

made for an inch or two beyond the diseased surface, allowing the solution to arrest and destroy the organisms on their inward path.

## DISCUSSION.

DR. A. J. OCHSNER, Chicago, thought Dr. Laplace's suggestions worthy of trial. If it is possible to change the virulence of the streptococcus regularly in this manner, the paper, he stated, marks a very important step in the progress of therapeutics and in our ability to manage this disease scientifically. The change from streptococcus to staphylococcus seems most remarkable. So far as the practical part of the paper is concerned, he would look on it with very much less enthusiasm than on the scientific observations which it contains. There is no doubt but that, in cases of erysipelas seen early, it is a simple matter to dispose of the infection. Dr. Ochsner called attention to the fact that about fifteen years ago the *Berliner klinische Wochenschrift* contained an article based on a very large number of observations made in one of the German prisons where erysipelas was endemic. The medical director of this prison discovered empirically that if these prisoners, at the very beginning of the attack of erysipelas, were at once treated by means of careful washings with strong alcohol, repeated at intervals of an hour, directed toward the point of infection instead of away from it, in order not to carry the infection further, he could regularly abort the disease. The number of cases observed in this prison was so large, and the description of the cases seemed so honest and reasonable that from that time Dr. Ochsner has used this treatment and he has found it reliable. Since that time recurrent cases of facial erysipelas that have come under his observation, and the observation of those who have worked with him, have invariably resulted in cutting short the attack when this mode of treatment was employed. Of course, he said, it is possible that the use of alcohol in this manner has an effect similar to that of the acid described in the paper. These observations, he thought, show either that these aborted streptococci will return to be virulent streptococci or that they remain indefinitely in the staphylococcic form. If there is any uniformity in this, it is certainly a most important observation. Of course it is known from clinical observation that there is a tremendous difference between erysipelas and erysipelas. There are cases of erysipelas that never amount to anything so far as their severity is concerned, although they may extend over the entire body. Other cases run a very severe course, and, he thought that the facts stated in this paper might be an explanation of the clinical observations with which we are all familiar.

DR. ERNEST LAPLACE, Philadelphia, said that the streptococcus, when cultivated in an acid medium at 104 F., seems gradually to diminish in virulence. Pasteur laid special stress on the varying virulence of germs under different circumstances. A notable example of this consists in what takes place in inflammation of the appendix, where the micro-organisms, being located within the cavity, gradually increase in virulence to the extent of causing gangrene, reminding one of the bygone days of surgery where lack of antiseptic precautions favored the development of hospital gangrene.

**The Best Professor of Clinical Medicine in the World.**—A breezy little article giving advice to a medical student in the *Gaz. Méd. Belge*, page 352, concludes with the remark that the best professor is the patient himself. "Besides what you can learn from him, all the rest is of trifling importance. He is the one you must listen to, for he will not deceive you nor brag of his own ideas and discoveries, and while you are listening devour him with your eyes. Try to get on the best terms with him. Go to him early in the morning. Be the first at the hospital; you can leave when you choose after every one else is there. In taking your vacation, plan to be in the hospital when the rest have gone on their vacations. In selecting teachers seek those who talk to the patients rather than about themselves at the bedside."

THE SUDDEN APPEARANCE OF APNEA IN  
THE COURSE OF TABES DORSALIS  
AND ARTERIAL SCLEROSIS.\*

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The first patient, a young married woman 26 years old, had a syphilitic infection seven years ago. The past six months the patient has suffered from lancinating pains in the thighs and legs. She has also been annoyed with the feeling as though there was some substance interposed between the soles of her feet and her shoes. There have also occurred several attacks of nausea and vomiting, which, from her description, could very well have been gastric crises. Besides these attacks of nausea and vomiting there were no signs of vagus involvement.

