EFFECT OF CHOLINERGIC DRUGS ON RECOVERY OF FUNCTION FOLLOWING LESIONS OF THE CENTRAL NERVOUS SYSTEM IN MONKEYS*

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Recovery from the effects of destructive lesions of the central nervous system has been studied since the early recognition of the focal effects of such lesions. The paralysis which appears following lesions of the cerebral cortex or its efferent pathways has been particularly studied because it has more obvious symptoms than many other syndromes which are the result of injury elsewhere. Yet it is a remarkable fact that in man during the early acute stages of this paresis the rate and extent of recovery often cannot be predicted and that relatively little is known of the factors other than size and site of lesion which affect it.

There have been many attempts to expedite such recovery by various therapeutic means but with little success. One reasonable approach to the subject is based on the theory that stimulation of the nervous system promotes recovery. And since cholinergic drugs are believed to act as such stimulants they have become the object of inquiry. The present paper deals with this question as related specifically to the effects of such drugs on recovery of motor function following lesions of the cerebral cortex in monkeys.

Previous Literature

The earliest attempt to correlate recovery of function with cholinergic stimulation was made in France where Chavany[16] advocated the use of acetylcholine in the treatment of hemiplegia. Lortat-Jacob[61] then reported that acetylcholine was beneficial in a case of aphasia resistant to other forms of therapy. Following him, Villaret and Justin-Besancon[87] discussed the possible pathogenesis of the lesions of hemiplegia and the action of acetylcholine in these

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cases. Flipo[27] produced favorable results by using acetylcholine in six cases of hemiplegia, and Rosnoblet[78] used acetylcholine on a case of blindness due to softening of the occipital lobes and obtained a partial remission. Zlatscheff,[95] Meignant,[63] and Seze[80] discussed the action of acetylcholine in such cases and concluded that its beneficial effect was due to its vasodilating action. Laignel-Lavastin, Bailliart, and Boquien[54] used acetylcholine therapy on a case of blindness caused by a cerebro-vascular accident and obtained quite remarkable results, and Ley[58] reported more cases of cerebral softening benefited by acetylcholine therapy. This was followed by Villaret[86] and by Villaret, Justin-Besancon, and Cachera[88] who substantiated the previous findings.

Sciclounoff[79] reported the first extensively controlled series of hemiplegics treated with acetylcholine. Of 221 patients with cerebral softening due to thrombosis or angiospasm, 151 cases were treated with the accepted conservative treatment, and 70 with acetylcholine chlorhydrate, in doses 0.1-0.3 grains per day subcutaneously. His results showed that treatment with acetylcholine tripled the chances of complete cure, doubled the chances for marked improvement, and reduced by one half the risk of a fatal outcome (Table 1).

TABLE 1

EFFECT OF ACETYLCHOLINE ON HEMIPLEGIC PATIENTS
SERIES OF SCICLOUNOFF, 1934

	Conservative treatment		*Acetylcholine treatment*	
	Cases	*per cent*	*Cases*	*per cent*
Cures	12	8	19	27
Improvement	24	16	19	27
Stationary	57	38	17	24
Died	58	38	15	22

He observed that the earlier the treatment was started the better were the results, and he also obtained better results with the younger patients. The mechanism of action in these cases was ascribed by the author to the vasodilating effect of acetylcholine. He thought that the drug aided the circulation to the involved parts of the brain and might even abort threatened extension of the thrombosis. Furthermore, he believed that the ischemia and resulting local acidosis might favor the local action of the drug at those sites, that the drug might promote the establishment of collateral circulation, and that its peripheral vasodilating action might be beneficial in preserving the nutrition of the involved muscles.

For some reason, the work of this French school was never recognized in the English literature and thus it was unknown to many when Wolf[93] reported that he was able to increase greatly the rate of recovery from lower motor neuron paralysis by the oral administration of potassium chloride, acetyl-beta-methyl choline (Mecholyl) or prostigmine. In his experimental work, lesions were produced in the sciatic nerve of cats and rats by section in some cases and by alcohol injection in others. He found that whereas the control group showed no improvement after 200 days, the treated group showed complete recovery in at most 144 days. The controls showed more axonal and myelin degeneration than did the corresponding treated animals and the muscles of the untreated group likewise had more atrophy.

Wolf claimed to have shortened the duration of the paresis and hastened the recovery of patients having Bell's palsy. His explanation was that cholinergic drugs facilitated the passage of impulses through the lower motor neurons by preservation of acetylcholine bombardment at the dendrites of the anterior horn cells and that neuronal regeneration is hastened by this constant stimulation.

Methods

A. *Choice of experimental animal.*

Monkeys (*Macaca mulatta*) were selected as experimental animals because the effects of cortical ablation and the rate of recovery therefrom in untreated animals were already well established in this laboratory; because their high cortical organization and intricate motor performance make recovery easy to follow; and because the results are more applicable to man than are the findings in the more common laboratory animals.

The 14 monkeys used were all selected as medium-sized animals of approximately the same age and weight because it was known that age plays an important part in the speed of recovery in these animals. One much smaller and younger animal was used for control of this point, which can therefore be ruled out as affecting recovery in all other animals.

B. *Operative procedure.*

In each instance the entire motor area, areas 4 and 6 of Brodmann,[8] was removed from the left frontal lobe in order to produce a maximal cortical hemiplegia of the contralateral leg, arm, and face. Operations were carried out with sterile technic by a single operator and with great care that the excisions should be as nearly identical as possible (Fig. 1).

Because time is a factor in recovery, i.e., there is more return of function in the extremities of an operated animal two weeks after operation than during the first postoperative days, the animals were operated on in groups. Those of each group were operated upon as nearly simultaneously as possible and the animal with the oldest operation and therefore the greatest recovery was always used as the control, since in this way confusion of effects of improvement by drug and by the time element was best avoided.

C. *Choice of drugs.*

There were four untreated controls, two animals treated with strychnine and thiamin, one with doryl, three with doryl and thiamin, two with doryl and atropine, and two with thiamin alone.

1. *Doryl* (carbaminol choline)* was chosen because it is one of the few choline derivatives which has been shown to have a stimulating effect on the ganglion cells of the nervous system, i.e., a nicotinic effect. Like acetylcholine and mecholyl, it is a powerful stimulant of the parasympathetic nervous system, but unlike the others, it is very stable and not decomposed by the blood esterases. This drug exhibits a strong muscarinic effect, i.e., dilatation of the blood vessels, fall of blood pressure, slowing of the pulse rate, sweating, salivation, increased motor and secretory activity of the entire gastrointestinal tract, contractions of the urinary bladder and uterus, constriction of the pupil, and lowering of the intraocular pressure. Doryl also produces a very marked nicotinic effect and differs fundamentally in this respect from mecholyl which exerts a pure muscarinic action. It is readily absorbed from parenteral sites and from oral administration, but the latter route yields irregular results and the effects are cumulative over a period of days.

2. *Strychnine* was selected for comparison with doryl because of its known effect as a stimulant of the central nervous system. In contrast to doryl, however, it has no effect on the vasomotor system. It was thought that in this way the effect of vasodilatation as a factor in recovery might be ruled out.

3. *Thiamin* likewise is known to be a stimulator of nervous tissue, and was chosen also because it was thought possible that, even with the adequate diet provided for the animals, recovery of function might require additional vitamin sources.

* The doryl for this series of experiments was furnished through the kindness of Merck & Co., Inc.

D. *Methods of examination.*

The animals were at all times fed the usual laboratory diet. They were kept in individual cages and their environment and opportunities for activity were as similar as possible. They were weighed at weekly intervals. The health and development of each animal were satisfactory throughout the experiment.

The treated animals were given their medication twice a day. Doryl was injected subcutaneously in the right leg, atropine subcutaneously in the left leg, and the one daily dose of thiamin was given intramuscularly in the left leg. The solution of strychnine was given by stomach-tube, being washed down with 5 cc. of water to make sure that all the strychnine solution reached the stomach. To give these medications, each monkey was placed in a holding box.

The rate of recovery was recorded daily over the first few postoperative weeks and thereafter at least three times a week. Behavior was observed during the first postoperative days in their cages only because of their disability and the risk of injury to the site of operation; thereafter they were allowed to run about the corridor between the cages. Observations were made on the following points: the time of return of motion to the various joints—shoulder, hip, elbow, knee, fingers, toes; ability to use the extremity for active support in locomotion; time of reappearance of active prehension in the hand and foot; ability to use the extremity actively in climbing; speed of movement of the paretic extremity as compared with the normal side; coordination of the paretic extremities when used in voluntary motor performance; and comparison of freedom, ease, and frequency of movement as compared with the normal extremity. Skill in performing finer movements with the hands and feet, strength of the extremities, abnormal reactions such as reflex grasping, tremor, etc., were later observed, as were the postural reactions of the paretic limbs.

