THE EFFECT OF CAFFEINE AND GLYCINE WITH THE MUSCLE ELECTROLYTE POTASSIUM CHLORIDE UPON THE RECOVERY FROM MUSCULAR FATIGUE IN THE MOUSE

A Thesis

Presented to

the Faculty of the School of Arts and Sciences

of the

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

George L. Walmsley

August 1950

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ABSTRACT

It was the purpose of this study (1) to reaffirm the positive findings established for caffeine and glycine in their roles of being beneficial in the prolonging of fatigue and in the recovery from fatigue; (2) to determine what effect caffeine and glycine, with muscle electrolyte potassium chloride, has on the recuperation and total recovery time of a fatigued mouse.

Female white mice were used under a plan of double work periods with a ten minute rest between periods. The substances under consideration were injected subcutaneously at the beginning of the rest period. The percent recovery was calculated by dividing the first work period revolutions by the second work period revolutions and the quotient was multiplied by one hundred.

Potassium chloride, in combination with caffeine sodium benzoate and glycine, was found to be beneficial in increasing the percent recovery in a fatigued mouse.

ACKNOWLEDGMENTS

The student would like to express his sincere appreciation to Professor H. J. Sawin and Professor N. C. Brown Cominsky for their suggestions and encouragement during the preparation of this study. The student would also like to express his appreciation and gratitude to Edmond K. Doak, M. D. whose interest in this study was invaluable.

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CHAPTER I

THE PROBLEM AND DEFINITIONS OF TERMS USED

The recovery from fatigue has, for a long time, been of prime concern to man in his attempt to accomplish more work in a shorter length of time. The research concerned with this problem has produced many divided opinions. The problem has been broken down by various proponents, and their particular treatment of specific functions has done much to make the whole picture of fatigue cause more clear. The recovery from fatigue cannot be one or a number of reactions alone, it must be the readjustment of the animal as a whole. The study of the recovery from fatigue by the intact animal has been slighted in this respect.

I. THE PROBLEM

Statement of the problem. It was the purpose of this study (1) to reaffirm the positive findings established for caffeine and glycine in their roles of being beneficial in the prolonging of fatigue and in the recovery from fatigue; (2) to determine what effect caffeine and glycine, with muscle electrolyte potassium chloride upon administration, has on the recuperation and total recovery time of a fatigued mouse.

Importance of the study. A person or animal engaged in physical exercise of a sufficient rate over a prolonged period of time eventually becomes fatigued and incapable of additional physical work. This condition known as fatigue is a protective state common to all living animals. It keeps a person or animal from extending itself to the point of exhaustion for after reaching the state of fatigue the animal or person must rest until its body readjusts itself and is again capable of physical achievement. The time required for the recovery from fatigue is dependent upon many physiological condition which are peculiar to particular individuals or animals at different times.

The ability of a person to recover from fatigue in a short interval of time enables him to accomplish more work, the amount of which is directly proportional to the length of the recovery time. The recovery of a person from muscular fatigue in a short period of time has great application to many fields of physical endeavor. Perhaps this is of more importance in the strenuous physical exertion that is required in the higher competitive sports and in times of war. Very often, in the case of athletes and military personnel, the time of recovery from fatigue is often the factor that spells victory or defeat.

In a recovery time that is too short to be explained

in terms of metabolite removal and in the fact that a muscle with tied-off circulation recovers from maximal static contractions more quickly than a freely circulated one, there is reason to seek a cause for fatigue and recovery unrelated to the creation and payment of an oxygen debt.

II. DEFINITIONS OF TERMS USED

Fatigue. A progressive diminution in physical output resulting from the repeated performance of a given action, specifically the running of a mouse in a treadwheel. The depletion of fuel sources due to transmineralization and shifting of ions which is paralleled by changes in membrane potentials.

Recovery from fatigue. The capability of the animal to perform forty percent of his previous physical achievement.

Oxygen debt. The transportation of metabolites to the tissue site falls short of the necessary amount and the animal goes in debt to itself.

Fatigue tracing. The space interval between similar reoccurring tracings on the kymograph paper which are characteristic of fatigue in particular mice.

Colloidal osmotic pressure. The negative osmotic pressure exerted by proteins in the blood.

