends within the body.

Upon clinical and postmortem observations extending over some six

[1] See the British Medical Journal, June, 1901; Studies from the Institute Medical Research, Federated Malay States, Vol. ii, No. 1, May, 1902; Brain, Winter Number, 1903-1904; Studies from Institute Medical Research, Vol. ii, No. 2, December, 1903; Journal of Hygiene, Vol. v, No. 2, April, 1905.

years, I have classified beriberi into (1) acute pernicious beriberi; (2) acute beriberi; (3) sub-acute beriberi; and (4) beriberic residual paralysis or the disease as it appears after the specific organism and its toxin have been eliminated and the engendered paralyses have failed to clear up.

Clinical Summary of Acute Pernicious Beriberi. — This form of the disease is rapidly fatal as the result of the severe impact of the beriberic virus on the cardiac nervous system. If one happens to be watching a community in which beriberi rages, it is observed that even the more robust members suddenly complain of symptoms that suggest acute indigestion. There is loss of appetite, or a disinclination for solid food, malaise, oppressive feelings in the deep epigastric region, cold or hot flushes in the legs or trunk, and sometimes sore throat. The throat is found reddened, pressure of the epigastrium is resented and causes obvious pain. The patient often indicates quite definitely that the epigastric sensations are deep, and in the position of the pylorus and duodenum. In a few days, or even hours, the knee jerks, disappear, rarely they become plus, a pretibial edema develops, subjective and objective sensory disturbances occur in the feet and legs, motor weakness of the peroneals and anterior tibials is demonstrable, the cardiac rhythm is found to be embryonic in character, or it gallops, one or several cardiac sounds reduplicate, hemic murmurs may be heard, the cardiac area extends with alarming rapidity to the right, a marked precardiac impulse contrasts with a weak irregular pulse, the cervical veins and epigastrium throb, dyspnea intrudes, delirium cordis develops, and in a few days or even hours the patient dies of cardiac failure. In the meantime the sensorimotor disturbances and edema have together, or separately, marched to the thighs, hands, arms, and trunk. The face may not escape, and not infrequently the diaphragm, pharynx, larynx, and the internal and external ocular muscles become involved.

Pathologic Summary. — The external appearance of the cadaver depends largely on the amount of edema which has developed before death. A general anasarca will mask other signs. Where edema has not extended beyond the legs, the cervical veins are greatly swollen. Rigor mortis is early if there has been a long agony. The eyes are partially closed and a bloodstained froth is found on the lips. The pharynx is moderately reddened. The serous cavities contain varying amounts of clear straw-colored fluid. The stomach and duodenum are toneless, dilated and empty. Their mucosa is deeply congested, rugæ and valvulæ are flattened and present numerous small hemorrhagic injections. Rings and patches of brilliant congestion occur, and prove to be markedly dilated capillaries. They suggest sprinklings of red pepper. This con-

gestion and injection may be found as low as the cecum; in a few instances I have found it in the ascending colon. As a rule it is most marked and occasionally wholly confined to the pylorus and duodenum. A thin pellicle of treacle-like mucus has occasionally to be stripped from the congested mucosa, but no true membrane is ever formed. Infrequently the congestion proceeds to hemorrhagic erosion of the gastro-duodenal mucosa. The first chain of mesenteric glands is usually swollen. The liver, spleen and kidneys are markedly congested and may be moderately swollen, but in uncomplicated cases exhibit no other gross change. The contents of the thorax present a characteristic appearance. The lungs look massive from hypostatic congestion and edema of their bases, and from acute emphysema of their apices, and ventral borders. The heart looks large. It is only greatly dilated, especially the right chambers. The latter are full of dark semifluid clot. A moderate amount of similar clot occurs in the left ventricle. The right chambers are enormously dilated, the walls are thinned and the tricuspids are relatively incompetent. The muscle may have a greasy feel, but the fatty degeneration is not usually apparent to the naked eye. Occasionally the outer wall of the right ventricle is spongy and on pressure exudes a considerable amount of blood. The left ventricle is usually slightly dilated. There is no hypertrophy in uncomplicated cases. On the contrary, both right and left walls may be thinned. The encephalon and cord are normal looking, also the peripheral nerves.