Recently the thigh and leg pains grew so intense that morphin was required to allay the pain. The patient showed no disturbance of coordination. The pupils reacted sluggishly to light. The patellar and ankle reflexes were absent. The tactile sense and perception of temperature and of tuning-fork vibrations were unimpaired. There was, however, well pronounced hypoalgesia in the feet, legs and thighs, and the plantar surfaces of both feet exhibited a marked delay in transmission of the pain sense. The absence of patellar reflexes, the presence of hypoalgesia and delay in transmission of the sense of pain without trophic symptoms or any other signs, of multiple neuritis or syringomyelia, justified the diagnosis of tabes dorsalis. During the morning of the same day on which I examined her the patient was given  $\frac{1}{4}$  grain of morphin hypodermically. About forty minutes after the injection of morphin the patient suddenly, and without the slightest sign of distress, ceased breathing and lapsed into a semicomatose state. The attending nurse used artificial respiration for about twenty minutes, when suddenly automatic respiration and consciousness were simultaneously resumed.

The patient had been given  $\frac{1}{4}$  grain morphin hypodermically as I entered the house, and a few minutes after I had finished my examination there recurred the same symptoms seen in the morning. The patient became unconscious and ceased breathing. There was a slight cyanotic tinge to the skin of the whole body, the lips were pale and cyanotic. The pulse, which had been 80 up to the advent of apnea, now had a rate of 120. The radial artery widened its lumen. The diameter of the radial artery seemed to have increased threefold, but the maximum pressure was greatly diminished. At the same moment a pulsation in the dorsal veins of the hands was plainly visible. The pulsation was centripetal and strictly synchronous with the arterial pulse. The veins of the hands were dilated, but there were no signs of stasis from the right heart, either in enlargement of the heart's area of dullness to the right or dilatation of the jugular veins. In other words, the patient had vasomotor relaxation in the veins as well as in the arteries. The instant automatic respiration was resumed (after a lapse of about twenty minutes) all signs of vasomotor relaxation disappeared; the artery retracted to its original caliber. The veins retracted at the same instant to their usual size, the venous pulse disappeared and the pulse rate dropped from 120 to 80.

\* Read in the Section on Practice of Medicine of the American Medical Association, at the Fifty-eighth Annual Session, held at Atlantic City, June, 1907.

All these changes in the vascular phenomena occurred instantly and with the return of consciousness and automatic respiration. We did not permit the patient to remain in the apneic state for a longer time than thirty seconds without employing artificial respiration. During the entire period of twenty minutes the apnea was unbroken by a single complete respiratory effort on the part of the patient. At the conclusion of a series of artificial respirations there would be a very slight indication of an inspiratory effort, but not sufficient at any one time to inflate the lungs. So during a lapse of twenty minutes the patient's sole respiration was artificial. There was a striking disproportion between the degree of cyanosis and respiratory disturbance. The slight cyanotic tinge to the skin seemed to be dependent on the vasomotor phenomena rather than on the apnea.

Another patient, a man 33 years old, who had a syphilitic infection eight years before, came recently under my observation. This patient had no ataxia, but he had unequal pupils which reacted sluggishly to light but more promptly to accommodation. The patellar and ankle reflexes were both absent, though he assured me the patellar reflexes were present only two weeks prior to the time he consulted me. This patient had a fracture of the internal malleolus of the left leg, crepitus could be elicited and, though the patient perceived the grating, it caused him no pain. The tuning-fork vibrations were clearly perceived over the whole body as well as over the fractured fragment. Perception of temperature was everywhere intact. The tactile sense also was normal. There was, however, a marked hypoaesthesia over both thighs and legs and a marked delay in the transmission of pain over the hypoaesthetic areas.

There was a clear history of gastric crises and intestinal crises accompanied by rectal hemorrhages; severe lancinating pains in the thighs and legs had persisted for three years, and there was hypotonia of the muscles of the thighs and legs. These symptoms were sufficient to convince me of the existence of tabes dorsalis.

