

innocuous the introduction of the various toxic materials employed. It is very probable that in animals debilitated by old age, malnutrition and disease, the aorta is no longer normal and is probably the seat of minute microscopic lesions such as stretching of the elastica and insufficiency of the muscular fibers. In such animals various toxins introduced into the circulation, especially those tending to raise blood-pressure, will bring out this latent disposition and cause arterial necrosis, calcification and aneurysmatic dilatation.

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**On the influence of various substances, applied directly
to the medulla oblongata, upon the respiratory
rhythm in frogs.**

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Recent experiments by Maxwell¹ have shown that the nerve cells in the cerebral cortex are not stimulated by the ordinary nerve stimulants, such as oxalates, citrates, tartrates, etc. On the other hand we are in the possession of the well-known fact that an increase in the CO₂ tension of the blood supplied to the brain at first accelerates and later, if the increase in CO₂ tension be sufficiently great, inhibits the rhythmic discharge of impulses from the respiratory center or centers. It appeared possible that although the ordinary nerve stimulants do not excite nerve cells yet some other group of substances might be found which does so. Accordingly the following experiments were undertaken.

The roof of the skull, in frogs, was removed by means of a fine pair of bone forceps as far down as the tip of the fourth ventricle; in some instances the membrane covering the floor of the fourth ventricle was removed, in others not. The cerebrum was removed by cutting across the thalamencephalon just in front of the optic lobes; by this means it was found that a more regular respiratory rhythm was obtained, the frog was quieter, and the results were more uniform. The cavity left in the skull by the removal of the

¹ Maxwell: *Journ. of Biol. Chem.*, 1906, ii, p. 183.

cerebrum was then plugged with absorbent cotton and absorbent cotton was placed all round the wound so as to absorb any fluid which might escape from the depression left by the removal of the roof of the skull. With practice the operation could be performed in 3 to 4 minutes, and, if successful, within 3 to 5 minutes after the operation respiration, which at first is suspended, is resumed. After about 5 to 10 minutes, the rhythm of respiration usually becomes constant and, if the frog be left untouched, remains so for over two hours.

After an interval of 15 minutes, to allow all shock effects to subside, drops of various solutions were placed upon the exposed surface of the medulla oblongata and their effect upon the respiratory rhythm noted.

It was found that N/10 solutions of acids (hydrochloric, sulphuric, lactic, oxalic) caused a notable acceleration. Thus in a frog breathing at the rate of about 19 respirations a minute the application of N/10 H_2SO_4 quickened the rate, within two minutes, to 50 respirations per minute. In other instances less acceleration was obtained, but in all cases it was very marked, except when the respiratory rhythm before the application of the acid was very convulsive and irregular in character owing to injury of the medulla during the operation; in these instances it is possible that only the spinal centers were functioning.

One per cent. KCN caused complete stoppage of respiration within three to five minutes. Strong reducing agents (1 per cent. formaldehyde, M/10 K_2S , M/10 hydroquinol, $3/4N$ sulphurous acid) caused marked slowing or stoppage of respiration. Oxidizing agents (20 per cent. Kahlbaum's C. P. H_2O_2 , N/10 $KMnO_4$, N/10 Fe_2Cl_6) accelerated the rhythm but not markedly. Respiration was inhibited by N/10 $CuCl_2$ and slowed, but not markedly, by N/10 $HgCl_2$. Solutions of much higher osmotic pressure than the blood (*e. g.*, pure glycerol) moderately accelerate the rhythm and render it irregular; prolonged action of solutions of much lower osmotic pressure than the blood (distilled water, tap water) greatly slows the respiratory rhythm and may ultimately suppress it altogether. In confirmation of Maxwell's results I find that sodium oxalate has no effect upon the rhythm.

It may be questioned whether the effects observed are really

due to the direct action of the substances upon the respiratory center or whether they are reflex effects due to the action of the substances upon nerve fibers. If, however, we cover the lower limbs of the frog, treated as above, with a sheet of filter paper saturated with N/10 HCl, after 3 or 4 minutes of violent struggling the frog becomes quiet and the respirations, at first inhibited, are resumed; although occasional convulsive movements occur, these become less and less frequent and respirations continue except during the actual convulsions. The rate of the respirations is, however, unaltered for the first six minutes; in ten to twelve minutes they may be accelerated 10 per cent. but not more. Now the time which elapses before the respirations are quickened is only 1 to 2 minutes when the acid is applied directly to the medulla and the animal usually does not struggle at all. Moreover, the two effects, the effect upon the respiratory center and that upon nerve fibers can readily be distinguished from one another in the case of N/10 oxalic acid. At first the normal effect of an acid upon respiration is observed, namely a marked quickening of the rhythm so that after 10 minutes the rate may be doubled. If further applications of oxalic acid be made the rate continues to increase until over one half hour after the first application of oxalic acid when the muscles of the whole animal go into prolonged tetanic contractions; the former effect is that of the acid upon the respiratory center, the latter effect is that of the oxalic acid anion upon nerve fibers.

The results are such as to indicate that the processes occurring in nerve cells during the passage of a reflex are of the nature of oxidations and that they are accelerated by acids.

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Metaplasia and metastasis of a rat tumor.

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We reported to this society on several previous occasions some facts regarding a tumor of the rat which we have propagated for more than two years. This tumor is now in its twelfth genera-