The reflexes—knee-jerk, biceps, and Rossolimo or flick reflex—were studied. This last consisted of putting the thumb against the sole of the monkey's foot and dorsi-flexing the foot and then flicking the extended small toes. When positive, there is volar flexion of the terminal phalanx of the great toe. The mechanism of elicitation is similar to that of the Hoffman in man and, while its significance is not entirely clear, it is a constant finding immediately after operation in all cases of pyramidal tract involvement to the leg in the monkey. Tone and resistance to passive manipulation of all extremities were noted, weakness and muscle strength in the paretic limbs, and atrophy in these limbs, if present, were gauged.

Although it was hoped that some more objective method of following recovery could be found, no single reflex change or other phenomenon became evident which would give an accurate index of recovery. The degree in any given case depended largely on a combination of the observations on behavior supplemented by the reflex and muscle status. The evaluation was thus largely a clinical one, but great pains were taken to be as objective as possible.

All medicated animals received their medication for a period of 6 weeks or more postoperatively, at which time recovery was more or less stationary and the drugs were discontinued to see if regression occurred. Six of the animals were then sacrificed at 8 weeks.

Careful notes were made as to the presence and extent of atrophy in all cases and the gastrocnemii and biceps muscles of the six animals sacrificed 8 weeks after operation were removed at autopsy and weighed. As nothing significant was found, however, the results will not here be discussed further.

Histological sections, by Marchi technic, were prepared from the brain stem and cord of these cases. Nissl studies of the tissue extirpated and of the remaining cortex were made. In neither case was anything significant observed.

Experimental data

A brief account of the experimental data follows, with abstracts from protocols of representative animals in each experiment.

EXPERIMENT I. In this experiment four animals were used, two as controls (Recovery Series I and II) and two receiving daily doses of strychnine and thiamin (R. S. III and IV).

Operation:	R. S. I	1/19/42	Wt. 4.6 kg.
	R. S. II	1/21/42	Wt. 4.5 kg.
	R. S. III	1/23/42	Wt. 4.1 kg.
	R. S. IV	1/26/42	Wt. 3.8 kg.

One week postoperatively.

R. S. I. (Control). This animal is quite agile and exhibits moderately good function in the leg except for the foot where only a few gross motions of the ankle and toes are present. The arm is actively used to only a very slight extent. Both foot and hand are used a little in climbing. The arm is held in extension and the leg tends to be held in a like manner. The K. J. on the right is pendulous and markedly hyperactive. A positive Rossolimo reflex is present on this side only. The right foot is colder than the left. No reflex grasping is seen in the hand. Weak movements are present at the shoulder and elbow with only slight fanning movements of the fingers of the right hand.

R. S. II. This animal also shows quite good agility. The leg is actively used with fair motions at the hip and knee on the right, but no active use of the foot and toes is noted. The arm is not used actively and is held in extension, in which position the leg tends also to be held. No reflex grasping is present in the right hand nor is a placing response in the foot elicitable. The K. J. is hyperactive and a positive Rossolimo is present on the right.

R. S. III. This animal is active and agile and shows strong muscle power in the right arm and leg, both of which are actively used in climbing. Prehension is present in both the right hand and foot. The knee-jerk is 2-plus on the right and the Rossolimo and placing reflexes are absent on the right. The right leg is slightly hypotonic, but is not much colder than the normal side. Facial paresis is absent or minimal on grimacing.

Medication: Since the day of operation this animal has been receiving—

Thiamin 5 mg. q.d.

Strychnine 15 mg. b.i.d.

This dosage will be continued daily until further notice.

R. S. IV. This animal uses both extremities actively, but is clumsy and tires easily. The leg is used actively, while the arm is used only occasionally and support by this extremity is partly passive. The arm is carried in extension. No Rossolimo reflex or placing reaction is present on the right. The right leg is hypotonic and the foot is colder than that on the normal side. A minimal facial paresis is present. No reflex grasping is noted.

Medication: Since the day after operation this animal has been receiving—

Thiamin 5 mg. q.d.

Strychnine 13 mg. b.i.d.

This medication will be continued daily until further notice.

Two weeks postoperatively.

R. S. I. This animal is active and agile in climbing, using both arm and leg moderately well. On the right side the leg is much better used than the arm, the latter usually being carried in a semi-extended position. Prehension is present in both the foot and hand.

R. S. II. This animal is active and fairly agile, although it tires easily when climbing about the corridor and at this time shows a tremor on the left side. The leg is used fairly actively in climbing but only slight prehension is present in the foot. The arm is used to a lesser degree with not very much prehension in climbing. No placing reaction or Rossolimo reflex is present on the right. The limb is slightly hypotonic and the temperature of the foot is about equal to that on the left. No reflex grasping is seen in the hand. A slight facial weakness is noted on grimacing.

R. S. III. This animal still has difficulty in climbing and most of its activity consists of walking. When excited it will climb, however, using both the right foot and hand occasionally. In walking, the leg and arm are partly dragged. A positive Rossolimo reflex is present on the right only. The right leg shows fair tone in the muscles at the hip but the lower leg is flaccid.

R. S. IV. This animal climbs quite actively and with fair agility using both extremities on the right. Prehension is present in both the hand and foot but dexterity is better in the leg which is used with fair agility. The knee-jerks are bilaterally hyperactive and equal. The Rossolimo reflex and the placing reaction are absent on the right. No difference in the temperature of the feet is noticeable. No reflex grasping is present in the arm.

Three weeks postoperatively.

R. S. I. As compared with the two treated animals, this animal shows far greater deficit in motor performance. The motor deficit is very slightly greater than that of R. S. II—the other control. It uses all four extremities but the right arm is hardly useful at all and the right leg is not strong enough to bear weight. The fingers of the right hand are not used in any way, while the toes of the right foot are used only occasionally when they strike against the bars of the cage (Fig. 2). There is no reflex grasping. The posture is such that the right extremities extend more than the left and when the animal is excited they become moderately rigid. There is no increase in passive manipulation of the right arm or leg. The K. J. on the right is slightly greater than on the left. The Rossolimo is present on the right only.

R. S. II. It climbs rapidly but shows very little and very poor use of the right extremities. There is a marked weakness in the right leg. The right arm is used very little for support, although it moves rhythmically in progression. There is no finger grip and likewise little toe grip. The animal tends to fall when it tries to support itself with the right leg. The movements on the right side, as in R. S. I, are markedly slower in initiation, in cessation, and throughout their whole process than are those of the two treated animals. The knee-jerks are equal on the two sides and no increased resistance to passive manipulation is noted. The Rossolimo reflex is markedly present on the right and slightly positive on the left. This animal is now to be given medication and will therefore be dropped from this experiment.

R. S. III. The present animal injected with strychnine and thiamin shows a markedly greater recovery than either of the control animals. Movement is excellent and posture is more nearly normal, and the speed of movement is much more rapid on the right side as compared with the controls. The animal will attempt to fend off a threatening stick, using the right hand. Posture is very often bilaterally symmetrical. The right extremities are obviously weak, and it cannot support itself very well in climbing about the corridor but it moves the four extremities in rhythmic progression and there is some support obtained from the right side. K. J.s are greater on the left than on the right, while resistance to passive manipulation is greater on the left than on the right, i.e., there is no spasticity. A positive Rossolimo is present in the right while a minimal response is present on the left.

R. S. IV. This animal, which has had strychnine and thiamin since its operation, shows a very marked degree of recovery of function on the right side. The posture of the two sides is very often equal, but when the animal becomes fatigued the right extremities are held more extended. The fingers and toes are weakly used for support, the toes better than the fingers. No reflex grasping is seen. Movements on the right side are quick, accurate, and there is a very fair degree of function in walking as well as climbing. The K. J.s are greater on the left and resistance to passive manipulation is also greater on the left. The Rossolimo reflex and placing reactions are negative on the right. There is no atrophy or only a questionable atrophy in the gastrocnemius on the right.

Medication: As the strychnine-treated animals failed to show as great a degree of recovery as those animals receiving doryl, it was thought that this might be due to overdosage with strychnine, hence this animal's daily dose of strychnine will be reduced by about one half. Thus, it will receive daily:—

Thiamin 5 mg. q.d.
Strychnine 5 mg. b.i.d.

Four weeks postoperatively.

R. S. I. This animal has shown no change from the above observations.

R. S. III. This animal shows little change. The right side is used in climbing and running with fair agility but the arm is used only slightly. K. J.s are bilaterally equal. The Rossolimo reflex is positive on the right and minimally present on the left.

R. S. IV. After one week on reduced strychnine medication, this animal shows no improvement in the rate of recovery as compared with Recovery III which is receiving the full dose, and in fact the rate of recovery may be somewhat diminished. It is definitely less active than the others although no reason is known for its inactivity. There is marked impairment of motor function on the right side although the hand and foot are used for grasping. The K. J. is greater on the left. The Rossolimo is markedly positive on the right and minimally so on the left. This animal has developed a tremor which is rather marked. This was not present immediately after operation but appeared after some time and seems to be increasing in intensity.

Medication: To show that this animal is capable of further recovery provided the proper means are employed, strychnine will now be discontinued and doryl substituted.

Five weeks postoperatively.

