

do not return to normal simultaneously. The first to reappear is the response of the muscle to indirect stimulation at high frequencies, then the response to lower frequencies, then the sensitivity to curare, and lastly the post-tetanic potentiation.

The recuperation of normal functional phenomena as described above takes place in muscle in which the atrophic state persists, which suggests a lack of definite relationship between these disturbances and muscular atrophy.

A hypothesis was previously advanced¹ that

the cause of disturbances resulting from tenotomy might be an alteration of the postural reflexes. The present study shows that the change is reversible, an observation in accord with the previous hypothesis. Of course there is also the possibility that the change in tension resulting in the muscle from the sectioning of its tendon may influence the neuromuscular junction directly.

Summary. The disturbance in neuromuscular transmission caused by sectioning of the tendon disappears when the tendon is spontaneously re-established.

15199

Effect of Neostigmine (Prostigmin) and Physostigmine upon the Denervated Iris of the Cat.

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It has been shown by Anderson^{1,2} that physostigmine constricts the pupil in normal cats but fails to do so after the ciliary ganglion has been removed and time permitted for degeneration of the post-ganglionic fibers. Similar studies have never been reported for neostigmine (prostigmin). In view of the differences known to exist between physostigmine and neostigmine (the latter being much more effective in relieving muscle weakness in myasthenia gravis) it is possible that neostigmine may have a direct action upon muscle in addition to its known anticholinesterase action. We decided to test this hypothesis so far as iris muscle is concerned.

Methods. Cats were anesthetized with sodium pentobarbital intravenously or intraperitoneally. The hair was shaved from the region of the left eye, the lids were sutured together and a skin incision was then made below and lateral to the orbit. A portion of the zygoma and lateral wall of the orbit was removed. The conjunctiva and Tenon's cap-

sule of the globe were opened and the external rectus muscle identified. The latter was retracted upward and the ciliary ganglion was exposed. If difficulty was encountered, the nerve from the inferior oblique muscle was traced back to its branch which leads to the ciliary ganglion. The ganglion was grasped by a fine hemostat, all its branches were severed, and the ganglion was removed. The wound was then flushed with penicillin solution and the incision was sutured. Since the operation abolished corneal sensitivity and secretion at least temporarily, the chief post-operative complication was desiccation and ulceration of the cornea; a number of cats had to be discarded for this reason.

In some cats the left superior cervical ganglion was also removed. This ganglion was distinguished from the vagus ganglion at the level of the carotid bifurcation and the former was extirpated completely.

Criteria of a successful ciliary ganglionectomy were: (a) pupillary dilation on the operated side, (b) failure of the iris to contract after exposure of the retina to strong light, (c) sensitivity to 0.5% pilocarpine and

¹ Anderson, H. K., *J. Physiol.*, 1905, **33**, 156.

² Anderson, H. K., *J. Physiol.*, 1905, **33**, 414.

TABLE I

Cat No.	Ciliary ganglion-ectomy	Superior Cervical ganglion-ectomy	Effect of neostigmine bromide (5%) instilled locally into eyes with denervated iris muscle												
			Days										Weeks		
			1	2	3	4	6	7	8	9	10	14	3	4	10
1	×										0				
2	×										0				
3	×										0				+
4	×														+
6	×								0						+
7	×						0								+
8	×						0								+
10	×	×	++												
11	×	×	++												
12	×	×	++												
13	×	×		++	++								0		
14	×	×		++											
15	×	×	++	++	0	0			0						
16	×	×	++		0										
17	×	×	++		0										

0 = No response to 5% neostigmine bromine.

+ = Normal response to 5% neostigmine bromine.

++ = Increased response to 5% neostigmine bromine.

20% mecholyl on the operated side, and (d) failure of 2% physostigmine to constrict this pupil.

Pupillary diameters (horizontal) were measured with a millimeter rule, in the dimmest light compatible with accurate reading; this light was kept constant throughout the experiments. Five per cent neostigmine bromide was used throughout; 2 drops were instilled into the conjunctival sac of the eyes on both the normal and operated side.

Results. The effect of neostigmine upon the operated eyes is shown in Table I. In cats No. 1 to No. 8 the left ciliary ganglion had been removed and in cats No. 10 to No. 17 both the ciliary and superior cervical sympathetic ganglia had been extirpated. While complete data covering a period of 3 months are not available on any single cat, the results obtained in this series of 15 cats indicate:

(1) In the first 1 to 3 days postoperatively the denervated iris is unusually sensitive to neostigmine, the denervated side constricting much more fully than the normal side (Table I).

