REFLEXES FROM THE LIMBS AS A FACTOR IN THE HYPERPNEA OF MUSCULAR EXERCISE

J. H. COMROE, JR. AND CARL F. SCHMIDT

From the Laboratory of Pharmacology, University of Pennsylvania, Philadelphia

Received for publication October 10, 1942

It has been known for many years that in the two commonest and most important physiological emergencies calling for increased pulmonary ventilation, viz., muscular exercise and anoxemia, the hyperpnea is not referable to an increase in the amount of any known chemical stimulant in the arterial blood. Various suggestions have been advanced to explain this discrepancy, such as the existence of an unknown chemical excitant (3, 9), inadequacy of existing chemical methods to detect the responsible acid change in the arterial blood (5), or an acid shift within the respiratory center though not in the arterial blood (4, 24), but the view most widely held until recently was that both hyperpneas are brought about by an increase in the sensitivity of the respiratory center to its normal chemical stimulus (12, 16). The brilliant studies of Heymans and his collaborators (10, 11), amply confirmed by others (see 19), have shown that this increased sensitivity during anoxemia actually is brought about by excitatory nerve impulses from the carotid and aortic chemoreceptors, which furnish an adequate explanation for the coexistence of hyperpnea, hypocapnia, and alkalosis during anoxemia. In view of this course of events with regard to one of these physiological emergencies it is reasonable to suppose that excitatory reflexes may also be prominently involved in the other, but so far little attention seems to have been given to this possibility. Yet Harrison and his collaborators (6, 7) concluded from experiments on men and dogs that reflexes aroused by movements of the limbs play a part in the hyperpnea of exercise, and Alam and Smirk (1) presented evidence that a chemosensitive reflex system capable of stimulating the vasomotor center is present in the extremities of man. In view of their potential importance it is rather surprising that these experiments have not been repeated. Since Harrison's results were not very striking and since Alam and Smirk present no data bearing on the respiration, we undertook to repeat both sets of experiments from the standpoint of a possible explanation for the hyperpnea of muscular exercise.

1. Experiments of the Alam and Smirk Type on Man. These were performed on healthy male subjects (staff members, medical students, and technicians) reclining on a couch. A comfortable rubber face mask fitted with valves was used and the expired air was passed through a gas meter for measurement. A pneumogram was also made. Blood pressure was measured at frequent intervals in the left arm by the Riva-Rocci method and another

1 This investigation was partly financed through the National Committee for Mental Hygiene from funds granted by the Committee on Research in Dementia Praecox founded by the Supreme Council, 33rd Scottish Rite, Northern Masonic Jurisdiction, U. S. A.
cuff was applied to the right arm so that the arterial inflow could be cut off when desired. Exercise of the right forearm and hand was brought about by flexion of the fingers in time with a metronome beating once per second, each effort raising a weight of 1360 grams a distance 5 to 7 cm. With certain exceptions which will be indicated, a complete experiment comprised five periods, each lasting two minutes: 1, resting control (two minutes of observation after a steady state had been shown to be present); 2, occlusion of the circulation cut off (terminated as soon as any unpleasant sensations were experienced, often in less than two minutes); 3, exercise of the right forearm and hand with circulation intact; rest and recovery, then 4, repetition of the exercise with the circulation cut off (terminated as soon as any unpleasant sensations were experienced, often in less than two minutes); 5, cessation of the exercise without restoration of the circulation. This report is based on the results of 23 satisfactory experiments of this type on 11 subjects. The results are summarized in table 1.