The patient told me that a year ago he received a hypodermic injection of morphin ( $\frac{1}{4}$  gr.) for the relief of supposed sciatica. About thirty to forty minutes afterward he suddenly lapsed into unconsciousness and ceased breathing and for fifteen or twenty minutes artificial respiration was employed. When consciousness and automatic respiration returned he could remember nothing of what transpired, so his loss of consciousness was complete. A few weeks later morphin was again given him for the same purpose, but this time only  $\frac{1}{8}$  grain of the drug with  $\frac{1}{100}$  grain of atropin were used. Exactly the same events followed as after the former dose of  $\frac{1}{4}$  grain. Apnea and loss of consciousness supervened about thirty minutes after the injection of morphin was given and lasted about fifteen minutes.

Both these patients on frequent occasions had received hypodermic injections of morphin on account of lancinating pains without the least untoward results. On account of the alarming signs which developed twice in each patient morphin was not again used for several months, but later injections of morphin were used without the development of any respiratory or circulatory symptoms.

Both these patients exhibited signs of profound hypoaesthesia of the respiratory center at a time varying from thirty to forty-five minutes after the administration of morphin. This is the time which uniformly elapses between the administration of morphin and the

maximum respiratory depression in animal experiments. Both the patients were in the preataxic state of tabes dorsalis. They were both in a period which marked the transition from symptoms of excitation to symptoms of depression. Both patients had suffered from involvement of the vagi as evidenced by gastric crises. Neither patient had any recurrent laryngeal symptoms.

There seems to have existed in these patients a certain depression of cellular response of the respiratory center, though insufficient to cause any symptoms. The added depressor effect of a small dose of morphin sufficed to cause hypoaesthesia of the respiratory center and precipitated the attack of apnea. Though I witnessed only one of the four attacks mentioned, it seems reasonable to suppose the vasomotor symptoms described in one attack must have occurred in all, because in all the attacks there was loss of consciousness, and that depends on vasomotor and not on respiratory depression.

It seems certain death would have followed in each instance had not artificial respiration been employed by persons in attendance on these patients. We occasionally hear of death after the administration of small doses of morphin, and this experience suggested possibly there may be found in medical literature some fatalities which occurred in tabetic patients after administration of moderate doses of morphin.

Suppose one of these patients, suffering from what is believed to be sciatica (but in reality has the sciatic pains of an early tabes dorsalis) finds himself in a strange hotel and a physician is summoned who gives him a hypodermic injection of a quarter grain of morphin. In about fifteen minutes the acute pain is subdued and the patient is left alone. Should unconsciousness and apnea follow after the usual elapse of time I believe death would follow.

I was unable to find any case reported in the Surgeon General's Library. All the reported cases of apnea or Cheyne-Stokes respiration following the use of morphin proved to be cases of cardiovascular disease, or patients who could not be said to have locomotor ataxia. With a single exception, in the literature on locomotor ataxia, the only respiratory symptoms described are the laryngeal crises. This exception is found in a case reported from Salpêtrière in 1899 by Eggers.

This patient had tabes ten years. She was bedridden on account of paresis, muscular atrophy and ataxia. She had suffered many laryngeal, gastric and intestinal crises, so there was sufficient evidence of vagus involvement. This patient had a usual automatic respiratory rate of three to five to the minute. After eating a meal or drinking hot liquids the respiratory rate would rise to thirteen to the minute and then gradually lapse to three or five to the minute. If the patient would take about ten deep inspirations, there followed immediately a total suspension of automatic respiration for sixty seconds, then automatic respiration resumed at the rate of two a minute, and within a few minutes rose to the usual rate of three or five. In this patient there was no disturbance of consciousness during the periods of apnea, and no vasomotor symptoms are described.

To avoid stimulation of the vagi by sectioning, Gad and Marckwald devised the plan of freezing both vagi, in a dog, and in this manner procured a bradypnea of three or four a minute.