Microscopically, the gastrointestinal mucosa exhibits all the signs of an acute inflammatory process. There is a more or less extensive small-celled infiltration, the vessels are engorged with red cells and leucocytes bearing debris, the epithelium of the villi and necks of the glands is markedly necrosed, and a small amount of fibrin has been precipitated. Lying between the necrosed cells and in the bodies of the glands, are varying numbers of a bacillus of constant morphologic character. In some instances it exists in pure culture, in others it is predominant. In length it is from 4 to 9 microns, and in breadth from 1 to 1.05 microns. The ends are slightly rounded. It stains with the ordinary basic dyes, and *is not to be decolorized by Gram.* All stains leave from one to three finely striated bars across the organism. The muscle fibers of the heart exhibit an extreme fatty degeneration. There is usually some fragmentation of the fibers of the right heart. There is also some dissociation of the individual fibers. A few foci of small cells are found beneath the membranes. The capillaries are crowded with red cells. The lungs exhibit the changes characteristic of hypostatic congestion and moderate edema. The kidneys are unchanged except the intense congestion. In uncomplicated cases there are no changes of note in the

liver and spleen. As in the kidneys, their vessels are crowded with erythrocytes. The nervous system is profoundly implicated. The effects of the beriberic toxin are exhibited by the peripheral terminations and trophic centers of the fibers. Sensory, motor and cardiac fibers show the same kind of change, though it differs somewhat in degree. Fibers first and most severely implicated, such as the anterior tibial and cardiac, react most plainly to Marchi. Of all the fibers implicated, the vagal are the most important, and so they will best serve as an example. Their terminations in the heart, in the gastroduodenal walls and in the deep cardiac plexus, exhibit by Marchi, black dots and dashes at the nodes and internodes. It is rare to see droplets of altered myelin. The medullary sheath does not appear to have broken down, but only to have been chemically changed. It is probable that the earliest act of the beriberic toxin is invisibly microchemic, and breaks the synapses between fiber and muscle or skin, followed by a visible chemic change in the medullary sheath readily detected by Marchi. In any event, the changes found in acute pernicious beriberi are not truly degenerative, but only toxic. In the vagal twigs, no single fiber termination is greatly changed, but every termination is poisoned. It is this that makes the poisoning of the vagal cardiac terminations so serious a matter. A few terminations completely destroyed would not cause death, but the moderate damage of the whole number soon leads to cardiac failure.

Acute beriberi in its clinical aspect differs from the acute pernicious form only in degree. The gastroduodenal syndrome which ushers in the disease is as marked, and the consequential paralyses, sensory disturbances and edema may be severe and widely distributed, but the terminations of the cardiac nervous system are never so deeply implicated. Death from cardiac failure is, therefore, a rare event in the early acute stage of the disease. When it does occur within the first 20 days or so, the anatomic changes are not different from those of acute pernicious beriberi.

Subacute beriberi is insidious in its onset, and patients seldom complain of or recall symptoms anterior to the actual edema and sensorimotor paralyses of the legs. The cardiac nervous system is but slightly, or not at all involved. The disease is not therefore, of itself fatal.

Course of Beriberi. — Cases of acute beriberi which do not succumb in the active, acute stage of the disease, follow one of two courses: First, they run a fairly definite course, ending in recovery. This is especially so when the disease is taken seriously and accorded the treatment usually meted to acute neuritis in an occidental hospital. About 15 or 20 days after the onset of the disease the symptoms of gastroduodenal irritation clear up, the slight pyrexia which may have been present

disappears, and the deep epigastric pain is no longer demonstrable. If the patient has been strictly confined to bed the edema will have almost vanished, and now subsides entirely. The sensorimotor disturbance ceases to spread, and soon begins to resolve. By the fifth or sixth week of the disease the heart rhythm has steadied, the cardiac area has contracted to normal, the motor paresis has disappeared, and except for the continued absence of the knee-jerks, the patient may be said to be well again.

The second course of beriberi is a serious one and generally incapacitates the subject for life. Up to the end of the third or fourth week cases in this category proceed as those in the first. The gastroduodenal irritation, deep epigastric pain, any pyrexia that has shown and the edema subside. The sensorimotor paresis contracts to the hands, arms, and legs, or altogether to the legs, and it looks as though the patient was about to reach normal. Then from some more or less obvious reason, such as that the patient is allowed on his feet too soon, or has not been compelled to rest from the onset, or because the impact of the beriberic virus has been crushing, there is a halt in the subsidence of the different paralyses and sensory disturbances. And now, what may have been an almost complete flaccid paresis, a wide affection of sensation, or a marked cardiac weakness and irregularity, resolves into narrowly confined atrophic paralysis of the legs, and arms perhaps, definite anesthesia of the legs, trophic changes in the tendons, and a weakness and irritability of the heart, troublesome on exertion. What has been a general anasarca remains so or fluctuates between that and edema of the legs. In course of time these residual paralyses become more marked, or some one predominates. It may be cardiac weakness, atrophic motor paralysis, anesthesia, analgesia or edema, and we then have beriberi, as most often seen in endemic areas.