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>Resp. rate</th>
<th>Resp. min. vol.</th>
<th>Systolic B-P</th>
<th>Diastolic B-P</th>
<th>SENSATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>P. D.</td>
<td>-14</td>
<td>-3</td>
<td>0</td>
<td>+24</td>
<td>0</td>
</tr>
<tr>
<td>J. C.</td>
<td>+5</td>
<td>0</td>
<td>+14</td>
<td>-50</td>
<td>-8</td>
</tr>
<tr>
<td>J. R.</td>
<td>+15</td>
<td>0</td>
<td>-27</td>
<td>0</td>
<td>-16</td>
</tr>
<tr>
<td>R. E.</td>
<td>+4</td>
<td>+4</td>
<td>+9</td>
<td>-9</td>
<td>+40</td>
</tr>
<tr>
<td>O. H.</td>
<td>0</td>
<td>0</td>
<td>+20</td>
<td>+20</td>
<td>0</td>
</tr>
<tr>
<td>C. S.</td>
<td>-11</td>
<td>+55</td>
<td>+22</td>
<td>0</td>
<td>+33</td>
</tr>
<tr>
<td>J. W.</td>
<td>-11</td>
<td>0</td>
<td>-12</td>
<td>-8</td>
<td>0</td>
</tr>
<tr>
<td>H. P.</td>
<td>+11</td>
<td>+20</td>
<td>-5</td>
<td>+10</td>
<td>+12</td>
</tr>
<tr>
<td>J. S.</td>
<td>+33</td>
<td>0</td>
<td>+33</td>
<td>0</td>
<td>+28</td>
</tr>
<tr>
<td>F. H.</td>
<td>+8</td>
<td>0</td>
<td>+15</td>
<td>0</td>
<td>+11</td>
</tr>
<tr>
<td>L. S.</td>
<td>+4</td>
<td>0</td>
<td>+9</td>
<td>+13</td>
<td>+27</td>
</tr>
<tr>
<td>Average</td>
<td>+10</td>
<td>-1</td>
<td>+14</td>
<td>+6</td>
<td>+14</td>
</tr>
</tbody>
</table>

1 = change from control to exercise alone.
2 = change from control to ischemia alone.
3 = change from control to exercise plus ischemia.
4 = change from control to continued occlusion after exercise.

Sensations: D, discomfort; N, numbness; P, pain; T, tingling; W, weakness; 0, none; blank, not recorded.

in the right arm by inflation of the cuff by a pressure higher than the systolic arterial level; release and recovery to normal, then 3, exercise of the right forearm and hand with circulation intact; rest and recovery, then 4, repetition of the exercise with the circulation cut off (terminated as soon as any unpleasant sensations were experienced, often in less than two minutes); 5, cessation of the exercise without restoration of the circulation. This report is based on the results of 23 satisfactory experiments of this type on 11 subjects. The results are summarized in table 1.
The respiratory findings at the various stages of these experiments justify brief comments. First, since simple ischemia did not cause hyperpnea, it follows that there are in the forearm and hand of man no chemoreceptors comparable in sensitivity to those in the carotid bodies, which are strongly stimulated by total ischemia of considerably less than two minutes' duration (23). Second, voluntary exercise, even of a relatively small mass of muscle, caused a distinct (average 14 per cent) increase in respiratory minute volume even with intact circulation. Third, exercise in the presence of ischemia brought about a much greater (average 28 per cent) increase in pulmonary ventilation, which might have been due either to a specific reflex aroused by chemical substances acting locally in the muscles (since their escape was prevented by the inflated bandage), or to a nonspecific reflex of the pain type. Our findings point toward the latter explanation, because in 15 of the 22 experiments respiration returned toward normal when the exercise was discontinued even though the ischemia persisted and the concentration of chemical stimuli could not have diminished. That pain was the dominant factor here was further suggested by the variability of the response of a given individual at different times (which is difficult to reconcile with the requirements of a specific reflex system subserving an important function), and by the fact that, in all of the five instances in which the hyperpnea was greater during the final period of ischemia after exercise, pain also persisted; all of the other subjects felt more comfortable as soon as they ceased exercising.

Our findings with regard to the blood pressure seem to us to be without significance. They are much less striking than those reported by Alam and Smirk (1). Whether this is because our subjects were not exposed to as severe pain as theirs, or because we did not happen to encounter any of the unusually reactive individuals who comprised only one-fourth of those tested by Alam and Smirk, we are not prepared to say.

In order to exclude the influence of pain and other psychic factors we next undertook a series of experiments on anesthetized animals in which observations could be made along the same general lines but under more controllable conditions.

2. Experiments of the Alam and Smirk Type on Animals. Our purpose was to test the effects of exercise alone, of ischemia alone, and of exercise plus ischemia. To induce "exercise" without direct sensory involvement we resorted to stimulation of ventral spinal roots.

