products contain lesser amounts, whereas plant materials show no measurable activity.

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Observations on Diaphragm and Stomach of the Dog Following Phrenicotomy.* (17476)

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In a recent communication we have pointed out some of the relationships between the left diaphragm and gastro-intestinal mechanisms in the dog.[1] The significant feature of these observations was a decrease in gastric emptying time in the presence of a relatively dilated stomach after left sided transthoracic phrenicotomy. The dogs were kept for prolonged periods in order to observe whether the denervated diaphragm would resume its respiratory function. This was done in view of Noack's work, who reported that regular rhythmic respiratory contractions of the diaphragm reappeared in the human from one and a half to two years after phrenic exeresis in the neck.[2] Noack's statement has been accepted by a number of authors. The mechanism of recovery of diaphragmatic function was postulated to be through the twelfth thoracic intercostal nerves and through sympathetic innervation. If the innervation of the diaphragm and recovery of its function following interruption of the phrenic nerve in man and dog are comparable, experiments on the latter offer the advantage of better control of most experimental conditions and ensure a complete section of the phrenic nerve, which is not always possible in the usual operations in the neck of man for phrenic exeresis. Long term observations comparable to those done by Noack on the human were done on the dog. The animals were observed fluoroscopically, in order to determine if and when there would occur reactivation of the diaphragm after complete left transthoracic phrenic section, the right diaphragm serving as normal control. Sauerbruch[3] described a gastrocardiac symptom complex following left side phrenic exeresis, which was later called Roemheld's syndrome. The symptoms were bradycardia, premature systoles, anxiety, epigastric distress, lack of appetite, pallor, nausea, vomiting and eructations.

Experimental. Sixteen dogs were operated upon transthoracically under aseptic conditions, using pentobarbital sodium anesthesia. In 13 animals a section of the left phrenic nerve from the hilum of the lung to the diaphragm was removed. Two dogs had simple phrenic section at the level of the diaphragm, and one had the nerve cut at the hilum of the lung. The cut ends of the nerve were doubled up and tied with non-absorbable suture. The dogs appeared normal after a few days of postoperative care. All dogs were fluoroscoped at weekly intervals for the first 12 to 14 weeks after operation and then at monthly intervals, to watch for possible reactivation of the diaphragm and for the possible development of Roemheld's syn-

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1 Jefferson, Nelson C., and Necheles, H., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 166.

2 Noack, R., *Beitr. Z. Klin d. Tuberk.*, 1933, **82**, 397.

3 Quoted by Roemheld, L., *Münch. Med. Wchnschr.*, 1928, **75**, 1872.

drome. Observations were made also after standard barium meals[4] to determine if there was a relationhsip between the possible reactivation of the diaphragm and the return to normal of the gastric emptying time. Eight of the dogs were observed for periods of 14, 15, 16, 18, 19, 19, 20 and 20 months postoperatively, at which time acute experiments were done under pentobarbital sodium anesthesia and with artificial respiration, to determine whether impulses would reach the diaphragm upon stimulation of the phrenic nerve above the point of the previous section. In these experiments, gastric motility and blood pressure recordings were made before and after stimulation of the phrenic nerve with various strengths of induced current from a Harvard inductorium. At the termination of all experiments sections were made from the right and left diaphragm and from the proximal and distal phrenic nerve stumps for microscopic study.

Results. Using fluoroscopy, we have not seen in any of 15 dogs a completely denervated diaphragm reactivate during 20 months of observations. The shortened gastric emptying time returned to normal in periods varying from several weeks to several months. The large gas bubble within a moderately dilated stomach however persisted for many months. At no time was respiratory difficulty observed, but the dogs were not subjected to severe exercise. Acute experiments on 8 dogs 14, 15, 16, 18, 19, 19, 20 and 20 months after phrenic section revealed a fixed, elevated, atrophic left diaphragm more fixed by intra-abdominal pressure than by adhesions. The muscle was paper-thin and translucent. In one dog (19 months) there was a completely atrophied anterio-lateral one half of the left diaphragm and a normal posterio-lateral half. Upon inspection of the opened chest under anesthesia, the normal part showed rhythmic contractions, while the atrophied part did not. However careful dissection and inspection revealed one intact accessory phrenic nerve, which had not been cut. In this animal, fluoroscopy had been difficult, and we were not certain whether the diaphragm moved or not.

