Studies on the Cause of Death in Tetanus*
Human Tetanus as a Respiratory Problem
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The cause of death in tetanus is still unknown. Search for the mechanism of death is not merely an academic problem, being intimately related to the unsatisfactory status of treatment for tetanus. It is hoped that study of the respiratory and biochemical abnormalities together with careful analysis of the histopathology observed in a large number of patients with tetanus will lead to a better understanding of the cause of death.

Experience at the Hospital das Clínicas1 has shown that with the exception of laryngeal spasm, paroxysmal spasms should not be looked upon as a cause of death. The seizures in fulminating tetanus are frequently less severe than in the more benign cases, and in the hours preceding death, the paroxysms may even cease. Fulminating tetanus is often accompanied by only slight muscular rigidity. The lethal effects of laryngeal spasm are easily avoided by early tracheotomy. Studies of experimental tetanus in mice, to be presented elsewhere, have shown that the majority of mice die without a single gross seizure although something similar to laryngeal spasm is sometimes seen. Large doses of tetanus toxin in mice lead to muscular paralysis rather than rigidity.

Muscle rigidity is also a symptom and probably an unimportant one. It may be observed in benign as well as in severe cases, being somewhat less common in the latter. Abolition of muscular rigidity by the curariform drugs or succinylcholine in the so-called "total paralysis regimen" has been disappointing in our limited experience with these drugs, and the literature available to us expresses little enthusiasm for this form of treatment in severe tetanus.

Pelloja,* in his book on experimental tetanus, devoted little more than one page to discussion of the cause of death. He concluded that the action of the toxin is a complex one. Both Baker2 and Delavergne et al.3 thought that paralysis of the vagus must play an important role in this disease. Christensen and co-workers4 believe that severe tetanus is another instance of Selye's adaptation syndrome. Alhady et al.5 described a case of tetanus with toxic myocarditis and expressed the opinion that the effect of tetanus toxin upon the heart is an important lethal factor.

The majority of authors, however, impressed by the clinical signs of respiratory embarrassment exhibited by most patients before death occurs, concentrated their attention upon this point. Their views on the mechanism of respiratory failure differ widely. Abel and Hampil6 believed that death is the end-result of slow asphyxia brought about by rigidity of respiratory muscles rather than being due to increased excitability of the higher nervous centers. Finding that their animals died earlier when tetanus toxin was injected close to the respiratory center, Firor et al.7 concluded that death was due to the direct action of the toxin upon the medulla. Yokoï8 in experimental tetanus, found that respiratory failure was a consequence of muscular paralysis.

The present study is an attempt to evaluate clinically the respiratory problem in human tetanus. Many unforeseen difficulties limited the scope of the investigation.

VITAL CAPACITY AND MAXIMUM BREATHING CAPACITY IN TETANUS

Vital capacity and maximum breathing capacity were determined with the patient in the sitting position. All possible measures were taken to prevent fatigue. Predicted
vital capacity and maximum breathing capacity were calculated from the formulas proposed by Baldwin, Cournand and Richards. Body surface area was calculated according to Dubois' formula.

Cases of localized tetanus were excluded. Otherwise, the series is unselective. No patient had a respiratory infection at the time of testing. Muscular hypertonia was present in all patients. When tetanus was of average severity, the tests were carried out later in the disease after the tracheotomy wound had healed. Twelve patients were studied. Figure 1 presents the data with particular delineation being given to the two extreme cases.

The two cases which represent the extremes of our series are briefly summarized:

CASE 1

A 27-year-old man who presented with extreme trismus and hypertonia of the abdominal wall. Stiffness of the legs was less pronounced, and he was able to walk on the second day of hospitalization. No paroxysmal spasm was seen. Dyspnea was never present. Tracheotomy was unnecessary.

CASE 2

A 29-year-old man who exhibited pronounced rigidity throughout all muscles. Mild tonic seizures were evident during the first six days in hospital. He complained of dyspnea upon slightest effort throughout the first week, and his cough was extremely weak. Dysphagia was not present and tracheotomy was not necessary. He was able to walk a few steps on the 15th day after admission.

Reduction in vital capacity commonly was accompanied by a proportional reduction of the inspiratory and expiratory reserve volumes. If the reserve volumes were unequally affected, the expiratory reserve generally was more reduced as shown in Fig. 2. Occasionally, the inspiratory reserve volume was primarily affected.