A. Cats. The animals were narcotized by chloralose (0.05 gram per kgm. intravenously) or barbital sodium (0.35 gram per kilo intraperitoneally). The ventral lumbar spinal roots were exposed by Sherrington's method (20), cut free on the central side, and placed on insulated electrodes raised above the cord to obviate escape of current. The stimulus was obtained from a thyratron stimulator, the frequency being 4 per second throughout and the strength adjusted so as to elicit maximal muscular activity. In some cases only the 7th lumbar pair of ventral roots were stimulated, in others the 6th lumbar, and in a few the first sacral also, were added. Respiration was recorded by a small oxygen-filled spirometer to which the animal's tracheal cannula was connected through a canister containing soda-lime. Blood pressure was registered from a carotid artery by means of a mercury manometer, 25 per cent Na₂S₂O₃ serving as the anticoagulant.
We made 29 observations of the effects of "muscular exercise" thus induced in 15 cats, and in every case there was some increase in respiratory minute volume. Other noteworthy results were the following: First, the stimulation involved slight to moderate increase in depth of breathing, rate being increased seldom and never markedly; second, there was a latent period of at least 15 seconds between the start of the stimulation and the onset of the increased depth of breathing; third, the depth increased progressively to reach a plateau; and finally, recovery was gradual and slow after the stimulus was withdrawn. Ischemia alone (produced by clamping the femoral arteries and veins or the abdominal aorta and vena cava) produced no changes in respiration. "Exercise", tested 14 times in the presence of ischemia, regularly had less effect on breathing than it had when the circulation was intact, and often it had no effect at all. When the vessels were reopened, however, hyperpnea promptly appeared. Blood pressure commonly fell during the "exercise"; it never rose even when the vessels were closed during the "exercise" period.

Characteristic examples of these findings are shown in figure 1. The results strongly suggest that the hyperpnea of "muscular exercise", induced in the cat by stimulation of ventral spinal roots, is largely due to liberation into the bloodstream of chemical products which act either on the center or on chemosensitive nerves endings elsewhere than in the leg. This was confirmed by the effect of transection of the spinal cord in the lower dorsal region in 5 cats. After that operation "exercise" still increased breathing much as it had done before. If there is any peripheral reflex component in the hyperpnea of this type of "exercise" in the cat, it must therefore be small.

These results with cats are quite unlike those obtained in man, in whom the hyperpnea of voluntary exercise was definitely increased by ischemia and therefore could not have been due to direct stimulation of the center by chemical substances. This suggested that species differences may exist.

B. Dogs. These were prepared in the same way as the cats. The anesthetic was sodium barbital (0.25 gram per kilo intravenously) or chloralose (0.03 gram per kilo intravenously after 2 mgm. of morphine per kilo subcutaneously).

Out of 39 tests of ventral root stimulation in 11 dogs, 35 showed definite respiratory stimulation, the increase in minute volume varying from 8 to 200 per cent and averaging 62 per cent. In one there was no change (only one root was stimulated here) and in 3 there was pure depression of breathing, for which we have no explanation. The noteworthy features were as follows: First, the stimulant effect was mainly on the rate of breathing; depth might be unchanged, slightly increased, or slightly decreased. Second, the polypnea came on immediately with the start of the stimulation and was maximal within the first 30 seconds, after which it often diminished during the remainder of the period of stimulation. Third, when the stimulus was withdrawn breathing returned to normal almost immediately. Fourth, the response was unaltered when the femoral vessels were occluded during the stimulation, and there was no consistent effect on breathing when the vessels were reopened after the stimulation. Finally, transection of the spinal cord in the lower dorsal region completely abolished this polypnea.
in each of 4 dogs on which the point was tested. Section of the dorsal lumbar roots likewise abolished the effect in other animals.

Typical examples of the dog experiments are shown in figure 2.

That these findings were not due to escape of current to the dorsal roots or to the cord itself was shown by the following: First, the polypnea did not increase further when the strength of the stimulus was increased above the level that sufficed to produce maximal muscular activity. Second, elevation of the electrodes to the fullest extent permitted by the cut ventral roots had no influence on the results. Third, the response was entirely lacking when the stimulation was repeated after the corresponding spinal nerves had been cut outside the vertebral canal; under these circumstances movements of the legs were also lacking, but escape of current into the dorsal roots or cord should not have been prevented.