It should be needless to point out that in these residual paralytics we have to do with nervous wrecks, left by the toxin of a specific organism long since eliminated. The real factor in these residual paralyses is not a toxin constantly acting, but the extension of a degenerative tendency imparted to the neuronal terminations by a toxin in the active, acute stage of the disease. The residual paralyses are, as a rule, confined to those sensorimotor and vasomotor areas which were the first to be implicated in the acute stage; to the cardiac and anterior tibial muscles, and the sensory areas of the legs and feet, for instance. As time passes the degeneration in these neuronal terminations, which do not recover on the elimination of the beriberic virus, not only extends laterally in each individual termination, but migrates along the fiber toward its trophic center.

For bases of beriberi which take this second course I have proposed the term, beriberic residual paralysis. This term may be modified so as to indicate which of the neuronal systems, cardiac, motor, sensory, or vasomotor is most deeply implicated.

Patients with beriberic residual paralysis may live for many years, depending largely upon the progress of the degeneration of the vagal cardiac fibers. Death is usually due to some cause inherent in the disease itself, generally cardiac failure, or to some intercurrent disease.

Pathologic Summary of Beriberic Residual Paralysis.— The appearance of the cadaver depends upon the duration of the disease, and upon the neuronal system most involved. There may be marked wasting of the leg, arm, and hand muscles. On the other hand, edema may be the salient feature. I propose to take for example a case of say two years' standing, in which the patient has finally succumbed to heart failure. If no rigor mortis is present, the wrist, ankle and knee-joints are remarkably loose. The latter permit of an extensive retroflexion. The stomach and small gut are generally slightly dilated, but there is a complete absence of the gastroduodenitis seen in the acute stage of the disease. Varying amounts of clear, straw-colored fluid are found in the abdominal and other serous cavities. The spleen is generally swollen and passively congested. A slight increase in the connective is sometimes present. The liver is round edged and passively congested. A moderate increase in the connective is found, and fatty and brown atrophy is common. The kidneys occasionally suggest cloudy swelling, but generally nothing but a marked passive congestion is present. The pancreas and other abdominal viscera exhibit nothing of note. The lungs are deeply congested at the bases and cut with more resistance than when normal. The apices and anterior borders are emphysematous. The heart is large. The right chambers are full of dark, semifluid clot. A small amount of similar clot is found in the left ventricle. The right side is, in the great majority of cases, eccentrically hypertrophied. In a small number there may be a thinning of the walls. A moderate hypertrophy of the left wall is not uncommon. The muscle is not firm and dark red, as is usual in hypertrophy, but fatty looking, and decidedly greasy to the finger. The whole organ is flabby. The tricuspids are generally relatively incompetent. The encephalon and cord appear normal to the naked eye. Nerve fibers to the atrophic muscles are thinned.

Microscopically, it is seen that the atrophy of the somatic muscles is of the parenchymatous type. Fatty degeneration and thinning of the individual fibers is more or less marked. The hepatic cells exhibit a moderate fatty and pigmentary degeneration. The protal canals are marked out by a moderate fibrosis. Foci of small cells are found beneath

the capsule and about the interlobular vessels. The capillaries are engorged with red cells. The glomerulæ and epithelium of the convoluted tubules of the kidneys are rarely fatty and cloudy. A few subcapsular foci of small cells are seen. The spleen, barring an extreme passive congestion, exhibits no change. The cardiac muscle is profoundly changed. Fatty and pigmentary degeneration is often combined and is always extreme. Rarely, there is a slight increase in the intermuscular connective tissue. Fragmentation of the fibers is not often seen. Foci of small cells are frequent beneath the membranes. A few of Remak's and Bidder's cells are always profoundly atrophied.