CHAPTER II

REVIEW OF THE LITERATURE

Much work has been done on muscle fatigue in excised muscles, on drugs which prolong the incidence of fatigue and on the initial site of fatigue; but only a brief summary of the work of experimenters on problems very closely related to the one at hand will be given.

Literature on effects of caffeine. Caffeine increases not only the capacity for muscular work in rested individuals, but also the speed of muscular recuperation.[1] It is obvious that in human experiments it is impossible to determine whether the caffeine achieves its effect through a central mechanism, acts on the neuromuscular junction, or stimulates the muscle directly.

However, through experimental work done by F. Huidobro and E. Amenbar[2] it was found that caffeine acts on the neuromuscular preparation through a double mechanism: First,

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1 E. E. Foltz, A. C. Ivy and C. J. Barborka, "The Influence of Amphetamine (Benzedrine) Sulfate, Desoxyephedrine Hydrochloride (Pervitin), and Caffeine Upon Work Output and Recovery When Rapidly Exhausted Work is Done by Trained Subjects," Journal of Laboratory and Clinical Medicine, 28:603, 1943.

2 F. Houidobro and E. Amenbar, "Effectiveness of Caffeine (1, 3, 7, Trimethylxanthine) Against Fatigue," Journal of Pharmocology and Experimental Therapeutics, 84:82-92, 1945.

by a direct action on the muscle, and second, by a direct action on the neuromuscular junction. Since the hypotension produced by the caffeine when injected intra-arterially is of such a slight degree it cannot be said that the strengthening effect of caffeine on indirect muscular contraction and on the response of the muscle is due to the general vasodilation effect of the drug. Nevertheless, it could be claimed that the local vasodilation which the drug produces could improve the neuromuscular circulatory condition and that this in turn could be the cause of the strengthening effect of caffeine, and not a direct action of the drug on the neuromuscular junction. However, other drugs, such as Epinephrine, produce vasodilation but do not give this effect.

It is concluded that caffeine lowers the excitatory threshold of acetylcholine since the effect of caffeine maintains a special relationship to the frequency of stimulation, a fact which without a doubt points to a neuromuscular mechanism and not a vascular one.[3]

Literature on effects of glycine. There has been quite a bit of controversy as to the actual effect of

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3 F. Houidobro and E. Amenbar, "Effectiveness of Caffeine (1, 3, 7, Trimethylxanthine) Against Fatigue," Journal of Pharmocology and Experimental Therapeutics, 84;82-92, 1945.

glycine. The benificial effects of glycine excess in the diet to promote increased work output has been put forward by a number of people particularly the manufacturers of gelatine, of which glycine is a major component.

Glycine given with urea is said to have produced an increased of 79 percent in the energy output of men, but an irregular increase varying from 16-62 percent in women.[4] No explanation was given for the wide range of increase in women. The glycine was given in wine.

Literature on heat cramps. Esdall,[5] in his investigations, found a diminished excreation of chloride and an increased excretion of nitrogen in the urine in patients after the onset of heat cramps. It must be remembered that heat cramps were usually experienced in an atmosphere of extreme heat, 130-140°F. Occupations tending to produce this atmosphere would be; boilerstokers, steel mill workers, etc. However, of more recent origin was the five cases of heat cramps observed among workmen during the building of the Boulder Dam.[6] Talbott and Mickelson[7] showed in their studies that the significant chemical changes in

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4 H. H. Beard and J. K. Espenan, "Effect of Glycine Injection With and Without Urea Upon Human Endurance," Medical Record, 154;191-192, 1941.

5 D. L. Edsall, "Further Studies of the Muscular Spasms Produced by Exposure to Great Heat," Treatise of the Association of American Physicians, 24;625, 1908.

6 J. H. Talbott and J. Michelson, "Heat Cramps," Journal of Clinical Investigation, 12;533, 1933.

7 Ibid., p. 533.

the blood serum of the men was a diminished concentration of fixed base and chloride and an increased concentration of protein.

In the men who had heat cramps a normal or high blood sugar level was found to be present, hence eliminating all possibility of a low calorie diet.[8] Hall and Wakefield[9] in a general conclusive statement concerning the production of "heat cramps" consider the lowering of the sodium and chloride in the serum, from loss in the sweat without adequate replacement, as the principal causative mechanism.