We conclude that the respiratory stimulation associated with "exercise" induced by ventral root stimulation in the dog, unlike the corresponding effect in the cat, is essentially due to afferent nerve impulses from the limbs. Our next step was to determine whether these impulses arose from proprioceptors
HYPERPNEA OF EXERCISE AND REFLEXES FROM LIMBS

responding to changes in length or position, or from chemoreceptors responding to changes in muscle metabolism. The latter seemed unlikely because the response was not appreciably enhanced by ischemia during the stimulation, but the possibility remained that adaptation (or actual deterioration in reactivity) might occur when the ischemia was as nearly absolute as it was in these experiments.

3. Attempts to Demonstrate Chemoreceptors in the Limbs. These experiments were of three general types: a) crossed perfusions in which blood from a donor animal was circulated through one or both hind limbs of the recipient by means of a perfusion pump; b) auto-transfusion experiments involving injection into one femoral artery of blood collected from the opposite femoral vein during "exercise", ischemia, and "exercise" plus ischemia on the side of collection; c) intraarterial and intramuscular injection of various chemical substances known to be associated with muscle metabolism, as well as some others. Cats and dogs were used for all three sets. It may be said at once that no definite evidence of the presence of a specific, physiologically important chemoreflex system has been obtained by any of these procedures. Detailed descriptions of the methods employed and of the individual results are therefore unnecessary, but a brief account seems desirable.

The crossed perfusion experiments were intended to test the ability of blood rendered anoxic, hypercapnic, or acidic (by appropriate manipulation of the donor) to cause a reflex hyperpnea in the recipient. No signs of any such effect were seen.

In the auto-transfusion experiments blood was collected from a branch of the femoral vein into a syringe, heparin was added to prevent clotting, and the same blood (5 to 20 cc.) was then injected into the opposite femoral artery through a suitable cannula tied into the profunda femoris, the main artery being clamped above this point during the injection. Even when the collection was made during stimulation of the muscles with the artery closed (it was opened for brief periods to permit the collection of blood from the vein), and although the appearance of the blood indicated almost complete change to reduced hemoglobin (which may be taken as an indication of the amounts of metabolic products that must have been present), there was no effect on breathing when the blood was injected into the opposite femoral artery. The same animals were responsive to intra-arterial injections of KCl (see below), so that their leg reflex systems were not unreactive.

The experiments in which various chemicals were injected intra-arterially were carried out by the same general methods as those just described. The only essential difference was the use of decerebrated cats and dogs instead of anesthetized animals because the former proved more reactive. The results were confirmatory in the main of those of the similar experiments reported by Moore and his associates (15). Acids (hydrochloric, lactic, phosphoric) were active when injected in concentration of 0.1 N or stronger but thrombosis of the artery frequently followed repeated injections. To determine the sensitivity to hydrogen ions we turned to buffer mixtures of sodium phosphates. They were made isotonic with NaCl and injected at 38° C. in 1 cc. dosage with the arterial inflow cut off during the injection, restored just afterward. The threshold value turned out to be about pH 6.7, which was effective only weakly and occasionally in cats. To obtain consistent and fairly strong stimulant effects a mixture of pH 6.3 or less had to be used in dogs and cats. Potassium chloride was the most consistently effective and repeatable of all the chemical stimulants used by us. The minimum effective dose on intra-arterial injection in cats was 0.1 mgm. in 1 cc. of warm 0.9 per cent NaCl (the latter being entirely ineffective alone), corresponding with 0.0013 M solution of KCl. This was active only weakly and occasionally; for consistent and fairly powerful effects doses of 1 to 5 mgm. in 1 cc. (0.013 to 0.065 M) were required in cats, 1 to 10 mgm. (0.13 M) in dogs. We were also able to test a number of intermediary products of muscle metabolism that were placed at our disposal by Professor Meyerhof. Positive results were obtained with a number of them but all of the active solutions proved either to contain barium (which Moore et al. (15) found to be highly
effective) or to be more acid than pH 6.0. We did however make some valid tests with creatine and phosphocreatine, both of which proved entirely ineffective. Creatine was used in 3 per cent solution in isotonic sodium phosphate buffers at pH 7.0, 6.7, and 6.5 and the amounts injected ranged from 1 to 10 cc. in decerebrated dogs and cats. Phosphocreatine, carefully freed of barium, was used in 0.5 per cent solution in phosphate buffers at pH 7.0 and the amounts injected (in dogs and cats) were 1 to 5 cc.