It is in the nervous system that we find the most remarkable changes. The slight poisoning in the acute stage has been succeeded by a true degeneration. Two factors are concerned in this conversion — the impact of toxin of great potentiality on neurons of low power of resistance, and inadequate treatment. The degeneration is not strictly terminal, as is the poisoning of the acute stage of the disease, but often migrates well toward the plexuses. I have never, however, even in cases of 15 years' duration, found degeneration in the plexuses. Between the centralward extension of the degeneration and the trophic cells there is always an hiatus. There is another important difference between the fibers as seen in residual paralytics and the acute stage of the disease. Whereas, in the latter, all the terminations in a given nerve twig are more or less poisoned, in the former only a moderate proportion are degenerated. The general poisoning of the acute, active stage of the disease, has resolved into a narrow degeneration of the residual stage of the disease. In the vagi, which we may take as an example, from a quarter to a third of the fiber terminations have failed to recover on the elimination of the beriberic toxin, but have developed a true degeneration, Wallerian in appearance. These degenerated fibers are not numerous enough to kill suddenly, but are in sufficient numbers to affect profoundly the nutrition and action of the heart (and plus strain), ultimately to cause death. What is true of the vagal cardiac fibers, is true in a general sense of the nerve fibers to the somatic muscles. The trophic centers in the cord and bulb of all atrophied fibers exhibit degenerative changes, the extent of which is closely related to the amount of degeneration in the fibers.

It will be seen that in beriberic residual paralysis, we have to deal with true degeneration causing atrophy, while in acute beriberi, we have to deal with a simple poisoning causing flaccid paresis.

Working Theory of the Cause and Nature of Beriberi. — Taking all the facts of beriberi into consideration, I have propounded the following theory as to the cause and nature of the disease: That it is an acute

infection with an incubation of from 10 to 14 days; that the exciting cause is a specific bacillus not yet isolated; that this bacillus ordinarily effects its purpose by invading the alimentary canal; that the chief site of its activity is the contents and mucosa of the pylorus and duodenum; that its local action causes a necrosis and inflammatory reaction in the mucosa of the affected parts of the alimentary canal, which for convenience may be termed a gastroduodenitis; that its remote action is on the peripheral terminations of the nerve fibers by means of an extracellular toxin elaborated at the site of the local lesion; that the remote effects on the fiber terminations are of the nature of a poisoning, which rapidly clears up on the elimination of the causal organism and its virus; that nevertheless the impact of the virus on the terminations may be, and often is destructive in its tendency and so leads to true degeneration in the terminations, with consequent atrophic paralysis of the somatic muscles, anesthesia, and cardiac weakness; that the active stage of the specific bacillus is about three weeks; that the bacillus escapes in the feces and becomes deposited in dark, damp places, whence by the agency of flies, or by manipulation, it contaminates food and drink; that by the ingestion of such food and drink the disease arises again. The working theory includes the possibility that the specific organism may gain a wound, and through the agency of its toxin, give rise to acute beriberi minus the gatroduodenal irritation.

Stated concisely, beriberi is caused by a specific bacillus that, multiplying in a mucous surface or wound, elaborates an extracellular toxin, which induces its effects by poisoning and setting up a degenerative tendency in the peripheral terminations of sensorimotor and autonomic neurons.

Treatment of Beriberi. — In April, 1902, I made certain recommendations to the government of the Federated Malay States and Straits Settlements for the control of beriberi. They were based on the forgoing working theory of the disease, and were to be applied to the Kuala Lumpur gaol, where beriberi had been epidemic for seven years. The chief recommendations were that the ventilation of the gaol be improved; that the gaol be made dryer; that the entire gaol be disinfected at short intervals; that the prisoners be no longer permitted to defecate in their cells, and that all gaol work should be done in the open air so far as possible. It was also recommended that in all acute cases of beriberi the patients be isolated for a month; that their stools be treated as typhoid stools are treated. A long series of observations and investigations had convinced me that diet, considered as diet, was not an active factor in the causation of beriberi. It was therefore pointed out to the

authorities that so long as the diet of the prisoners was wholesome it need not be regarded.

Since the institution of these recommendations, the gaol diet has been of the standard that obtained when beriberi was epidemic. In spite of this, the result of the application of the hygienic measures has been most brilliant. Beriberi has, in fact, disappeared from the gaol. From August 1895, when beriberi invaded the gaol, to October, 1902, some 1,500 cases of beriberi had occurred in the gaol, among a daily average of about 400 inmates. The death rate had averaged about 20%, and another 15% were left in a state of residual paralysis. The application of the hygienic measures as outlined was begun in May, 1902, and became effective in October of the same year. Since November 1, 1902, there have been about 35 cases of beriberi, with no deaths, in a daily average of about 500 prisoners.