If the muscles of respiration, primary or accessory, were functionally impaired to a significant degree by abnormal muscular spasm, one might hope that the intravenous injection of a so-called muscle relaxant would improve the capacity to exchange air. Accordingly, four patients were selected for measurement of vital capacity and maximum breathing capacity before and after intravenous administration of a
gested that the ventilatory problem in tetanus might be explained on the basis of restriction of chest wall movement and pulmonary infection to which restriction would predispose. Studies on Case 6 supported this conviction.

**CASE 6**

A 19-year-old man with a benign form of tetanus. Muscular rigidity was very severe, but he never had seizures and did not complain of either dyspnea or dysphagia. Cough was weak. Walking was not attempted until the 13th hospital day. On the tenth day after admission his vital capacity was 68 per cent of normal and the maximum breathing capacity 82 per cent of normal. Maximum inspiratory and expiratory flow rates were measured on a low inertia, high-speed registering spirometer. The maximum inspiratory flow rate was 97.5 liters per minute (normal=500 liters per minute) and the maximum expiratory flow rate was 90 liters per minute (normal=400 liters per minute). A bronchodilator aerosol did not alter these determinations. On the following day, pulmonary static compliance was determined by simultaneous registration of spirometric air volumes and esophageal pressures led into a Waters Multi-Channel Recorder. The esophageal balloon pressures were transduced by a P-23-C250 strain gauge. Compliance during inspiration was 0.068 liters/cm. H_2O. The normal value is 0.32 liter/cm. H_2O. The oxygen cost of breathing was determined next by having the patient breathe into a 50-liter bag before and after mild voluntary hyperpnea. Gases were analyzed by the Haldane method. The oxygen cost of breathing was found to be 10.8 ml. of oxygen per liter increase in ventilation. Bergofsky, et al. state that the normal value is less than 1.0 ml. provided ventilation does not reach one-half of the MBC. In the

**TABLE 1—VITAL CAPACITY AND MAXIMUM BREATHING CAPACITY BEFORE AND AFTER THE INJECTION OF A MUSCLE "RELAXANT"**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Days in Hospital</th>
<th>Drug Tested</th>
<th>Dose I.V.</th>
<th>Time in Relation to Injection</th>
<th>VC (ml)</th>
<th>MBC (liter/min.)</th>
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<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>Thiocholchicoside</td>
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<td>3125</td>
<td>69</td>
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<tr>
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<td></td>
<td>60 min.</td>
<td>2625</td>
<td>60</td>
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<td>2050</td>
<td>2050</td>
<td>59</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Before</td>
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<td>1775</td>
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<td>30 min.</td>
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<td>Before</td>
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<td>15 min.</td>
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<td>Before</td>
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<tr>
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<tr>
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<td>30 min.</td>
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<td>3</td>
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<td></td>
<td>30 min.</td>
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<td>68</td>
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</table>

**Figure 2:** Reduction in vital capacity affecting mainly the expiratory reserve volume.

"relaxant" drug. The data appear in Table 1. The volumes determined are all within the range of variability of successive measurements in unmedicated people. In the dosage given, neither drug had any effect upon vital capacity or maximum breathing capacity at the stage of illness represented by these four patients.

**INEFFECTIVE BELLOWS ACTION OF THE CHEST IN TETANUS**

The alterations in vital capacity and maximum breathing capacity strongly sug-
series of kyphoscoliotic patients studied by them, the oxygen cost of breathing was found to be 4.0 to 11.0 of oxygen per liter increase in ventilation. This patient felt well and complained only of his very ineffectual cough. On the 12th hospital day, x-ray studies showed normal displacement of both hemidiaphragms. The difference between maximum inspiration and expiration was 4.6 cm.

**Paralysis of the Diaphragm**

I have previously reported the sudden development of pectus excavatum in three patients with tetanus. The complication was followed by serious deterioration in the clinical picture and death of two patients. Pectus carinatum is observed much more commonly in tetanus, and has been attributed to vertebral collapse and deformation of the chest cage by Veronesi and Camargo. Pectus excavatum might be due to the same cause, but could be produced by hypertonia of the diaphragm and this possibility should be considered. I have reported that clinical signs suggestive of diaphragmatic immobility are common during the course of tetanus except in benign cases. The latter never call upon the accessory muscles of respiration.