R. S. I. Very little change has occurred in motor performance. The right arm and leg are used very poorly for climbing and running and are usually held hyperextended when at rest. The fingers and toes are limp, but the remainder of the extremity is rigidly held in extension while the animal is moving. Very often the movements are much slower and less accurate on the right than those of the left side. The deficit becomes worse with fatigue and with emotion. K. J. is less active on the right. The Rossolimo is present on the right and absent on the left.

R. S. III. This animal is a good deal more active and agile than the control animal. The arm is actively used in climbing with fair prehension in the hand. Coordination is moderately good and movements are quicker than those of the control. Both the extremities on the right are held more extended than are those of the left side. K. J. is slightly greater on the left and resistance to passive manipulation is about equal on the two sides. The Rossolimo is negative.

Six weeks postoperatively.

R. S. I. (Fig. 2.) There is little or no further improvement. It still has a very paretic right side which remains more extended than the left in all rhythmic movements and it has practically no use of the fingers and toes. K. J. is greater on the left and the Rossolimo is absent bilaterally.

R. S. III. (Fig. 3.) This animal continues to show less motor deficit than does R. S. I. It has some use of the right extremities for flexion, grasping, and support, but this is not very strong as yet. The extremities still tend to remain slightly more extended than those on the normal side. There is likewise some lag in speed of movement on the right. The left K. J. is greater than the right. The Rossolimo is bilaterally present.

Eight weeks postoperatively.

R. S. I. This animal has shown little if any improvement over the past four weeks. It climbs actively, but coordination and agility are poor. It uses the leg moderately well but obviously not so well as the left and movements are slower and coordination is not accurate. The arm is not used well in either climbing or running. Prehension is present in the arm to some extent, although the arm is held in extension. Postural adjustments are absent in both extremities on the right. The K. J.s are about equal bilaterally while the Rossolimo is positive on the right only. Tone is about the same in the two legs—being mainly in the extensor groups bilaterally.

R. S. III. It continues to show much greater agility and coordination than R. S. I. The right leg is used almost as well as the normal leg while the arm is used less but more than is that of the control. The K. J. is less active on the right and the Rossolimo is slightly positive on the same side. The tone of the right leg is slightly less than in the normal, and the tone which is present is mainly in the flexor groups. The feet are of the same temperature.

Results:

It is demonstrated that the two animals receiving strychnine and thiamin definitely show an increased rate of recovery of motor function as compared with two untreated controls. The absence of as large an effect as will be shown to be exerted by other drugs is not due to overdosage with strychnine, since reducing the daily dose of strychnine by one half did not increase the rate of recovery, but slowed it if anything. Thus the dose of strychnine used in this experiment is presumably suboptimal.

EXPERIMENT II. *Doryl and thiamin.* This experiment consists essentially of two parts. In the first section three animals were used: R. S. I served as the control; R. S. V and VI were given doryl and thiamin medication. In the second section, R. S. II, which was used as control for part of the experiment, was given doryl and thiamin for three weeks postoperatively to show that recovery can occur in a chronic animal. R. S. IV, which received strychnine medication in the previous experiment, was changed from this medication to doryl and thiamin to show that the animal was capable of further recovery and that the failure of strychnine to exert a maximal effect on the rate of recovery was not due to the animal. Representative excerpts from the protocols follow.

Operation:	R. S. I	1/19/42	Wt. 4.6 kg.
	R. S. II	1/21/42	Wt. 4.5 kg.
	R. S. IV	1/26/42	Wt. 3.8 kg.
	R. S. V	1/28/42	Wt. 2.8 kg.
	R. S. VI	1/30/42	Wt. 3.1 kg.

One week postoperatively.

R. S. I. (Control.) This animal is quite agile and exhibits moderately good function in the leg except for the foot, where only a few gross motions of the ankle and toes are present. The arm is actively used to a very slight extent. Both foot and hand are used a little in climbing. The arm is held in extension and the leg tends to be held in a like manner. The K. J. on the right is pendulous and markedly hyperactive. A positive Rossolimo is present on the right only. The right foot is colder than the left. No reflex grasping is seen in the right hand. Weak movements are present at the shoulder and elbow with only slight fanning movements of the fingers of the right hand.

R. S. V. There is far greater recovery of motor function than in the control. The motor performance in the present animal is very good; it climbs about using all extremities and is able to support itself with the fingers of the right hand. It is able to climb across the roof of the cage upside down and in so doing clings with all four extremities, although it is obvious that the grasp on the right in both the fingers and toes is weaker than normal. There are individual prehensile movements, though awkward, of the fingers and toes on the right. There is occasionally a trace of reflex grasping in the right hand. K. J.s are bilaterally equal and there is no difference in resistance to passive manipulation. The Rossolimo is not present on either side and no atrophy is present.

R. S. VI. There are very rapid and accurate movements on the right side, although neither speed nor accuracy are as great as on the left. The animal is able to use the right fingers for support and can hang from the side of the cage using the right side only. K. J.s are bilaterally equal and there is no difference in resistance to passive manipulation. The Rossolimo is faintly positive on the right only. There is no atrophy.

Three weeks postoperatively.

R. S. I. This animal shows a far greater motor deficit than do the treated animals (Fig. 2). It uses all four extremities, but the right arm is hardly useful at all and the right leg is not strong enough to bear weight. The fingers are not often used, while the toes are used only occasionally when they strike against the bars of the cage. There is no reflex grasping. Posture is such that the right extremities extend more than those of the left. There is no increase in tone on the right. The K. J. is slightly increased on the right. The Rossolimo is present on the right only.

R. S. II. This animal, which was used as a control and has received no medication, is now to be started on doryl and thiamin to see what effect this medication has in the chronic paretic. It now shows little and poor use of the right extremities, while there is marked weakness of the right leg. The right arm is little used for support. There is no finger and but little toe grip. The movements in this animal, as in R. S. I, are slow and incoordinate. The K. J.s are equal and the right leg is hypotonic. The Rossolimo reflex is markedly present on the right and slightly present on the left.

Medication: The animal will henceforth receive:—Thiamin 5 mg. q.d.
Doryl 0.25 mg. b.i.d.

R. S. V. Continues to show an increased rate of recovery. It climbs upside down and vertically with excellent agility and continues to use the right leg with a dexterity almost equal to that of the left (Fig. 2). The right arm is also used in an agile fashion, but not to the same degree as the leg. Movements of both extremities on the right are quick and well coordinated. K. J.s are bilaterally equal and hyperactive. The Rossolimo is absent on the right as is the placing reaction. The tone of the right leg is less than that of the left. The feet are of equal temperature.

R. S. VI. Is also active and agile, using both extremities on the right very well. The leg is about as agile as the normal leg, while the arm is less so though motions are fairly quick and prehension quite strong. K. J.s are equal and a slightly positive Rossolimo is present on the right only. Tone in the right leg is fair. Although the animal shows far less deficit than does the control, the degree of recovery is slightly less than that of R. S. V.

Four weeks postoperatively.

R. S. I. This animal has shown no change from the above observations.

R. S. II. Although doryl was started only a few days ago, the change in performance is remarkable. It seems to have entirely caught up with the stage of recovery exhibited by the strychnine-treated animals and possibly also with R. S. V and VI as well. The right extremities appear looser, move more rapidly and more freely, and individual movements are more easily performed without the accessory grosser movements of adjacent muscles which one sees in the animals recovering from paresis. Fingers and toes are used for climbing and the right leg can be used for the sole support of the animal. The right arm is used slightly less well but it also shows good coordination and speed of movement. The K. J.s are equal.

R. S. IV. This animal, which has received strychnine and thiamin medication since operation, will now be started on doryl to see if this drug will produce further recovery. The animal is not very active, although its agility is definitely better than that of the control. Postural adjustments in the right arm seem to be the same as in the control. Both arm and leg on the right are used in climbing, but coordination is not very good. The K. J. on the right is slightly hypoactive. The Rossolimo is positive bilaterally. The right leg is still almost flaccid.

Medication: This animal will henceforth receive:—Thiamin 5 mg. q. d.
Doryl 0.25 mg. b.i.d.

R. S. V. Motor function on the right side is really excellent. The right extremities move quickly and almost as accurately as those of the left. Posture is almost symmetrical, although the extremities on the right occasionally lag behind movements on the left. Sitting postural adjustments are normal in the right leg. K. J.s are hyperactive and equal. Rossolimo is absent.

R. S. VI. There is extremely good motor function on the right, although perhaps not quite so good as that of R. S. V. The leg is used perfectly for support, for grasping, and in the movements of rhythmic progression. The arm, however, does not function as rapidly or accurately and the right hand is only poorly used for grasping. K. J.s are bilaterally equal and hyperactive; the Rossolimo is bilaterally absent.

Five weeks postoperatively.

R. S. I. Very little change has occurred. The right arm and leg are used poorly for climbing and running and are usually held hyperextended when at rest. The fingers and toes are limp, but the remainder of the extremity is rigidly held in extension while the animal is moving. Very often the movements are much slower and less accurate on the right than those of the left side. The deficit becomes much worse with fatigue and with emotion. The K. J. is less active on the right. Rossolimo is present on the right and absent on the left.