We find under other conditions a behavior of the respiratory center very like the cases above described. The one example of apnea with which all physicians are familiar is apnea at birth. Here we have a hypoaesthesia

of the respiratory center caused by the manner in which either the placental or umbilical cord circulation is affected during parturition. A sudden interruption of the placental circulation or a sudden compression of the umbilical cord stimulates the respiratory center of the fetus, and as a result the child is born asphyxiated from inhalation of the contents of the utero-vaginal tract. If the cord or placental circulation be very gradually obliterated for a protracted period, then exhaustion of the respiratory center follows and the child is born with apnea. Though generally automatic respiration is uninterrupted after once established, there are some cases on record in which lapses of automatic respiration occurred.

Morrow, of Montreal, reports the case of a child born apneic who, after the usual methods were employed for twenty minutes to stimulate respiration, breathed well. Several hours later apnea supervened and the child was cyanotic for half an hour; whether any automatic respirations occurred or not during this period is doubtful. Artificial respiration promptly restored automatic breathing. During the following twenty-four hours there were twelve attacks of apnea, but artificial respiration promptly restored the child. The child later proved to be perfectly healthy.

In Morrow's case we have an instance in which cellular response of the respiratory center had been modified during parturition. Unusually prolonged treatment was required at birth to establish automatic respiration. After respiration had been established for a period of several hours apnea suddenly developed without the least premonitory symptom and reappeared twelve times within the first twenty-four hours of extrauterine life. Thus we have another example of modification of the respiratory center without symptoms other than the sudden appearance of complete apnea. In this case there was neither organic disease nor drug intoxication. During parturition the respiratory center was depressed to a point which required treatment for twenty minutes before respiration could be established, but the tone of the respiratory center was insufficient to prevent recurrences of apnea.

Another case of *tabes dorsalis* recently came under my observation in whom sudden death occurred during an attack of apnea. The patient was a man, 37 years old, who gave a doubtful history of syphilitic infection in 1887. Four years later his wife had two miscarriages. Since 1903 the patient had suffered from lancinating pains in the thighs and legs and irritability of the bladder with occasional enuresis. The pupils were unequal and reacted sluggishly to light and to accommodation. The patellar and ankle reflexes were absent. All sensory perceptions with the exception of the perception of pain were normal. Hypoalgesia was confined to the feet, legs and thighs. On the plantar surfaces of both feet there was a marked delay in the transmission of pain. There was not the slightest impairment of coordination either in the upper or lower extremities. There was, however, hypotonia of the muscles of the thighs and legs.

A few weeks after I saw this patient he was seized with violent nausea and vomiting and epigastric pain. The patient was taken home and put to bed, suffering from a sense of profound exhaustion. He arrived at his home about 10 o'clock at night, and his family physician was summoned. The physician told me, during the time from 11 p. m. until 2 a. m., the patient had four attacks of apnea. Each period lasted a few

minutes. About 2 a. m. the patient called to the doctor, who was in a neighboring room. By the time the doctor arrived at his bedside, respiration and heart beat had both ceased. No autopsy was made.

All these phenomena which I have described occurred in tabetic patients who were in the preataxic period and who could easily have been overlooked as cases of locomotor ataxia. In fact, one patient had been treated by diet and lavage for disease of the stomach, and one other was treated for disease of the prostate. In reality both patients were suffering from excitation symptoms of *tabes*.

In cardiovascular disease we see occasional lapses of respiratory activity which assume either Biot's or Cheyne-Stokes type of respiration. A man, 60 years old, with chronic aortitis, general arterial sclerosis, chronic interstitial nephritis and moderate hypertrophy and dilatation of the left ventricle, had for three months been suffering from nocturnal apnea, followed by prolonged apnea. For a year the patient had awakened frequently at night suffering from intense air-hunger; after breathing deeply for several minutes he would be able to go to sleep and rest for the remainder of the night. These attacks all came during the first hours of sleep. For three months he had been greatly distressed by complete suspension of respiration directly he fell asleep, and then awakened with intense air-hunger, which was relieved after a few minutes rapid deep breathing.