In an attempt to evaluate diaphragmatic mobility, forced inspiratory and expiratory roentgenograms of the chest were taken of seven unselected patients. Only three patients showed normal movements of the diaphragm. We therefore had to conclude that alteration of respiratory mechanics in tetanus is more complex than we previously thought. A brief summary of each of the seven patients follows.

**Case 4**

A 19-year-old man with generalized, benign tetanus. Hypertonia was average and walking was attempted on the third hospital day. On this day the vital capacity and maximum breathing capacity were respectively 43 per cent and 49 per cent of normal. X-ray study showed that the right hemidiaphragm moved four cm. and the left hemidiaphragm three cm. between inspiration and expiration.

**Case 6**

This patient has been summarized previously. On his 12th hospital day, both hemidiaphragms had a range of motion of 4.6 cm.

**Case 7**

A 32-year-old man with generalized, benign tetanus. Hypertonia was average. On the 19th hospital day his vital capacity was 45 per cent of normal, his maximum breathing capacity 68 per cent of normal, and x-ray showed a range of diaphragmatic motion of 5.2 cm. on the right and 5.7 cm. on the left.

**Case 8**

A 35-year-old man with tetanus of average severity. Tracheotomy was done on the second hospital day because of dysphagia and retention of secretions. Attempts at coughing were always
CASE 11

A 68-year-old woman with benign tetanus. Hypertonia was pronounced, and she developed pes equinus which is uncommon in tetanus. Fever appeared on the sixth hospital day and a chest x-ray film was taken to rule out pneumonia. No infiltration was present, but the right leaf of the diaphragm was very high. This finding was unchanged on x-ray examination on the 25th day after admission. Nine days later, however, both hemidiaphragms were moving normally even though hypertonia was still pronounced and the patient was still confined to bed.

The available literature contained no report of diaphragmatic paralysis in tetanus although it has been reported as a complication of tetanus antitoxin. All of our patients received tetanus antitoxin at the time of admission (100,000 I. U. for adults, 50,000 I. U. for children). In view of the difference in the clinical pattern of diaphragmatic paralysis observed by us during tetanus and that reported by Miller and Stanton, following tetanus antiserum, it is believed that in our cases paralysis was a consequence of tetanus toxin alone.
GAS EXCHANGE IN TETANUS

Even if the resting oxygen consumption of muscle during tetanus is normal, the patient with tetanus is never in a basal condition. Agitation and attempts at hyperpnea manifest force him to high oxygen consumption. One patient with very benign tetanus, exhibiting average rigidity and no seizures, was studied for oxygen consumption. Expired gas was collected in a 50 liter bag and analyzed. The results are tabulated in Table 2.

Table 2—Oxygen Consumption in a Patient with Benign Tetanus (Case 12)*

<table>
<thead>
<tr>
<th>Days in Hospital</th>
<th>Psychic Condition</th>
<th>Oxygen Consumption (ml/min.)*</th>
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<tr>
<td>11</td>
<td>Calm</td>
<td>375</td>
</tr>
<tr>
<td>11</td>
<td>Agitated</td>
<td>430</td>
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<tr>
<td>13</td>
<td>Calm</td>
<td>312</td>
</tr>
<tr>
<td>22</td>
<td>Calm</td>
<td>234</td>
</tr>
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</table>

*Calculated normal: 226 ml/min.

Arterial oxygen saturation was determined in a few patients and seemed to be satisfactory. Small deviations from the normal may, however, be dangerous for the patient with severe tetanus, particularly if unsaturation sets in suddenly. In this respect, no comparison of arterial oxygen saturation between tetanus and emphysema or “Pickwickian syndrome” is valid. Biochemical studies to be reported subsequently have shown that a block of anaerobic glycolysis is always present in experimental tetanus, and animals injected with crude toxin are much more sensitive to hypoxia than normal animals, even during the period of incubation.

In our experience, cyanosis in tetanus is rare. Arterial oxygen saturation was determined in very few of our patients, but none showed a high degree of unsaturation. The data on arterial blood gases and pH are assembled in Table 3.