Sections† from the left diaphragm revealed degeneration and disappearance of nerve fibers and degenerated muscle, replaced by fibrous tissue and fat. Control sections from the right diaphragm were normal. The phrenic nerve above the point of section revealed degenerating, regenerating, or normal nerve fibers. The phrenic nerve distal to the section revealed complete degeneration. Stimulation of the distal or proximal ends of the cut phrenic nerve did not reveal any effect on the diaphragm in the 7 dogs with complete phrenicotomy, which were tested in acute experiments. Stimulation of the proximal phrenic stump caused a rise in blood pressure and, in some experiments, increased respiration. When the stump was cut central to the electrode these reflexes were abolished. The gastro-cardiac symptom complex of Roemheld was never observed.

Discussion. Credit for first interrupting the phrenic nerve in man is given to Stuertz[5] and to Sauerbruch.[6] The exhaustive study of Felix[7] established a basis for the operation. He found that the phrenic nerve receives sympathetic fibers in the neck and at the level of the diaphragm, as well as spinal fibers from lower cervical and first thoracic nerves. The phrenic does not give branches to the pericardium. The left phrenic divides into an anterior, lateral and posterior branch to supply the diaphragm. The importance of an accessory phrenic is stressed, which may be easily missed by the surgeon, and which will allow for continued phrenic impulses to the diaphragm. He concludes that the motor innervation of the diaphragm consists of the phrenic, the 12th intercostal nerve, and probably sympathetic fibers. The phrenic supplies the main part of the diaphragm, the 12th intercostal the root of the diaphragm from the 12th rib, and sympathetic and phrenic to-

† We acknowledge the help of Dr. O. Saphir, Pathologist of Michael Reese Hospital.

[4] Kozoll, D. D., and Necheles, H., *Surg.*, 1942, **2**, 360.

[5] Stuertz, *Deutsche Med. Wchnschr.*, 1911, **37**, 2224, quoted by Felix.[7]

[6] Sauerbruch, F., *Chirurgie der Brustorgane*, ed. 3, II, Julius Springer, Berlin, 1930.

[7] Felix, W., *Deutsche Z. f. Chir.*, 1922, **171**, 283.

gether supply the lumbar section of the diaphragm. Schwatt[8] studied 138 cases after phrenic exeresis or/and phrenicotomy and observed that, during the earlier period of from two to eighteen months after the operation, paradoxical movements of the diaphragm were the rule. Ultimately however, probably because of degeneration and atrophy of the diaphragmatic musculature plus pleural adhesions, fixation occurred. Davies[9] lists 3 operations for paralyzing the diaphragm, namely: phrenic avulsion, phrenicotomy, and phrenic crush. "The immediate effect of these operations is paralysis of the hemidiaphragm; the muscle fibers degenerate and the dome becomes a sheet of fibrous tissue within approximately four months. As a result of the paralysis there are three changes of the dome, namely: a loss of tone, a rise into the thorax, and a cessation of respiratory movements." Klein[10] states that many failures to secure paralysis of the hemidiaphragm are due to the presence of accessory branches of the phrenic nerve, which join the main trunk deep in the thorax, and which can carry on the function of the phrenic nerve if they are not cut. Twenty per cent to thirty per cent of all individuals are supposed to have accessory branches. Geraghty and Aycock[11] state that the length of phrenic nerve avulsed is of importance, because of the possibility of return of diaphragmatic function unless all auxiliary branches are interrupted. In their series the maximum avulsed length was 30 cm., and the minimum 2.5 cm. Matson[12] states that an avulsion of not less than 10 cm means a return of diaphragmatic function in 25 to 30% of all patients. Schwatt[13] concludes that an avulsion of 10 to 12 cm is necessary, as this approximates the distance from the operative site to the hilum and was sufficient to interrupt all accessory fibers. Anderson[14] states that the diaphragm may continue to rise for 6 months and that the immediate rise is by no means the maximum. Aufses,[15] in a review of the anatomy of the phrenic nerves, states that most of the accessories are not too intimately connected with blood vessels and join the main trunk within a distance of 11 to 13 cm from the level at which it crosses the scalenus anticus. Therefore, if avulsion of the nerve is performed, and at least 13 cm are removed, one may be confident that a total permanent paralysis of the hemidiaphragm will ensue. Further he states that the phrenic nerve is the sole motor nerve to its corresponding hemidiaphragm, and that interruption causes immediate paralysis of the muscle with atrophy which begins in a few weeks and progresses until it becomes complete at about the third or fourth month.