It was discovered he could avoid this period of intense air-hunger if he were awakened directly apnea commenced. So his wife would watch him as he fell asleep and waken him the instant respiration ceased. This plan enabled the patient to escape the period of air-hunger which always followed spontaneous awakenings. Very commonly he would have to be wakened as often as a dozen times before respiration would continue after falling asleep.

This patient presented the type of Biot's respiration, a modification of Cheyne-Stokes respiration in which apnea and hyperapnea alternate without the gradual increase and diminution in rate and depth of respiration which intervene between the periods of apnea in Cheyne-Stokes phenomenon. Owing to sclerosis of the basilar arteries with consequent impairment of blood supply to the medulla he suffered what may be termed intermittent claudication of his respiratory center. There was not the slightest sign of impairment in the gross hydraulics of his blood circulation so far as the right heart, pulmonary circulation, liver or the pendant parts were concerned. There were no signs of respiratory involvement during his waking hours, but the instant the added factor of sleep ensued there was induced a sufficient anemia of the respiratory center to cause apnea, and automatic respiration was resumed only after the partial pressure of carbonic acid in the blood reached a point sufficient to arouse his depressed respiratory center to action. This train of events explains those cases of arterial sclerosis which waken with suffocation during the early hours of the night when sleep is most profound, and when examined during their attacks reveal no signs of pulmonary stasis, no emphysema or bronchial râles and no change in character or rate of the arterial pulse. It is not a dyspnea; it is a prolonged hyperapnea, and has for its basis circulatory changes in the medulla which are not insufficient to produce symptoms during the waking hours, but with the diminution of blood supply to the encephalon which comes with pro-

found slumber a sufficient anemia of the medulla occurs to produce hypoesthesia of the respiratory center.

Here we have again (as in the tabetic patients) a sudden precipitation of apnea from a slight cause which is only a cumulative factor in betraying cellular changes in the respiratory center which are concealed until the sudden development of apnea.

All the cases of Cheyne-Stokes respiration which are produced in cardiovascular disease by the injection of small amounts of morphin occur in elderly people or patients with arterial disease. In all these patients we have the cumulative effect of morphin on a respiratory center already affected by an impaired blood supply. The patient above described recovered from his respiratory symptoms after taking nitroglycerin and caffein citrate, a further proof of the theory I have presented.

A man, 71 years old, had Biot's type of respiration, i. e., sharply alternating periods of apnea and hyperapnea. The periods of apnea lasted as long as sixty-seven seconds. There were clinical signs, of arterial sclerosis, high blood pressure, pulse of long duration, hypertrophy and dilatation of both the right and left ventricles of the heart, and renal infarcts. During the periods of prolonged apnea the patient talked irrationally and incoherently; during the periods of apnea there was profound slumber. This clinical picture had continued for nearly three weeks when nitroglycerin, 1/100 gr. every hour, and 5 gr. of caffein citrate every three hours were given. Though there was moderate edema of the legs, the improvement which followed the treatment could not be ascribed to increased renal elimination. Biot's respiration ceased and the mental symptoms all disappeared within a few hours. The patient died suddenly two days later with symptoms of embolus in the pulmonary artery.

I cite these cases because I believe in cardiovascular diseases we are too ready to assume all respiratory distress must be ascribed either to impairment in the pulmonary circulation or to diminished secretion of urine; when in reality we are dealing with an ischemia of the respiratory center, and the other factors are merely coincident to the respiratory phenomena and not their cause.