R. S. II. This animal is active and now much more agile than the control animal. The arm is used with good prehension in the hand. All movements are much quicker and better coordinated than those of the control. The K. J. is slightly hypoactive and the Rossolimo is negative.
Medication: It has been receiving doryl and thiamin for two weeks and will now be deprived of all medication to see if regression occurs.

R. S. IV. The arm and leg are now quite well used and postural adjustments are better than those of the control. It seems as though this animal has shown definite increase in the rate of recovery since it was put on doryl medication, but it is reacting severely to doryl. It vomits, and after the usual dose of 0.25 mg. it appears to be much more knocked out than do the other animals. On one occasion it was still ill and salivating profusely three hours after medication.
Medication: For this reason, the daily dose of doryl will be reduced to 0.12 mg. b.i.d., reducing this to one dose per day if the animal continues to react.

R. S. V. This animal shows by far the best performance of any monkey with the exception of R. S. VI. At times it is difficult to see much paresis, but with fatigue the right side becomes less accurate than the left. When first let out of the cage it can hang from either arm and uses both legs equally well, moving the extremities on the right very quickly and accurately. There is no Rossolimo and the K. J.s are equal.

R. S. VI. There is no great change since the above note. Although the animal is very active and agile, coordination and speed of movement of the right side are not quite so good as those of R. S. V. The K. J.s are bilaterally hyperactive and equal. The Rossolimo is slightly positive on the right side alone. Tone on the right is quite good.

Six weeks postoperatively.

R. S. I. There has been little or no further improvement. The right side is still very paretic and remains more extended than the left in all rhythmic movements. There is practically no use of fingers and toes on the right. The K. J. is greater on the left and the Rossolimo is absent bilaterally.

R. S. II. This animal shows much greater motor power on the right than does the control. Fingers and toes are used fairly well but are rather weak. Posture is very much more nearly equal on the two sides. Movements are quick and the sagging and extension on the right are not so evident as in the control. K. J.s are bilaterally equal. Rossolimo is present on the right, absent on the left. There is slight atrophy in the thigh and gastrocnemius. The previous improvement has thus not regressed as yet, although medication has been stopped.

R. S. IV. Although this animal is inert and difficult to excite, there is no question but that its motor status on the right has improved under doryl medication over that which occurred with strychnine. It is, however, not as well off as those animals injected with doryl from the beginning. The K. J.s are about equal. The Rossolimo is still present on the right. There is a slight atrophy on the right.

R. S. V. This continues to be the best animal. The legs are used equally well in all respects and are almost indistinguishable in regard to coordination and skill. The arm is also used almost as well as the normal arm, but coordination is a little poor at times and the paretic extremity can be recognized easily. The knee-jerks are hyperactive and the Rossolimo is bilaterally negative. Until it is sacrificed this animal will be left on medication to see if further recovery occurs as compared with R. S. VI for which medication has been stopped.

Eight weeks postoperatively.

R. S. I. There is little if any improvement over the past four weeks. It climbs actively, but coordination and agility are poor. It uses the right leg moderately well but obviously not as well as the left and movements are slower and coordination is not accurate. The arm is not used well in either climbing or running. Prehension is present in the arm to some extent, but posture is that of extension. The K. J.s are equal bilaterally, while the Rossolimo is positive on the right only.

R. S. II. Continues to be much better than R. S. I. The right leg is used with almost the same agility as the normal one and movements are brisk. The arm is not used extensively, but its coordination and skill are much better than in the control animal. Occasional slight reflex grasping is seen in the right hand. It has maintained its recovery since doryl was stopped two weeks ago. The K. J.s are equal and hyperactive. The Rossolimo is weakly positive bilaterally. Tone is equal in the two legs.

R. S. IV. It uses its extremities definitely much better than does the control animal, but because of the difference in activity it is difficult to compare its behavior with the other animals of this series, since it is still hypoactive. It seems to show more recovery than R. S. III which received strychnine. The K. J.s are hypoactive and the right is slightly greater than the left. The Rossolimo is positive on the right only. The right leg is quite hypotonic.

R. S. V. Although there is remarkable recovery of function, there is still a noticeable paresis on the right which is manifested by a slight lag in movement on that side, by some weakness of the fingers and toes even though they grasp adequately, and by some awkwardness in posture. The animal of course picks food with the right hand, although it always prefers the left. The K. J.s are equal and hyperactive and there is no Rossolimo on either side.

R. S. VI. This animal, in contrast to the others of this series, has been left on doryl and thiamin medication until now. It has the best function on the right side of any of this series and seems to have recovered further under continued medication. It tears about the corridor jumping from shelf to shelf across the aisle but shows an evident deficit on the right side in spite of its excellent agility. The posture on the right is about the same as that on the left. Movement on the paretic side is almost as rapid as on the left, but the strength of the fingers and toes seems to be less. Feeding is done with the left hand assisted occasionally by the right.

Results:

(1) It is evident that the two animals which received doryl and thiamin from the time of operation (R. S. V and VI) have shown an excellent degree of recovery of motor function. (2) That this therapy is of use in "chronic" animals is demonstrated by the one animal given doryl and thiamin after three weeks without medication (R. S. II); this animal also showed good recovery of motor function but not to the degree seen in those in which medication was instituted immediately postoperatively. (3) The one animal given doryl after four weeks of strychnine therapy (R. S. IV) also seemed to show a greater rate of recovery than did its mate on strychnine and thiamin.

EXPERIMENT III. *Thiamin.* The increase in the rate of recovery noted in the treated animals described above might be due to either thiamin or to the doryl given in those cases. To elucidate further the part played by thiamin in this effect, two monkeys were given thiamin only. One animal (R. S. X) was compared with an unmedicated control (R. S. IX) of equal size. A second (R. S. XII) was compared with one doryl (R. S. XIV) and one doryl-atropine (R. S. XIII) injected monkey. Representative excerpts from the protocols of the first two animals follow.

Operation:	R. S. IX	3/2/42	Wt. 4.8 kg.
	R. S. X	3/3/42	Wt. 4.6 kg.

One week postoperatively.

R. S. IX. (Control.) Though active, this animal is clumsy and also tires easily. The right leg is used actively but tires rapidly. The K. J. is slightly less on the right and the Rossolimo is negative bilaterally. The right leg is hypotonic.

R. S. X. Though not so active as R. S. IX, this animal shows more agility. The leg is used with more dexterity and does not tire so easily. The arm is used slightly more than the control, but here coordination and agility seem to be about the same. The K. J.s are equal and the Rossolimo is positive on the right only. The right leg is hypotonic.

Medication: Since the day after operation, this animal has been given a daily injection of thiamin 5 mg.

Two weeks postoperatively.

R. S. IX. This animal is very active but agility and coordination are poor. The arm and leg are both used in climbing and running but with little skill. The foot is occasionally turned over in walking. For the most part the right extremities are extended. The K. J. is greater on the right and a positive Rossolimo is found on the right.

R. S. X. More recovery is certainly present in this animal than in the control. The leg is used with greater skill and strength and the foot is not turned under or dragged when walking. The arm is less skillfully used than the leg, but better than that of R. S. IX. Prehension is possible in the foot and hand. The K. J. is greater on the left and a positive Rossolimo is present bilaterally.

Three weeks postoperatively.

R. S. IX. Compared with R. S. X, the deficit of the present animal is greater. It moves the right side in rhythmic progression but uses the extremities very little for support or grasping. The extremities on the right are usually more extended than those on the left. The fingers and toes on the right appear flaccid and are seldom flexed.

R. S. X. Its posture is more nearly equal on the two sides and movements are more rapid on the right than those of R. S. IX, but the animal is extremely clumsy and does not use the fingers and toes for support very well and definitely not nearly so well as do those animals receiving doryl and thiamin.

Five weeks postoperatively.

R. S. IX. Continues to show a slightly greater deficit than R. S. X. Although very active, coordination is poor and movements are slow on the right. The foot can be used for support but the toes are little used. The arm is used in rhythmic progression but it is practically useless for support. Reflex grasping is occasionally present. Postural adjustments are sometimes present in the right leg. The K. J.s are bilaterally hypoactive and equal.

R. S. X. Movements of the leg and arm are somewhat quicker and more accurate than in the control. One of the most definite differences lies in the fact that this animal uses the right arm more. It climbs about using both of the right extremities rather poorly. Reflex grasping is very marked and the right extremities tire easily, after which they hang extended as they did immediately after operation. The K. J.s are bilaterally somewhat hypoactive, the right being greater.

Results:

It is quite definite that the animal given thiamin alone showed less motor deficit and a greater rate of recovery of motor function than did the untreated control. A second animal (R. S. XII), also treated with thiamin alone, recovered about equally (its protocol is not given here). Although the thiamin-treated animals showed superior agility as compared with the control, the motor deficit was much greater than in those animals treated with doryl. Thus, although thiamin does exert some effect on the rate of recovery, it cannot explain the greater rate of recovery seen in the doryl-treated animals.