Aree[16] states that the phrenic nerve has anastomoses with the sympathetic system when it enters the thorax, and that some of the branches of the phrenic are distributed to the pulmonary hilum. The latter fact makes it possible that phrenic section may produce a decrease of pulmonary reflexes. Textbook information assures that in the human, following crushing of the phrenic nerve, the diaphragm reactivates in about 3 months.[17] According to Noack,[2] after exeresis in the neck of 10 to 30 cm of phrenic nerve, the diaphragm reactivated in from 1½ to 2 years, and he attributes this to fibers of the twelfth intercostal nerve and to sympathetic innervation. Christopher[17] states that for permanent paralysis not less than 4½ to 5 inches of the main trunk of the phrenic nerve must be avulsed from within the thorax. This will usually sever accessory branches (present in 20% of cases) which join the main nerve along its course to the diaphragm. Occasionally one or more accessory nerves may have an independent course to the diaphragm. Therefore avulsion of the main nerve may or may not interrupt all accessory branches of the phrenic nerve. Since after 20

8 Schwatt, H., *Am. J. M. Sc.*, 1934, **187**, 338.

9 Davies, H. M., *The Lancet*, 1935, **229**, 418.

10 Klein, B., *Illinois Med. J.*, 1938, **73**, 418.

11 Geraghty, F. J., and Aycock, T. B., *The West Virginia Med. J.*, 1940, **36**, 546.

12 Matson, R. W., *Am. Rev. Tuber.*, 1930, **22**, 1.

13 Schwatt, H., *J. Thor. Surg.*, 1934, **3**, 503.

14 Anderson, B. W., *Edinburgh Med. J.*, 1934, **41**, 169.

15 Aufses, A. H., *Am. J. Surg.*, 1940, **50**, 715.

16 Aree, J., and Breu, M. M., *J. Thor. Surg.*, 1943, **12**, 544.

17 Christopher, F., A Textbook of Surgery, 3rd ed., W. B. Saunders Co., Philadelphia and London, 1943.

months we have found only atrophy of the denervated diaphragm in our dogs it would appear that either the innervation is not the same in the dog as in the human, or that our procedure on the dog involved complete section, while in man, where the procedure is done in the neck, all phrenic fibers may or may not be avulsed, no matter how much of the main nerve is removed. No emphasis seems to be placed by the many writers on tying the cut ends of the nerve with non-absorbable suture, a feature which to us appears to be of some importance. We have found that the phrenic nerve is able to regenerate within a period of 20 months.‡ Since the musculature of the diaphragm in both species consists of striated muscle, and the phrenic is a somatic nerve, it follows that, once true paralysis and atrophy has developed in the muscle it would never be capable of reactivation. The so-called paralysis as seen in the human is probably in many instances palsy and not paralysis, as outlined by Christopher.[17]

The fact that we obtained complete paralysis and not palsy may be speculated upon. Our operations were transthoracic, and all observable fibers were cut and tied with a non-absorbable suture. The one instance observed by us in which partial diaphragmatic function persisted and in which complete atrophy of one half of the left diaphragm was found 19 months after supposed complete section of the phrenic nerve, was demonstrated to be due to an intact accessory phrenic nerve missed at operation. This would of course indicate that once atrophy, always atrophy, and that in the human so-called reactivation might have been confused with such a picture as we observed in this animal.

The reason for the absence of Roemheld's syndrome in our dogs may lie in the explanation given by Noack,[2] namely, that the tearing of sympathetic fibers during phrenic avulsion in the neck and not section of the phrenic nerve itself leads to the syndrome.

Paradoxical movements of the diaphragm following phrenicotomy, as described by Schwatt[8] were not observed in our experiments.

Summary. 1. No reactivation of the left diaphragm was seen by us in 15 dogs up to 20 months after complete section of the left phrenic nerve.

2. Microscopically all diaphragms showed complete muscular atrophy with degeneration or disappearance of nerve fibers, 14 to 20 months after complete section of the left phrenic nerve. It is difficult to conceive how such atrophic muscles could ever regenerate.

3. It is highly possible that phrenic exeresis in the neck of the human does not always result in complete phrenicotomy with subsequent atrophy of the diaphragm, but in a number of instances results in diaphragmatic palsy.

4. We found no evidence that the twelfth thoracic intercostal nerve or sympathetic innervation could influence the reactivation of the diaphragm in the dog.

5. Our experience with one diaphragm leads us to believe that a hemifunction of one half of a diaphragm may lead the fluoroscopist to assume that complete reactivation of that diaphragm has occurred.

6. The phrenic nerve above the point of section was able to convey reflexes 20 months after section; this was demonstrated by rise in blood pressure and increased respiration upon stimulation of the central end of the nerve, which were abolished when the nerve was cut central to the stimulating electrode.

7. No evidence of the gastro-cardiac symptom-complex of Roemheld was seen.

‡ Unpublished work.

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