(2) After the 2nd or 3rd day following ciliary ganglionectomy the iris becomes insensitive to neostigmine whether the ciliary alone or this plus the superior cervical sympathetic

ganglia had been removed.

(3) By the 10th week (and possibly earlier) the "denervated" side had recovered its ability to respond to neostigmine.

We made no attempt to determine the earliest time at which pilocarpine sensitivity appeared following ciliary ganglionectomy but when this drug was instilled for the first time 7, 8, 9, or 14 days postoperatively, sensitivity already existed. Reactions to physostigmine were similar to those to neostigmine in every instance in which both were measured.

Comment. After an initial period of sensitivity to neostigmine (which was probably due to traumatic injury to the postganglionic fibers) the denervated pupil failed to respond to 5% neostigmine. Later (2½ months) neostigmine again produced pupillary constriction; this was probably due to regeneration of postganglionic fibers from ganglion cells still present in the distal nerve trunk.

The failure of the denervated pupil to react to neostigmine proves that in the concentration and by the route employed, neostigmine has no direct action upon the circular muscle of the iris. Even when the dilator sympathetic tone (which might oppose a weak constrictor effect of neostigmine directly on the iris) was removed, neostigmine was still without effect. The action of physostigmine

was similar in all respects to that of neostigmine. The studies on physostigmine confirm those carried out by Anderson¹ though the latter have been erroneously interpreted by Meyer and Gottlieb³ as evidence of a direct action of physostigmine on the iris.

The action of physostigmine and neostigmine therefore is one wholly due to inactivation

of cholinesterase, and consequent preservation of stimulant quantities of acetylcholine. For the production of acetylcholine, some or all of the ganglion cells must be intact or there must exist some local stimulation of postganglionic fibers.

Conclusion. Neostigmine (prostigmin) does not stimulate the denervated iris muscle of the cat. It causes miosis only when some or all of the ciliary (parasympathetic) ganglion cells are intact or when the postganglionic fibers are stimulated.

³ Meyer, H. H., and Gottlieb, R., *Die Experimentelle Pharmakologie*, 8th edition, 1933, Berlin, page 189.

15200

Effect of Intermittent Exposure to Simulated High Altitude in Erythropoiesis in the Guinea Pig.*

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Investigations on the effects of intermittent exposure to high altitudes have been pursued only since 1938 when Armstrong and Heim¹ subjected rabbits to a simulated altitude of 18,000 feet, 4 hours daily for 5 weeks. Their animals failed to show an increase in red blood corpuscles in adaptation to the lowered oxygen tension. They also found² that young men exposed intermittently to an altitude of 12,000 feet showed evidence of only slight acclimatization. On the other hand, Stickney and his collaborators^{3,4} found that dogs subjected discontinuously to an altitude of 18,000 feet for 16 weeks did exhibit an increase in the amount of hemoglobin and number of red blood corpuscles.

The purpose of this report is to present further data from a different species, the guinea pig. At first our study was incidental to an investigation of the effect of exposure to simulated high altitude on the structure of the brain⁵ and we made hemoglobin determinations only. Later the blood study was expanded, though done in conjunction with the neurological study; the same animals were used in both problems.

Material and Methods. Fifty-eight young adult male guinea pigs were used. Twenty-six of these served as controls; the remainder were subjected to discontinuous exposures to air at lowered barometric pressure for 6 hours daily, except Sunday. In the first experiment the simulated altitude was 23,000 feet (307 mm Hg pressure); in the second experiment, 30,000 feet (225 mm Hg pressure).

The conditions of the concurrent neurological experiment required that 3 to 6 animals be sacrificed periodically as the whole series accumulated exposure time. In the first experiment, groups were sacrificed after 100, 200, 300, and 500 hours of exposure. In the

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¹ Armstrong, H. G., and Heim, J. W., *J. Aviat. Med.*, 1938, **9**, 92.

² Armstrong, H. G., *Principles and Practice of Aviation Medicine*, Williams and Wilkins Co., Baltimore, 1943.

³ Stickney, J. C., and Van Liere, E. J., *J. Aviat. Med.*, 1942, **13**, 170.

⁴ Stickney, J. C., Northrup, D. W., and Van Liere, E. J., *Proc. Soc. Exp. Biol. and Med.*, 1943, **54**, 151.

⁵ Windle, W. F., and Jensen, A. V., *J. Aviat. Med.*, 1945, in press.