EXPERIMENT IV. *Doryl and atropine.* Since it is desirable to produce an increase in the rate of recovery of motor function without the disagreeable effects of parasympathetic stimulation produced by doryl, it was thought possible that atropine might prevent or lessen the muscarinic effects of doryl and leave untouched its nicotinic effect which stimulates the rate of recovery. Accordingly doryl, atropine, and thiamin were given to two animals (R. S. XI and XIII) and one untreated animal of the same age served as control (R. S. IX). Abstracts from the protocol of one treated and one control monkey follow.

Operation:	R. S. IX	3/2/42	Wt. 4.8 kg.
	R. S. XI	3/4/42	Wt. 4.6 kg.

One week postoperatively.

R. S. IX. (Control.) Though active, this animal is clumsy and also tires easily. The right leg is actively used with fair prehension but tires quite rapidly. The arm is used occasionally but likewise fatigues quickly. The K. J. is slightly less on the right and the Rossolimo is negative bilaterally. The right leg is hypotonic.

R. S. XI. In the general activity of running and climbing, this animal is definitely superior to both the control animal (R. S. IX) and to the animal treated with thiamin alone (R. S. X, see Expt. IV) which was also operated upon at approximately the same time. Agility is good and coordination of the right leg is better than in the previously mentioned animals. Speed of movement and accuracy is better than in the control or in the thiamin-treated animal. The K. J. is greater on the right and both are hyperactive. The Rossolimo is positive bilaterally.

Medication: Since the day after operation this animal has received—
Atropine 0.1 mg. b.i.d.
Doryl 0.25 mg. b.i.d.
Thiamin 5.0 mg. q.d.

Two weeks postoperatively.

R. S. IX. Is active but agility and coordination are poor. The arm and leg are both used but with little skill. The foot is occasionally turned over in walking. For the most part the extremities are extended. The K. J. is greater on the right and a positive Rossolimo is found on the same side only.

R. S. XI. Although this animal is not very active, its skill and coordination are better than either the control or R. S. X (thiamin) and its general behavior is obviously superior to both. The arm and leg are used well, the leg more so than the arm. Prehension is present in both foot and hand.

Three weeks postoperatively.

R. S. IX. The motor deficit of this animal is great as compared with the other. It moves the right side in rhythmic progression but uses the extremities very little for support or grasping. Posture on the right is usually more extended than that on the left. The fingers and toes are seldom flexed.

R. S. XI. This animal has greater recovery than either R. S. IX or R. S. X. Movements are more rapid on the right side, posture is more nearly equal to that of the left. It has some use of the fingers but they are too weak for its support in climbing.

Five weeks postoperatively.

R. S. XI. The animal now shows a vast improvement in motor function over either the control or R. S. X. The two legs are used with about the same agility, coordination, and speed. The arm is less well used, but its use is far superior to that of the others. Postural adjustments are present in the leg. Knee-jerks are bilaterally hyperactive; greater in the right than on the left. The Rossolimo is slightly positive bilaterally and the right leg is slightly hypotonic.

This animal during its course of treatment has shown none of the disagreeable symptoms of doryl administration—the sweating and salivation in particular—as these have been inhibited by the atropine. However, its recovery of function has been excellent.

Results:

It has been demonstrated that giving atropine in small doses to an animal receiving doryl and thiamin prevents the undesirable muscarinic effects of doryl but does not influence the latter's effect on the rate of recovery, for the two animals so treated showed as great an increase in the rate of recovery as did those treated with doryl and thiamin. The rate of recovery in the atropine- and doryl-treated animals was far superior to that obtained in the animal treated with thiamin alone. Thus thiamin is not alone responsible. The increased rate of recovery in the doryl-treated animals must therefore be ascribed to this drug's nicotinic action.

EXPERIMENT V. *Comparison of doryl, doryl and atropine, and thiamin.* This experiment was carried out to compare the above drugs, since the previous experiments have shown that each of the drugs was in some measure effective in augmenting recovery.

Operations:	R. S. XII	4/8/42	Wt. 4.25 kg.
	R. S. XIII	4/10/42	Wt. 4.6 kg.
	R. S. XIV	4/11/42	Wt. 4.5 kg.

Medication: From the day after operation these animals received—

R. S. XII	Thiamin	5.0 mg.	q.d.
R. S. XIII	Doryl	0.25 mg.	b.i.d.
	Atropine	0.1 mg.	b.i.d.

Since the protocols show histories much like those given above, no details are here given.

Results:

The animal injected with thiamin alone showed moderate recovery. That which received doryl alone showed much greater recovery. The animal receiving doryl and atropine recovered as much as did the one which received doryl alone; possibly the recovery was greater. The one injected with doryl alone exhibited, of course, all the side effects of the drug,—sweating, pallor, salivation, and gastrointestinal distress—while that which received atropine in addition to doryl had none of these untoward symptoms.

EXPERIMENT VI. *Late effects of cholinergic drugs.* Four of these animals (R. S. IX, XII, XIII, and XIV) have been kept six months since operation. The drugs given were as follows:

R. S. IX, control.
R. S. XII, thiamin.
R. S. XIII, doryl and atropine.
R. S. XIV, doryl.

When drugs were administered this was done during the first three months following operation, no animal receiving any therapeutic dosage during the last three months. Examination at the end of that time revealed that the changes effective immediately after drug administration was begun were lasting throughout this six-month period. The control animal and the one receiving thiamin showed greater motor deficit than did the other two, that of the control being the greatest. Of the two others—one given doryl, the other doryl and atropine,—there was very markedly greater skill and coordination in the use of the right hand and foot than in the first two. The animal which had received doryl and atropine was, if anything, somewhat better than the one which had received doryl only. All four showed some improvement over the status as recorded three months before when medication was stopped.

Discussion

It has thus been experimentally demonstrated that the rate of recovery from central nervous system lesions can be materially increased by medication, since strychnine, thiamin, and doryl have all been found to increase recovery. The possible mechanisms of the drug action and of the recovery processes will now be discussed.

1. *Doryl:* After it became evident that acetylcholine was a transmitter of nerve impulses from motor nerves to striated muscle or from neuron to neuron in the autonomic system, many neurophysiologists envisaged the possibility of the same mechanism at the central synapses and Dale[20] called attention to the fact that Sherrington[81] looked upon the transmission of excitation from a motor nerve ending to a voluntary muscle as probably furnishing a pattern of the changes which occur at a central synapse. Confirmation for this opinion was obtained by Dikshit,[22] who demonstrated the presence of acetylcholine in the cerebral hemispheres, in the cerebellum, and in even greater quantities in the basal ganglia. Later, Chute, Feldberg, and Smyth[17] found that acetylcholine was liberated from the perfused cat brain.

In order to explain the time relations of central synaptic transmission, it had to be shown that choline esterase, which inactivates acetylcholine, existed in sufficient concentration at synaptic regions to destroy quickly the acetylcholine liberated. This piece of evidence was supplied by Nachmansohn,[67] who concluded furthermore that in the gray matter of the central nervous system choline esterase is not evenly distributed but is present in higher concentrations at synaptic regions. The values obtained were high enough to permit the removal of that amount of acetylcholine necessary for a transmitter function during the short refractory period of the central nervous units. In addition, Nachmansohn found that choline esterase was present in diminishing quantities in cerebral cortex and cerebellum and in high concentrations in the basal ganglia, thus indirectly confirming the observations of Dikshit on the distribution of acetylcholine in the brain. Later, the investigations of Nachmansohn, Coates, and Cox[69] and of Nachmansohn and Meyerhof[70] led Nachmansohn[68] to state that "acetylcholine is intrinsically connected with the electrical changes occurring during nerve activity at the neuronal surface. Thus the controversy between 'electrical' and 'chemical' theory of transmission of nerve impulses becomes meaningless. Both are signs of the same event."

The effect of acetylcholine on cortical potentials has been investigated by Chatfield and Dempsey[15] and Williams and Russell[92] described the effects of eserine on the electroencephalograms of epileptic patients. Both the latter investigators and Williams[91] found that administration of acetylcholine and allied substances to patients with petit mal epilepsy caused an increase in the electroencephalographic outbursts and in the clinical attacks. Recently Brenner, Merritt, and Maguire[7] have reported local increase in E. E. G. at the site of application of acetylcholine to the surface of the brain. Most of the experimental data, therefore, indicate that acetylcholine in appropriate doses stimulates the central nervous system as would be expected on the basis of the neurohumoral theory.

Since it was desirable to eliminate the peripheral effects (salivation, sweating, vasodilatation, etc.) of doryl if the central actions which influence the rate of recovery could remain active, the effect of doryl and atropine was tried. The literature seemed to be divided on the subject of whether atropine abolishes the central actions of the cholinergic drugs. However, observations showed that the rate of recovery of motor function of the two animals so treated was stimulated to the same degree as by doryl alone.

Since all authorities are agreed that atropine will abolish the peripheral (muscarinic) effects of acetylcholine and the cholinergic drugs, and in this investigation also the signs of muscarinic stimulation were absent or minimal when atropine was given with doryl, the increase in the rate of recovery of motor function must be ascribed to the nicotinic action of the drug,—in this instance upon the central hemispheres.