#### DISCUSSION.

DR. ALLEN A. JONES, Buffalo, said that he had seen only one case of this sort, but this one case was sufficiently striking to make its impress on him for all time. A man of middle age, with tabes, who had been a morphin habitué for a number of years, took his usual quantity of morphin and smoked excessively during his stay in the hospital. One night the nurse reported that the man had stopped breathing and was dying. He was cyanotic but, under the influence of nitroglycerin hypodermically, he began to breathe again. Dr. Jones went to the hospital and for two hours that man went from one spell of apnea into another, but he finally recovered. During the attack he was given strychnia and camphor hypodermically. A few days afterward the man said he would stop his morphin and resort to an old remedy that he had gotten from answering an advertisement. One morning he was seized again with a "dying attack," and stopped breathing for three minutes. During this time he became very cyanotic, his pulse was small and frequent, but he responded to stimulation. He had several such attacks during the day and finally recovered. He is in better condition to-day than he was last year.

DR. C. F. HOOVER, Cleveland, Ohio, said that he thinks such occurrences are not uncommon, although he searched the literature and was unable to find a single case mentioned. He believed that if he had another such case of tabes with apnea, instead of resorting to artificial respiration, he would probably invert the patient to stimulate the respiratory centers. The same result will follow this procedure here as in tachy-

cardia. A patient had a pulse of 240 to the minute for twenty-eight hours. He inverted her, heels up and head down. That was not sufficient, but when she took deep breaths it brought the pulse down to 120. Her condition was due to postoperative depression. The patients should be held inverted for two minutes.

### THE PROBABLE DEMONSTRATION OF THYROID SECRETION IN THE BLOOD IN EXOPHTHALMIC GOITER.

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I showed in a former paper<sup>1</sup> that when small amounts of thyroid are fed for a few days to mice the latter acquire markedly increased resistance to acetonitrile.\* Further studies have shown that this is an exceedingly delicate test for thyroid; as small an amount as one-tenth of a milligram (1/640 of a grain) of the official dried thyroid fed daily for a few days may enable a mouse to recover from double the dose of acetonitrile fatal to the controls. Thus it has been possible to detect as little as one milligram of thyroid. Dr. Seidell, of this laboratory, has found that forty or fifty times as much thyroid as the above is necessary to give a distinct test for iodine, especially when the thyroid is mixed with a large amount of other organic material; moreover, it is doubtful if it is possible to determine, by any chemical method at present known, whether iodine found in dry protein matter is present in the form of normal iodothyroglobulin, whereas it is possible to distinguish sharply by the physiologic test between the iodized thyroid protein and artificially iodized proteins. Large amounts of other (non-toxic) substances do not interfere with the physiologic test; thus one milligram of the dried thyroid added to 40 gm. of cracker dust, or several grams of sugar or casein or blood was readily detected. Although I have found a few other substances which give this test, hundreds of times as much are required as of thyroid. (These results will be published shortly in a bulletin of the Hygienic Laboratory.)

It seemed probable that this test would throw light on the question whether there is an excess of thyroid secretion in the blood in exophthalmic goiter; at present the theory that there is a condition of hyperthyroidism in this disease rests entirely on clinical evidence, and this evidence is considered insufficient by many. Although I am able to report at present on but one case, it seems desirable, in view of the widespread interest in this disease, to record my results. Another reason for making this communication at present is the hope that it may lead physicians and pathologists to send me blood for further study.<sup>2</sup>

The blood on which the following tests were made was kindly sent to me by Dr. W. G. MacCallum, to whom I wish to express my thanks; it was obtained

\*Acetonitrile is methyl cyanid ( $\text{CH}_3\text{CN}$ ), a volatile liquid miscible with water. The name is given because it can be made to react with water to form acetic acid ( $\text{CH}_3\text{COOH}$ ). In the system, however, this reaction appears not to occur, but by oxidation hydrocyanic acid is slowly liberated, by which poisonous effects are produced.

1. Hunt: Journal of Biological Chemistry, 1905, 1, 33.

2. At least an ounce of the fresh blood is desirable; after the middle of September it could be sent direct to the Hygienic Laboratory, 25th and E Streets, N. W., Washington, D. C. It is very probable that the blood dried in thin layers at a temperature not exceeding 50 C. would answer equally well.