As can be calculated from the data in Table 3, carbon dioxide retention did not occur in those patients whose arterial pH could be measured. Low total carbon dioxide has been a usual finding, and will be discussed in another paper. We believe that the low total carbon dioxide is due not only to hyperpnea, but also to metabolic acidosis. These features can be explained as easily by histotoxic anoxia as by anoxic anoxia.

Several factors may contribute to susceptibility to pulmonary infections in the patient with tetanus. This has been found to be true even in experimental tetanus. Paralysis of the diaphragm is one such factor.* In our series of 84 cases, gross pneumonia was infrequent. Pulmonary edema and congestion, as well as patchy atelectasis and bronchopneumonia are almost always present. Of the first 11 necropsies currently being reviewed, only two revealed massive bronchopneumonia. One was a boy with fulminating tetanus who probably would have died of other causes within several days.

DISCUSSION

Studies at the Hospital das Clinicas on the pathogenesis and pathology of tetanus
are incomplete at the time of writing. Consequently, any generalizations made on the basis of the clinical studies must be tentative. Our current impression is that respiratory failure seems to be a direct cause of death in only a minority of fatal cases of tetanus.

Respiratory insufficiency in tetanus cannot be attributed solely to chest deformation and rigidity, and thus differs from respiratory failure in kyphoscoliosis and ankylosing spondylitis. Although diaphragmatic immobility plays an important part in the picture, it probably does not explain the pronounced decrease in vital capacity and maximum breathing capacity. These values were reduced in cases 4, 6, and 7 where diaphragmatic displacement was within normal range. The volumina returned to normal after two to three months of convalescence. This proves that abnormal ventilatory volumina are independent of chest deformation which is persistent or only slowly improves over a period of years.

At present, it is our clinical impression that hypoventilation is a cause of death in few patients. This impression is strengthened by two observations. Vital capacity and maximum breathing capacity are severely affected in benign tetanus. Secondly, hypoventilation can be overcome by the "total paralysis regimen" yet this method of therapy does not seem to have produced any sharp decrease in mortality. When tetanus is severe, hypoventilation may be one of several mechanisms which lead to death.

SUMMARY

A group of patients with generalized tetanus has been studied with the view of determining whether respiratory function was sufficiently impaired to be considered life-threatening. It has been found that:

1. Vital capacity and maximum breathing capacity were all low during the acute phase of the disease, even in benign tetanus. These volumina returned to normal after a period of two to three months. Pulmonary compliance, maximal inspiratory and expiratory flow rates, and cost of breathing were all abnormal in the one patient in whom these studies were made.

2. Reduced ventilatory capacity in tetanus is not a problem of chest rigidity alone. Roentgenographic studies of seven patients showed fixation of the diaphragm in the expiratory position in three and a decrease in mobility in an additional patient. Follow-up roentgenograms of two of the four patients showed complete restitution on diaphragmatic motion after 34 and 60 days.

3. Intravenous administration of mephenesin and thiocolchicide did not alter vital capacity and maximum breathing capacity. In the absence of diaphragmatic immobility such a procedure could be used for the evaluation of muscle relaxing agents.

4. Arterial oxygen saturation was not reduced to levels which by themselves could be considered a threat to life. Carbon dioxide retention was not observed.

The studies reported suggest strongly that respiratory failure is rarely a direct cause of death in tetanus.

ACKNOWLEDGMENTS: I wish to express gratitude to Dr. Mateus Romierio Neto who gave permission to use the Department of Lung Function Tests of the Second Medical Clinic (Prof. L. D. Decourt), Hospital das Clinicas. I also thank Mr. E. Macambira for performing the oxygen and carbon dioxide determinations. Prof. John H. Seabury of Louisiana State University has rewritten this paper and I here acknowledge his valuable help.

RESUMEN

Se estudió un grupo de enfermos con tétanos generalizado para determinar si la función respiratoria estaba suficientemente perjudicada como para que por sí amenazará de muerte. Se encontró lo que sigue:

1. La capacidad vital y la capacidad máxima respiratoria eran bajas durante la fase aguda de la enfermedad aún en el tétanos benigno. Estos volúmenes volvieron a la normalidad después de un periodo de dos a tres meses.