2. *Thiamin:* It is well known that thiamin is a necessary vitamin to the normal functioning of the organism and especially the central nervous system. A deficiency of this substance in the diet is also known to produce lesions of the nervous system in both man and experimental animals. Gildea, Kattwinkel, and Castle[39] fed dogs on a diet deficient in the anti-neuritic and pellagra-preventing portions of the vitamin B complex and produced lesions similar in many respects to those of combined system disease in man. Zimmerman and Burack[94] found that dogs on a diet deficient in vitamin B_1 developed spastic paralysis and tonic spasms not unlike those seen in strychnine poisoning, while the anatomic changes consisted of extensive demyelinization of the sciatic, median, ulnar, and vagus nerves

and the brachial plexuses. They found that dogs in which a chronic deficiency state was produced showed demyelinization of the peripheral nerves and also minimal lesions of the same variety in the columns of Goll. Recent interest in the subject has produced a very large literature which need not be quoted here.

Since it was possible that this pharmacological action of thiamin might be related in some way to the acetylcholine-choline esterase system, Glick and Antopol[41] studied the effect of thiamin on the choline esterase concentrations in horse and rat serum. They reported that inhibition of choline esterase by the vitamin was obtained, but only with concentrations of thiamin in excess of those known at present to occur within the living organism. The affinity of thiamin for choline esterase was calculated to be 26 times that of acetylcholine for the enzyme. Aring, Evans, and Spies[1] also showed that serum choline esterase was inhibited in vivo by thiamin. Byer and Harpuder,[13] on the other hand, claimed that thiamin had no effect upon the choline esterase in the tissues.

If it is true that the pharmacological action of thiamin is to inactivate choline esterase, by this method augmenting the action of acetylcholine, it would be expected that under the proper conditions thiamin should of itself stimulate the nervous system. Hence, it was not surprising that Brecht[5] was able to produce vasoconstriction in frogs by vitamin B_1 in concentrations of from $1:10^8$ to $1:10^4$. He also noted that the vasoconstrictor effect of acetylcholine in his preparation was intensified by the vitamin. That thiamin may have a nicotinic action was demonstrated by Byer and Harpuder,[13] who noted that thiamin is a contractor substance for the eserinized leech preparation. It would also be anticipated that it would stimulate the central nervous system of mammals, and Erspamer[26] demonstrated that thiamin, in intravenous doses of 200 mg./kg., killed rats by respiratory paralysis and that the intravenous injection of sublethal doses of thiamin increased the intoxication from sublethal doses of acetylcholine and sometimes caused death. And lastly, Mano[62] claimed that vitamin B_1 produced central motor and respiratory paralysis in frogs. He found that small doses injected into mice stimulated respiration while large doses produced chronic cramps and respiratory arrest. Intracisternal injection of 5 mg./kg. was noted to produce heavy convulsions. Thiamin solution in a concentration of 10^{-5} augments while a concentration of 10^{-3} decreases the contraction of skeletal muscle in rabbits. In summary, the consensus of opinion seems to be that the pharmacologic action of thiamin is to stimulate the nervous system in the same manner as acetylcholine. It would then be expected that thiamin would sensitize nerve trunks to electrical stimulation and this was shown to be the case by Minz and Agid.[64]

Although the above facts would indicate that thiamin acts as an inhibitor of choline esterase and thus that its actions would be those of the acetylcholine left free to act in the tissues, the studies of Nachmansohn and Steinbach[71] support the assumption that one function of thiamin may be its participation in the formation of acetic acid for acetylcholine. They do not admit that thiamin may have a pharmacologic action of its own which is physiologically important. It is true, however, that thiamin definitely has an enzymatic action in the oxidative processes involved in nerve cell metabolism, and Spies, Aring, Gelperin, and Bean[83] showed that vitamin B_1 is utilized as cocarboxylase in the body. Nachmansohn and Steinbach[71] demonstrated that cocarboxylase is concentrated at or near the nerve sheath, only a negligible amount being present in the axoplasm. Since Boell and Nachmansohn[4] showed that choline esterase is also found almost entirely in the sheath, it is obvious that the enzymatic action of this vitamin may be intimately connected with the metabolism of acetylcholine.

Aring, Evans, and Spies[1] examined the peripheral nerves of thiamin-deficient patients under treatment with crystalline vitamin B_1, and found marked loss and degeneration of myelin sheaths in the terminal portions of the internal branch of the anterior tibial nerve. The axons in these peripheral nerves were, on the whole, normal. In cases in which the peripheral nerve was examined as late as eleven months after treatment was instituted, the loss of myelin sheaths was severe. This study lends further support to the hypothesis that the initial spectacular improvement following thiamin therapy which is experienced by sufferers from nutritional neuritis is on a humoral basis.

The action of thiamin would therefore seem to be twofold:—1) An enzymatic action involving nerve metabolism or more specifically acetylcholine metabolism. 2) A pharmacological action consisting of inhibition of choline esterase with all the concomitant effects thereby produced. The first action is definitely established, while the second may perhaps only be obtained with concentrations of thiamin higher than those physiologically present in the organism.

On the basis of this knowledge, it is interesting to speculate on the results obtained by the administration of thiamin alone to the two animals in the present investigation. Some increase in the rate of recovery of motor function was produced in each, although not to the same extent as the marked increase noted with doryl and thiamin, or strychnine and thiamin medication. This effect can be ascribed to either the pharmacologic or enzymatic actions of the vitamin. Since an effect was produced, one possibility is that either the laboratory diet fed the animals was deficient in the vitamin during the process of postoperative repair which increased the requirements for thiamin to a point beyond that furnished. The other possibility is that the effect was produced by a pharmacological action of thiamin. If, in the doses used, it inhibited choline esterase in the treated animals, the acetylcholine normally liberated by the nervous system would have a greater action.

3. *Strychnine:* Recent work has indicated that strychnine acts on the nervous system ultimately as a cholinergic stimulant. Dusser de Barenne,[23] with McCulloch,[25] and with Garol and McCulloch[24] has described the action of this drug on both the spinal cord and the cerebral cortex and conceives of its action, for various well-substantiated reasons, as a facilitator to trans-synaptic transmission. Bartley[2] described the asynchronism produced by the local application of strychnine to the optic cortex, and Heinbecker and Bartley[44] further developed this conception of the manner of action of strychnine. Bremer[6] suggested that the electrical pulsations in the spinal cord produced by strychnine were due to a synchronization of the individual neuronal discharges by an intercellular electrical field phenomenon independent of synapses.

The first hint as to the nature of the intimate mechanism by which strychnine stimulates the nervous system was found by Heubner,[46] who noted that 'reflex tetanus' could be induced in frogs as regularly by physostigmine as by strychnine. Sjöstrand[82] carried this one step further when he noted that potential changes caused by local application of strychnine to the cortex of rabbits was increased in amplitude and made more regular if acetylcholine or especially eserine was put on the cortex before, together with, or after strychnine. Loewi et al.[59] reported that in the brain of the frog the amount of acetylcholine present rose from a normal level to a value twice as high after an intoxication by strychnine which produced convulsions. Cortell, Feldman, and Gellhorn[19] found that strychnine convulsions in frogs were accompanied by a marked increase in the acetylcholine content of the brain and spinal cord, while there was no significant alteration in the choline esterase activity.

It remained for Nachmansohn,[67] however, to formulate an adequate theory of this drug's mode of action. He noted[66] that strychnine in very weak concentrations inhibited choline esterase and this observation led him to the conclusion that strychnine causes excitation in the nervous system by this action on an enzyme strongly concentrated in the region of the central synapses. The anti-esterasic action of strychnine was confirmed by Kaswin.[52] All parts of the central nervous system on which strychnine acts—spinal cord, optical and acoustical centers, etc.,—contain large amounts of choline esterase. Thus strychnine probably acts as an anti-esterasic substance. This agrees with the hypothesis of Sherrington[81] that strychnine may poison an inhibitor mechanism at central synapses. In the light of this explanation of the action of strychnine, it is interesting to note that Cooper[18] reported that pigeons affected with polyneuritis to such a degree that untreated they would die within 24 hours, when given oral doses of from 0.2 to 25 mg. of strychnine, remained alive for as long as from 2 to 5 days, although the symptoms of polyneuritis remained as acute as ever.

Since it has been established that strychnine inhibits choline esterase and stimulates the central nervous system by the acetylcholine thereby allowed to act, it follows that strychnine should admirably fulfill the qualifications of a cholinergic stimulant. In the present investigation it was found that those animals receiving strychnine and thiamin medication exhibited an increased rate of recovery of motor function as compared with the control animals under no treatment. From our present knowledge that strychnine acts as a cholinergic stimulant, it would be expected that it would increase the rate of recovery in the same manner as did doryl, the other cholinergic stimulant used in this investigation.