In addition to these substances, NaCN and lobeline were injected into the femoral artery and found effective only after a latent period of about 30 seconds. The inference—that the response, when it occurred, was due to an action on the carotid and aortic bodies—was confirmed by the effects after denervation of these structures. After the denervation there was no hypopnea from doses which had previously caused a strong delayed response. Ether dissolved in saline was also tried and found to cause distinct hypopnea, even in concentrations as low as 0.1 per cent. The effect came on immediately and was abolished by denervation of the limb. The implications with respect to the cause of the well-known hypopnea of ether anesthesia (8,17,18) are obvious and are to be the object of further study.

Since the hydrion concentration and potassium content of muscle are known to rise during vigorous contraction, a specific chemoreflex system responding to those changes became a distinct possibility. However, when we injected these and other substances intramuscularly we found (like Moore and his collaborators (15)) that such injections were without effect. We injected warm isotonic solutions of phosphate and bicarbonate buffer mixtures, KCl, and phosphocreatine, in amounts ranging from 1 to 20 cc. and at pH ranging from 7.0 to 6.3, into the adductor, quadriceps, hamstring, gluteal, and gastrocnemius muscles of decerebrated dogs and cats, and in no case were there any definite stimulant effects, even from solutions that had strong effects when given intra-arterially.

It is difficult to conceive of a physiologically important chemo-reflex system, responsive to products of muscle metabolism, that would not be activated by any of these procedures except intra-arterial injections of foreign chemicals. We conclude that although the latter experiment shows a chemoreflex system to be present, the entire effect is probably due to pain impulses set up in or near the arterial wall and therefore has no great physiological importance. In this we confirm the findings and interpretations of Moore et al. (15). The increased breathing associated with ventral root stimulation, which we have shown above to be reflex in origin in the dog, therefore cannot arise from chemoreceptors.

The experiments next to be described were undertaken to determine whether it is referable to proprioceptor reflexes of the type described by Harrison (6).

4. Experiments of the Harrison Type. These were performed on dogs and cats prepared as described above (p. 530); in addition the femora were disarticulated or transected and their proximal ends were clamped rigidly so that movements of the legs were not communicated to the trunk. The feet were tied to a rod that was moved vertically (in a few cases horizontally) by an electric motor; in all of the experiments now under discussion the rate of movement was 200 per minute and the type was intended to simulate normal running movements. Nineteen experiments of this type were performed on dogs, 12 on cats.

Dogs. A typical example is shown in figure 3. Increase in respiratory minute volume was seen at least once in each experiment during passive movements of the legs; the increase varied from 22 to 125 per cent and averaged 52 per cent. Thus we are able to confirm Harrison's (6) findings with regard to passive movements of the limbs. The respiratory effect of these movements had the same characteristics as that of active contractions induced by ventral root stimula-
tion, i.e., it was predominantly an effect on the rate, and the onset and recovery were both abrupt. The reflex nature of the response was proved by demonstrating both its continued presence during occlusion of the femoral blood vessels and its complete absence after section of the spinal cord or of the nerves to the hindlegs. The reflex evidently is not set up by stretching muscles or tendons because in 4 experiments traction was exerted on one or more of the tendons of the quadriceps and hamstring groups, and in no case was there any respiratory stimulation; in all these, shaking the legs still caused a typical response after all the tendons were cut through. That the knee joint is prominently concerned was suggested in 6 experiments in which continuous flexion of one knee caused distinct respiratory stimulation, and the result was unaffected by division of all the quadriceps and hamstring tendons. Final proof of that fact was obtained by injection of 2 per cent procaine into and around the knee joint, for following this, shaking or flexion of the leg was entirely ineffective until, after about 30 minutes, the effects of the drug wore away and the response returned. In one experiment denervation of the knee was accomplished by division of all nerves in the vicinity, and this also abolished the effects of shaking or flexion. These experiments therefore show clearly that the respiratory stimulation produced in dogs by passive movements of the hindlegs is due to a reflex arising in and around the joints, particularly the knee.