La respuesta elástica, los flujos máximos inspiratorios y espiratorios, el gasto de la respiración fueron todos normales en un enfermo que estudiamos.

2. La capacidad ventilatoria reducida en el tétanos no es un problema sólo de la rigidez del tórax. Los estudios roentgenográficos de siete enfermos mostraron fijación del diafragma en la posición espiratoria en tres y un decrecimiento de la morbility en otro enfermo. Los roentgeno-
gramas en serie de dos de los cuatro enfermos mostraron completa restitución del movimiento diafragmático después de 34 a 60 días.

3. La administración intravenosa de Mef en sine y de tiocochlida no alteró la capacidad vital ni la capacidad máxima respiratoria. En ausencia de inmovilidad diafragmática tal procedimiento podría servir para valorar las drogas relajantes de los músculos.

4. La saturación arterial del oxígeno no se redujo a niveles que por sí amenazaran la vida.

No se observó retención de bióxido de carburo. Los estudios relatados sugieren fuertemente que la insuficiencia respiratoria rara vez es la causa de la muerte en el tétanos.

**Resumen**

L’auteur a étudié un groupe de malades atteints de tétanos generalisé en vue de determiner la función respiratoire dans le tétanos. Les études radiographiques f ... y sufre de atelectasis.

4. La saturación arterial del oxígeno no fue reducida a niveles que por sí amenazaran la vida.

No se observó retención de bióxido de carbono. Los estudios relatados sugieren fuertemente que la insuficiencia respiratoria rara vez es la causa de la muerte en el tétanos.

**Referencias**


CAUSE OF DEATH IN TETANUS

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ESOPHAGEAL DILATATION

A series of 46 children with benign esophageal strictures who have had a total of 441 dilatations has been studied. One hundred and forty-two dilatations were performed with the use of a bougie without a filiform or guiding string. Five perforations resulted. One hundred fifty-six dilatations were performed with the small esophagoscope itself; five perforations occurred. One hundred twenty dilatations were carried out by means of a bougie guided through the stricture by a filiform or string without a single instance of perforation. Twenty-one dilatations, using a Hurst mercury dilator, were done without difficulty. The authors would agree that dilatation of an esophageal stricture should not be done blindly and would recommend the use of a string or filiform guided bougie in children.


TRACHEOSTOMY IN PULMONARY EMPHYSEMA

Ventilation and arterial blood gas studies have been done in 14 patients when breathing through the mouth alone and compared with those found when patients breathed through the tracheostomy alone. When patients breathed through the tracheostomy alone, the total ventilation decreased, principally as a result of a reduction in dead space. There was a tendency for oxygen consumption to be reduced when subjects breathed through the tracheostomy. Only one patient showed an increase. The carbon dioxide tension remained constant, suggesting that its level was fixed by the respiratory control system and was not influenced by the manner of breathing. One hour after tracheostomy, there is often a deterioration in the concentrations of blood gases, but at 24 hours, the oxygen saturation is often increased and the carbon dioxide tension is decreased. It is believed that tracheostomy reduces the burden of ventilation in patients with severe pulmonary emphysema and that its value is not just limited to facilitating the removal of pulmonary secretions.


CHANGES IN PULMONARY FUNCTION FROM BRONCHOGRAPHY

In 47 patients, the arterial oxygen saturation was determined before and during bronchography. The saturation was found to decrease, sometimes to a not inconsiderable extent: the arterial carbon dioxide tension remained normal during bronchography. The degree of filling with contrast medium (unilateral or bilateral) plays a role in this respect. There are indications that the presence of pre-existent obstructive pulmonary disturbances also constitute an unfavorable factor.

A study of nitrogen washout curves revealed that in the majority of cases, the ventilation became more uneven during bronchography. It is probably this which largely affords an explanation of the changes in blood gases. Studies of the mechanics of breathing showed that elastance and viscous work increase during introduction of the contrast medium. The former is probably chiefly a consequence of increased uneven ventilation; the latter is explained on the basis of increased intrabronchial resistance as a result of introduction of contrast medium. Anesthesia alone does not change either elastance or viscous work. It is advisable, in cases in which a decrease in arterial oxygen saturation is contraindicated, to carry out bilateral bronchographic examination in two stages and, if necessary, with additional oxygen administration.