4. *Combination of drugs:* The fact that the strychnine-treated animals did not show so much recovery as did those animals treated with doryl demands comment. Since it was known that cholinergic stimulation will increase the rate of recovery, the most plausible

explanation for the failure of the strychnine-treated animals to show an equivalent increase in recovery was that the dosage of strychnine was suboptimal for a maximal effect. Accordingly, one of the strychnine-treated animals (R. S. IV), after three weeks of medication, was reduced to one half the previous daily dose of strychnine. As the dose previously given to both animals was almost at the subconvulsive level, it was thought that the most likely possibility was that it might be too high. However, the animal receiving the reduced strychnine dosage showed no increase in the rate of recovery over the animal receiving the full dose (R. S. III). The two possible explanations of this were either 1) that the full dose of strychnine was itself not high enough, or 2) that due to an individual variation of the animal, it was not capable of further recovery. To rule out the latter possibility, this animal, after receiving the reduced dosage of strychnine for over a week, was put on the same daily dosage of doryl as that which the other animals so treated had received. Under this medication, some further increase in the rate of recovery occurred. Hence, this animal was capable of further recovery, and the only explanation for the failure of the animal receiving the full dose of strychnine to show as much increase in the rate of recovery of motor function as did those animals given doryl medication must be ascribed to suboptimal dosage of strychnine.

In considering the action of doryl, one of the possibilities was that it produces its beneficial effect by a vasodilating action. Such an effect may, however, appear without vasodilation, for strychnine is not known to have any effect on the craniocerebral vasomotor system. Since it is assumed that strychnine acts on the central nervous system by inhibiting choline esterase, or essentially as a cholinergic stimulant, it may be assumed that doryl, another cholinergic stimulant, can act in the same way.

Granted, then, that substances such as doryl, thiamin, and strychnine which facilitate the action of acetylcholine within the body, can increase recovery of function, it is yet to be explained by what mechanism recovery of motor function takes place after removal of areas of the central nervous system which were originally part of the pathway through which impulses travel to produce this function.

Vicarious function. Goldstein[42] questions the existence of true vicarious function. He says, "A true recovery of function comes only as a result of restoration of the anatomical substratum, or under exceedingly rare and limited conditions, by a tedious process of relearning with the help of a remnant of the substratum which participated in the original function." He considers that most of the apparent recovery is really a readjustment by which the organism manages to get along without the functions which have been lost.

On the other hand, most workers have emphasized the plasticity of nervous organization and imply that the capacity for genuine restitution of function is always present. The assumption of function by other portions of the nervous system was first postulated by Fritsch and Hitzig.[33] They proposed this theory of vicarious function to account for the recovery of their dogs from the cerebral paralysis produced by removal of the motor cortex of one hemisphere. Foerster[28] thought that under the proper conditions the capacities for genuine restitution of function were almost unlimited and that functions may be taken over by structures not previously concerned in them. This was further elaborated by Bethe and Fischer.[3]

Functional reorganization. Jacobsen, Taylor, and Haslerud[48] postulate that following cortical lesions a dynamic reorganization occurs, within a partially destroyed system, which is not vicarious in nature. The locus of this dynamic reorganization has been indicated by many observers, although the exact details have not as yet been formulated. Gardner[35] reported a case of a woman who, after removal of an entire hemisphere, was able to move the contralateral lower extremity. Foerster[29] pointed out that in human beings, after destruction of the precentral cortex, there is recovery of voluntary motor power which is integrated by extrapyramidal cortical areas of the same hemisphere. He also demonstrated the influence of the ipsilateral hemisphere on the paresis in a case in which a degree of voluntary movements was restored to the hemiplegic fingers. Fulton[34] and Bucy[9] maintain that areas 4 and 6 constitute the origin of the major motor projection systems and that removal of these areas from one hemisphere produces a motor deficit entirely comparable to that produced by hemidecortication. Kennard[53] thought that the highly developed and coordinated motor performance which is present in the monkey deprived of motor and premotor cortex in infancy is due to integration from other cortical regions, and Lashley[56] states, "I believe that we must recognize that nervous tissue can reconstitute itself functionally in some way which resembles the reconstitution of structure in regeneration." Hence, most of the recent investigators seem to conceive of the recovery of function which occurs following cortical lesions as some form of functional reorganization of the remaining cerebral tissue.

Possible mechanisms of functional reorganization. Analysis of the concept of functional reorganization reveals that it requires a process of synaptic modification which must also be involved in such processes as conditioning and learning. The problem of synaptic modification is a basic one in neurophysiology and many theories have appeared in past years in the attempt to throw some light on the problem.

Regeneration. Although the bodies of the nerve cells were removed in the ablations which were performed in this investigation, it is necessary to consider what part regeneration may play in the restitution of function following lesions of the central nervous system. Ramon y Cajal,[76] in his classic descriptions of degeneration and regeneration on the cortex, wrote "We have stated that intra- as well as the extra-axonic neoformations grow for a certain time, sometimes ramify in a complicated way, form terminal buds and wings and finally, paralyzed by insuperable obstacles, come to a stop not far from the parent axon." Pfeifer[74] studied the cylindrical tracts of the brain following puncture and in these areas found newly formed axons, some of which were myelinated. Likwise, Glass,[40] after sectioning a four-year-old bullet tract, claimed to have found some newly formed axons, some of which were myelinated. Rio-Hortega and Penfield,[77] during a study of the cicatrix following stab wounds in the cerebral hemispheres of dogs, confirmed Cajal's observation that axons regenerate to a limited extent, and reported that they had seen genuine plexuses of newly formed axons about small areas of cerebral softening where vascular and connective regeneration was taking place. But Lee,[57] as well as most of the above workers, agrees that regeneration does not occur in the cerebral hemispheres to an extent sufficient to have any functional significance.

In the spinal cord, however, Gerard and Grinker[38] found inconclusive evidence of regeneration, while Sugar and Gerard[85] definitely established that regeneration is possible. Following complete transection of the spinal cords of rats, they noted that the spinal neurons with adequate blood supply started to regenerate their cut processes. These fibers grew along structural pathways like peripheral nerves and used bands of glial nuclei when possible and also scar tissue running transversely across the cord. When they successfully crossed the scar, restoring anatomical continuity, nervous transmission across the lesion was demonstrated.

Chemical and mechanical theories. The chemical theory of nerve growth, developed chiefly by Ramon y Cajal[75] and by Forssman,[30, 31] considers nerve orientation to be a chemotactic effect; specific substances diffusing from localized centers would attract the nerve fibers. The mechanical viewpoint, advocated by His,[47] Harrison,[43] and others, attributes to solid mechanical structures the rôle of tracks guiding the nerve fiber on its way. This theory has had recent confirmation in the experimental work of Weiss.[90] But although these theories are of interest embryologically, since no growth in the cerebrum has been demonstrated which could explain the restoration of function, these interesting speculations have no immediate bearing here.

Physico-chemical changes. In the attempt to shed some light on the mechanism of synaptic modification by which recovery of function following cerebral lesions occurs, several interesting though somewhat visionary theories have evolved. Cason[14] and Washburne[89] explained this mechanism in terms of ionic interchange. Johnson,[49] on the other hand, postulated that a tuning of membrane film-frequencies was responsible for the process. The essential basis of both such theories is the simultaneous activation of a neuron from two sources. At the present stage of our knowledge, these theories likewise have little practical application to the present problem.

Closed neural chain theory. Another interesting possibility of the method by which functional reorganization might occur in the cerebral hemispheres is suggested by some observations of Lorente de Nó.[60] He demonstrated that internuncial neurons are arranged in two types of chains:—multiple chains, in which several collaterals of a single fiber, after traversing one or more synapses, converge upon a motor neuron; and closed chains, in which a collateral excites a circle composed of several neurons. In the latter case, the chain of neurons may maintain its activity indefinitely in the absence of peripheral afferent impulses. Closed chains, set into activity either by stimulation by a 'learning' procedure or other methods, would continue in the absence of any external excitation and would summate with otherwise inadequate afferent impulses to produce the motor effects previously abolished by the cerebral lesion. As a consequence of this hypothesis, however, it might be assumed that anesthetics, which have been shown by Derbyshire, Rempel, Forbes, and Lambert[21] to modify profoundly cortical action potentials and thereby interfere with states of excitation, would produce a loss of the recovered function. This is not the case, however, and accordingly this theory cannot alone explain the phenomena of functional reorganization.

Electrical theory. The electrical hypothesis, brought forward by Strasser,[84] Kappers,[51] and others, postulates a direct orienting effect of electrical potential differences on the nerve fiber. This concept was further extended into an electrodynamic theory of development by Burr,[10] who introduced the idea of the electrical field, and the theory was formally stated by Burr and Northrop.[12] Experimental confirmation was obtained by Burr and Hovland,[11] and the theory has been expanded by Northrup and Burr[72] into an electro-dynamic theory of life.

Some observations of Gerard[36, 37] suggest a practical application of the electrical theory to the problem at hand. This investigator noted that caffeine applied to the isolated brain of the frog caused the generation of slowly traveling waves which were non-synaptic and answered all the criteria of electrical fields. Thus, the existence of dynamic patterns of brain activity superimposed on or independent of anatomical structure can be accounted for. Gerard goes on to say further that "the simultaneous activity of two nearby cortical regions, as in the course of conditioning, would alter the potential fields which would accompany the activity of either region alone and could so lead to the establishment of new functional patterns."