Cats. The responses were both less consistent and less marked than those seen in similar experiments on dogs. As with the ventral root stimulations, the stimulant effect was mainly on the depth of breathing, it began after a latent
period, and wore away gradually after the stimulus (shaking or flexion in this case) was discontinued. Nevertheless this effect was proved to be entirely reflex by its persistence during closure of the femoral artery and vein (3 experiments) and by its absence following section of the nerves to the legs (2 experiments) or injection of 2 per cent procaine into the knee joints (2 experiments).

In view of these marked species differences, a corresponding study was carried out on man.

Healthy adult males (staff members, technicians and medical students) were used as subjects. They reclined on a padded table from which a part had been cut away so that the left leg hung free from a level about 6 inches above the knee. The left foot was tied to a stirrup on the end of a rod that was moved back and forth a distance of about 2 feet by means of an electric motor; the number of movements was 100 per minute. The subject's expired air was collected through a comfortable valved rubber face mask and was measured directly by a gas meter; a pneumogram was also recorded. The control period was usually 15 minutes (longer if a steady state had not been reached), the period of passive movement 1 to 2 minutes, and the recovery period about 6 minutes. A total of 86 tests of this sort were made in 50 subjects. The results are summarized in figure 4.

It is quite evident that the respiration of these subjects was stimulated consistently and powerfully by passive movements of one leg. Only in 4 was the increase in respiratory minute volume less than 10 per cent. In 38 it was between 20 and 60 per cent and the largest number (14 subjects) were in the group showing an increase of 40 to 50 per cent. The responses partook of the characteristics of both dogs and cats in that the increased breathing involved rate (as in the dog) and depth (as in the cat), began almost immediately (as in the dog) but often faded away gradually (as in the cat).

While the psychic factor cannot be altogether excluded in experiments such as these, the passive movements were not associated with any discomfort or pain. Direct evidence that these stimulant effects were due at least in part to afferent impulses from the leg was obtained in 4 patients in whom the experiment was carried out just before and again after the induction of spinal anesthesia. The results are summarized in table 2. The uniformity with which the respiratory response was reduced by spinal anesthesia seems to us to indicate that psychic factors were not entirely responsible. We therefore conclude that in man, as well as in the dog and cat, passive movements of the leg give rise to reflexes stimulant to respiration.

Discussion. The results of these experiments fully confirm Harrison's claims (6) (7) as to the existence of stimulant reflexes to respiration associated with movements of the limbs, but we are not prepared to accept his conclusion (6, p. 220) that: "The increase in ventilation produced by mild muscular movements is reflex in origin." We have no hesitation in affirming that these reflexes play a part, but from the data now available we are forced to conclude that the reflexes fall short in several important respects from the requirements of a complete explanation. One of these is the difference between various species of animals; we found that in the dog the reflexes aroused by passive movements stimulated the rate of breathing predominantly while in the cat the main effects
were on the depth and in man both rate and depth were stimulated. Another shortcoming has to do with time relationships: in the dog the reflex hyperpnea came on and ended abruptly, in the cat both onset and recovery were gradual, and in man the onset was usually abrupt but the recovery was frequently gradual. The findings in the cat come closest in both these respects to a satisfactory explanation for the hyperpnea of exercise, but in this animal the reflex component was relatively very weak and the stronger effects associated with active muscular contractions (ventral root stimulation) turned out to be due to direct stimulation of the center by a product of muscle metabolism (p. 539). Still another shortcoming of the reflex explanation is that it leaves no provision for adjustment of pulmonary ventilation to the work done, but only to the rate and extent to which the limbs are moved. It is common knowledge among cyclists that hyperpnea is much more closely related to the load than to the rate of pedaling, and a considerable mass of objective evidence to that effect is available from experiments on the bicycle ergometer (13, 16). The reflexes also have quantitative deficiencies, for the reflex effects thus far described are not nearly intense enough to justify the belief that they alone could cause the hyperpnea of muscular exercise, which is the strongest of which the organism is capable.