This reduction of the gaol beriberi was no accident; for in the surrounding country from which the inmates of the gaol are drawn, the disease has not at all abated. Table No. I is of the cases in the gaol just before and after the application of the hygienic measures. Table No. II is of the inmates of the District Hospital, Kuala Lumpur, which draws its patients from the area which feeds the gaol with prisoners.

TABLE I. — NUMBER OF CASES.

	1902.	1903.	1904.		1902.	1903.	1904.
January	.....	6	0	July	38	0	3
February	.....	0	0	August	26	0	0
March	.....	0	3	September ...	28	1	0
April	.....	0	0	October	32	1	0
May	64	0	0	November	4*	0	0
June	49	0	1	December	11	0	0
				Totals	252	8	7

* Hygenic measures effective.

The number of cases per month from May to October, 1902, indicate the prevalence of the disease for the years 1895 to May, 1902, that is, before the nature of beriberi was made clear. The number since October, 1902, indicates how controllable beriberi is by efficient hygienic measures, since I determined the nature of the disease.

TABLE II.

	Admissions.			Deaths.		
	1902.	1903.	1904.	1902.	1903.	1904.
January	.....	67	48	.....	16	17
February	.....	61	50	.....	7	11
March	.....	61	73	.....	11	10
April	.....	69	70	.....	12	9
May	84	67	.....	23	17	.....
June	67	80	.....	16	16	.....
July	67	52	.....	14	12	.....
August	56	57	.....	10	17	.....
September	40	51	.....	5	18	.....
October	54	80	.....	12	12	.....
November	55	85	.....	6	30	.....
December	67	66	.....	14	24	.....
Totals	490	796	241	110	192	47

This table clearly indicates that beriberi remained epidemic in the area from which the prisoners in the gaol were drawn. In view of these results, it may be stated with considerable assurance that a correct personal and institutional hygiene, such as would be directed against diphtheria or typhoid, will surely stamp out beriberi.

Medicinal Treatment of Beriberi. — It is evident that if the foregoing theory of the cause and nature of beriberi is correct, we have to deal with a disease which calls loudly for an antitoxin; but before this can be had, the specific bacillus must be isolated. I am working to that end now. In the meantime, the chief measure in the treatment of acute beriberi is rest in bed. Because the sensorimotor and cardiac disturbance is slight, the patients are, as a rule, permitted to wander at will. The result is that the moderate poisoning of the neurons is given a degenerative turn, and the paralyses, instead of clearing up on the elimination of the toxin, become fixed or more pronounced. I insist on rest in bed until the pains in the calves subside and the heart sounds approach the normal. If the preliminary gastroduodenal irritation marks the local action of the specific bacillus, as I am convinced it does, then calomel ought to be exhibited in small doses at short intervals. In the case of parturition or wound beriberi, carbolic, or other antiseptic lotions are called for. In the event of threatened cardiac failure, strophanthus is the best drug; for, undoubtedly, a factor in the circulatory disturbance of acute beriberi is a low peripheral pressure due to a poisoning of the nervivasorum. Strychnin should not be used in the acute stage of the

disease. Its action on the trophic cells of the acutely poisoned neurons would probably be more inimical than its benefit to the circulation. I have tried bleeding to relieve the distended heart in acute beriberi, but with questionable success. The best results are obtained in Sir Patrick Manson's clinic from absolute rest in bed and restriction of fluids. Rest in bed and the simple diuretics are also the best remedies for the edema.

In the stage of residual paralysis, remedies which have proved effective in other forms of chronic neuronal degeneration are called for. Gentle exercise, massage, electricity, and small dose of strychnin or arsenic. The cardiac condition should be closely watched. It will be recalled that the cardiac disturbance is due to two factors: (1) In time, degeneration in the vagal and accelerator nerve fibers; and (2) fatty and pigmentary atrophy sequel to it. Compensation is partially established by the hypertrophy of the ventricles, principally the right. When this breaks, digitalis and strophanthus may be employed. It is often well to combine with them some strong stimulant, injections of ether for instance. Morphin injections often relieve the dyspnea; but there is really nothing that so quickly relieves threatened cardiac failure and dyspnea as rest in bed.