Accordingly, it would seem logical to assume that cholinergic stimulation could simultaneously activate two nearby cortical regions and so lead to the establishment of new functional patterns. The above hypothesis would thus form a quite satisfactory explanation of the mechanism by which an increase in the rate of recovery of motor function following cortical lesions was accomplished in this investigation by the use of cholinergic drugs. Further confirmation of the electrical theory is needed before any conclusions can be safely drawn.

Effect of stimulation on structure. In addition to the effect of stimulation (cholinergic) on mechanisms by which synaptic modification may occur, which has been discussed in the previous section, there may be an effect of stimulation on certain anatomical structures. Langworthy[55] reported that bilateral movements of the extremities begin to coordinate when the commissural fibers of the cord receive their myelin sheaths, and that animals turn the body at a time when myelinated vestibular fibers reach the spinal cord. These and other findings led him to postulate that myelinization of the nerve tracts is necessary for function of these tracts. If this be true, it would be of interest to know what effect stimulation or activity of the neurons has on the myelination of nerve tracts. Mott[65] states that Flechsig observed that a child born at eight months showed at nine months more marked myelination of the optic nerves than a child born at full term. Held[45] confirmed this observation experimentally. Using very young cats, dogs, and rabbits, he admitted light for varying periods to one eye by opening a lid, the other eye remaining closed. Examination of the optic nerve on the two sides showed a more obvious myelination on the side exposed to light than on the other. Opening the lid in darkness had no such effect. The obvious inference is that transmission of light impulses along the optic nerve had stimulated the process of myelination.

If this be true, it is then entirely possible that stimulation of the neurons of the cerebral hemispheres by cholinergic drugs can increase myelination of their fibers even in an adult if it can be shown that unmyelinated fibers capable of becoming myelinated are still present in the adult animal. This fact was supplied by Kaes,[50] who demonstrated that the cerebral cortex of man increases in the richness of myelinated fibers for a long time after birth and even to the fortieth year or longer, diminishing in old age. It would thus seem possible that the increase in the rate of recovery of motor function produced by cholinergic stimulation in the present investigation could also be due to a myelination of nerve cell processes produced by such stimulation.

In discussing the relation of stimulation to recovery, the work of Franz, Scheetz, and Wilson[32] should be mentioned. They found that in patients with long-standing hemiplegias, they were able to produce further recovery by re-education. Studying this problem further Ogden and Franz[73] observed that in monkeys with hemiplegias produced by cortical lesions, an increased rate of recovery could be achieved by forcibly restraining the normal arm, thus making the monkey use the paretic extremity as much as possible. Here also, stimulation of the nerve cells involved in the motor functioning of an extremity by forcing the monkey to try and use that extremity may have caused an increase in the myelination of cell processes previously non-functioning, thus establishing a new function for those cells.

Summary

The theories elucidated in the preceding discussion concerning the actions of cholinergic drugs and the possible mechanisms of recovery as influenced by these drugs are well substantiated by the evidence obtained in the present investigation. Conclusive evidence has been given from previous investigations that strychnine acts upon the central nervous system as a stimulant and that this action is probably due to interference with the choline esterase activity at the site of transmission of the excitatory impulse. There is suggestive evidence that thiamin acts in the same way. Doryl, it is certain, also stimulates activity within the central nervous system by a direct nicotinic action.

Since these drugs have all to a greater or lesser extent increased both the rate and degree of recovery of motor function in monkeys deprived of cerebral motor cortex on one side, it may be assumed that this has been brought about by stimulation of activity within a partially destroyed central nervous system and that it has accelerated within this system either anatomical or functional reorganization, or both.

Conclusions

A. It is experimentally demonstrated that in monkeys:

1. Strychnine and thiamin increase the rate of recovery of motor function following unilateral ablation of areas 4 and 6 of the cerebral cortex.
2. Doryl alone or doryl and thiamin increase the rate of recovery to an even greater extent.
3. Doryl, atropine, and thiamin increase the rate of recovery to the same degree as doryl and thiamin alone and without the undesirable effects of parasympathetic stimulation.
4. Thiamin alone is not entirely responsible for this improvement in motor status, although it has some effect on rate of recovery.
5. This effect is not a factor of age.

6. The increase in rate of recovery may occur if the administration of doryl is not begun until some weeks after injury. It lasts for at least as long as six months after injury, and for three months after medication has been stopped.

B. It is concluded that the measures employed in this investigation increase the rate of recovery of function by functional reorganization whose mechanism may be:

1. A synaptic modification produced by the electrical phenomena concomitant to cholinergic stimulation.
2. Development of previously absent or non-functioning neuronal connections by the stimulation arising from cholinergic activity.

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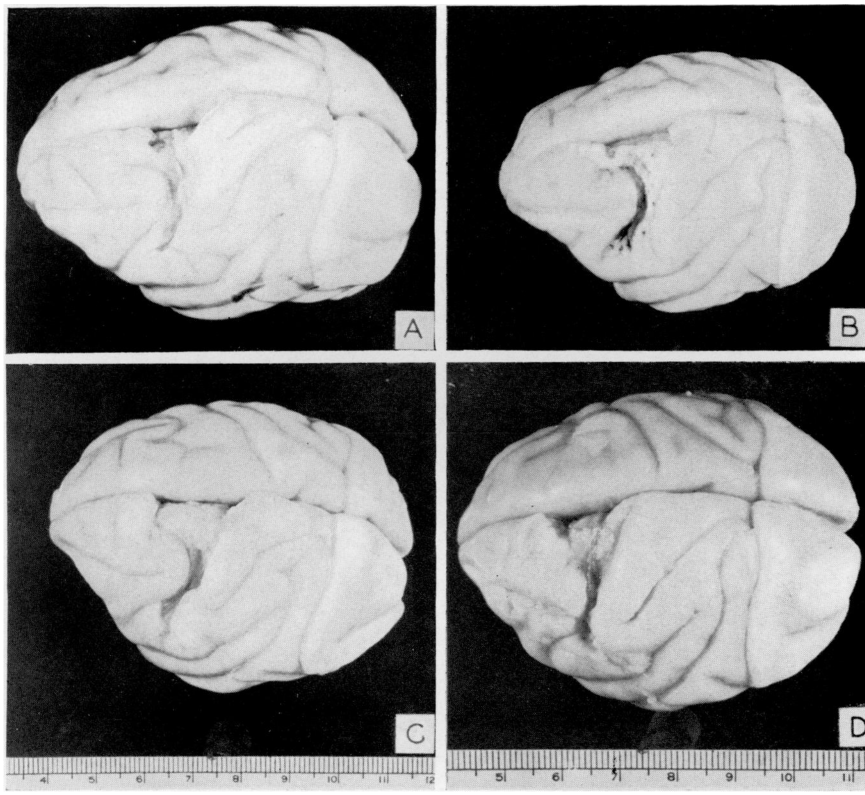

FIG. 1. The brains of four *Macaca mulatta* showing cortical excisions. A—R. S. II; B—R. S. III; C—R. S. IV; D—R. S. VI.

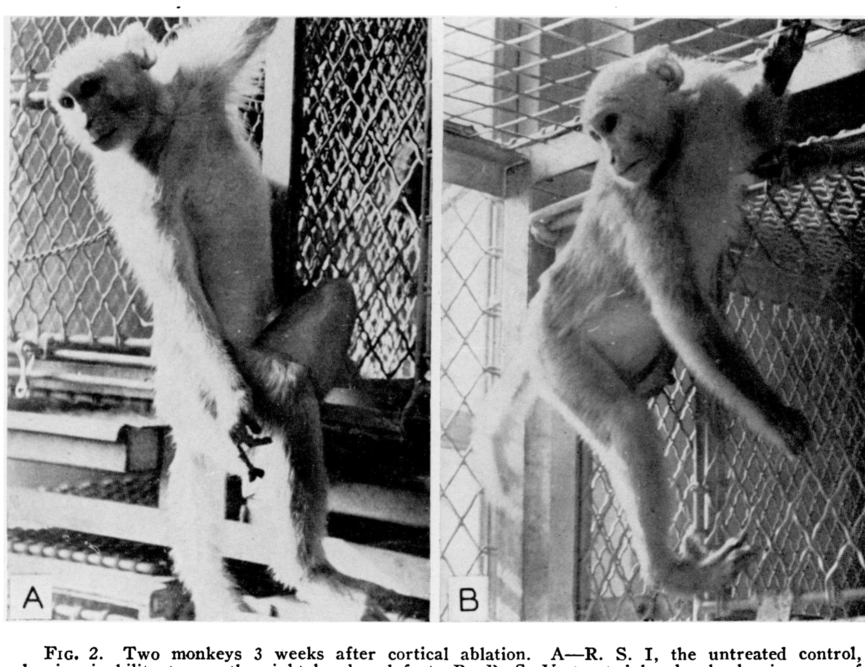

FIG. 2. Two monkeys 3 weeks after cortical ablation. A—R. S. I, the untreated control, showing inability to use the right hand and foot; B—R. S. V, treated by doryl, showing use of the right extremities for support.