Final decision on these points must be deferred until other joints and other types of movement have been studied. At present we prefer to conclude that the reflexes constitute only one of several factors involved in this hyperpnea. This conclusion seems to us to be advisable in view not only of existing experimental evidence but also of the history of respiratory physiology, which has been characterized by a series of attempts, all of which have eventually turned

| TABLE 2 |

Per cent change in respiration produced in man by passive movements of one leg

<table>
<thead>
<tr>
<th>PATIENT NUMBER</th>
<th>BEFORE SPINAL ANESTHESIA</th>
<th>DURING SPINAL ANESTHESIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>M.V.</td>
</tr>
<tr>
<td>1</td>
<td>+47</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>+22</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>+20</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>+18</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>+19</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>+20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+29</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>+20</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>+13</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>+13</td>
<td>43</td>
</tr>
</tbody>
</table>
out to be mistaken, to explain too many observations on the basis of a single, simple theory. From the evidence now available we believe that "increased excitability" of the respiratory center during muscular exercise (i.e., hyperpnea without corresponding increase in \( \text{pH} \) or \( \text{pCO}_2 \) in the arterial blood) is probably due in part to excitatory afferent impulses from the limbs, in part to irradiation of excitation from cortico-spinal nerve fibers into the reticular formation of the medulla, and perhaps in part to afferent impulses from the lungs, aroused there by the changes in the pulmonary circulation associated with exercise. To attribute great importance to reflexes involving the pulmonary circulation is in line with the most recent trend of thought concerning the dyspnea of heart disease (2, 7), but evidence as to the applicability of this conception to normal subjects is lacking at present. Irradiation of excitations, originally suggested by Geppert and Zuntz (3), is the explanation favored by Krogh and his collaborators (12, 14); its part in the total respiratory response to exercise must necessarily be ascertained by exclusion when all other factors have been evaluated. As for reflexes from the limbs, it is possible (though in our opinion improbable) that the sum-total of all the afferent impulses aroused during muscular exercise will eventually afford an adequate explanation for the concomitant hyperpnea, particularly when there is also an increase in metabolic activity to prevent reduction in the stimulus level in the arterial blood during the hyperpnea. On the basis of a priori reasoning one would expect reflexes aroused in muscle chemoreceptors by accumulated products of muscle metabolism to be a much more important factor than reflexes from proprioceptors in the joints, and it is interesting to note that the first modern attempt at explaining the hyperpnea of exercise ascribed the major rôle to reflexes set up in the muscles by carbon dioxide (21, 22). Yet our results compel us to discard this attractive possibility and to conclude that, although respiration and circulation can be stimulated by reflexes aroused in the limbs by chemical substances, these phenomena are related to pain and not to a specific reflex system of physiological importance.

**SUMMARY AND CONCLUSIONS**

In human subjects exercise of one forearm and hand caused distinct hyperpnea, which was increased if the circulation was cut off. This potentiation by ischemia was probably due simply to pain. In analogous experiments on anesthetized dogs and cats, "exercise" of the hind-limbs (produced by stimulation of the ventral spinal roots) also caused hyperpnea, which in the dog was not influenced by ischemia but was abolished by transection of the spinal cord while in the cat it was reduced or abolished by ischemia, unaffected by cord transection. This hyperpnea therefore was due mainly to reflexes in the dog and in man, to direct central stimulation by chemical products of muscle contraction in the cat.

Various methods were used to detect a specific, chemosensitive reflex system in the limbs, without success. Passive movements however produced hyperpnea in dogs, cats and men, the effect being most marked in man and least marked in the cat. The reflex nature of this hyperpnea was proved by its absence after denervation or chordotomy in animals and by its diminution during spinal
anesthesia in man. By means of traction on muscles and tendons and of local
anesthesia of the periarticular surfaces, the reflex was shown to arise largely or
wholly in and around the knee joint, not in the muscles or tendons.

The possible significance of these findings to the respiratory response to
muscular exercise is discussed and reasons are given for believing that while
reflexes of this type unquestionably account for some of the hyperpnea, they
probably cannot account for all of it.

REFERENCES

(6) Harrison, T. R. Failure of the circulation. Williams & Wilkins Co., Baltimore,
1939.
Int. Med. 50: 690, 1932.
(9) Henderson, Y. Adventures in respiration. Williams & Wilkins Co., Baltimore,
1938.
(12) Krogh, A. Comparative physiology of respiratory mechanisms. University of
(17) Ranson, S. W., W. F. Windle and L. R. Faubion. This Journal 64: 320, 1923.
pp. 91–94.
(22) Volkmann. Müller's Arch., p. 342, 1841.