Literature on Muscle Electrolytes. When there is a diminution of fixed base and chloride and an increase of protein concentration in the blood serum there must be accompaning it an increase of colloidal osmotic pressure in the venous circulation. Fluid is sucked back into the general circulation when the hydrostatic pressure falls below the colloidal osmotic pressure of the plasma proteins.[10] In this condition there is an interruption of the electrolyte balance between the tissue cells and the blood resulting from a mild dehydration of the tissue cells. This interfers

8 W.W. Hall and E. G. Wakefield, "A Study of Experimental Heat Strokes," Journal of American Medical Association, 89:177, 1937.

9 Ibid., p. 177.

10 I. S. Kleiner, Human Biochemistry (C. V. Mosby Company, 1945), p. 147.

with the removal of tissue metabloites and the effeciency of the muscle is impaired.

Driver[11] found in his studies on chloride absorption that the presence of sodium chloride in concentrations not exceeding 1 percent accelerated the absorption of glucose against a higher concentration. He also found that a special biological agent is responsible for absorption of electrolytes as well as other substances, such as sugars.

The sodium of sodium sulfate is not treated altogether as the sodium of sodium chloride, even by normal kidneys. When sodium sulfate was injected into dogs, chloride almost disappeared from the urine, even when enough sodium chloride was administered simultaneously to raise the concentration of chloride in the serum far above normal.[12]

Hoff[13] found that potassium salts have an antifatigue action on muscle and on neuromuscular transmission. His experiments also showed that chloride excretion was not renewed for quite some time after the concentration of sulfate in the urine had begun to fall, although serum chloride continued to rise. Administration of extra

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11 R. L. Driver, "Chloride Absorption," American Journal of Physiology, 133:76-77, 1941.

12 P. K. Smith, A. W. Winkler and B. M. Wchwartz, "The Destribution of Magnesium Following the Parenteral Administration of Magnesium Sulfate," Journal of Biological Chemistry, 129:51-56, 1939.

13 H. E. Hoff, A. W. Winkler and P. K. Smith, "Recovery of Fatigued Muscle Following Intravenous Injection of Potassium Chloride," American Journal of Physiology, 131:615, 1941.

sodium chloride only accelerated the elimination of sulfate and exaggerated the hyperchloremia. Serum sodium also rose to excessive heights, although the sodium excreted fell short of that given some ammonium was substituted for it in the urine. Comparable to this is the rapid excretion of potassium when potassium chloride is given, coupled with the fact that the chloride is excreted more rapidly than the chloride of an equivalent amount of the sodium salt.

Normally the mammalian muscle fibers contain only 12.7 m. eq. of sodium but 145.0 m. eq. of potassium.[14]

Potassium as chloride can be accumulated; this fact indicates that the membrane is permeable to cations and anions; however, sodium due to its greater ion diameter in solution, cannot permeate the muscle membrane.[15] The potassium level found in patients with heat cramps is normal or increased from 1 to 3 m. eq.

Since potassium can substitute for sodium, it must be taken into consideration that there is a possibility

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14 R. C. Mellors, E. Muntwyler and F. R. Mantz, "Electrolyte and Water Exchange Between Skeletal Muscle and Plasma in the Dog Following Acute and Prolonged Extracellular Electrolyte Loss," Journal of Biological Chemistry, 144:773-784, 1942.

15 P. S. Boyle and E. J. Conway, "Potassium Accumulation in Muscle," Journal of Physiology, 100:1-63, 1941.

of a larger amount of potassium being released.

The fact that potassium is an active participant in the process of muscular contraction can be concluded from the fact that 15-20 percent of the muscle potassium may be lost during extended muscular activity. Muscles with low potassium concentrations fatigue more easily and develop less total tension.[16] In cats the loss of potassium on stimulation is decreased somewhat by previous injection of calcium chloride.[17]

Since serum protein has a binding power on calcium an increased serum calcium concentration must be attributed to the increased serum protein concentration. Calcium is a definite part of the muscle fiber, being incorporated in the contraction band. This fact makes it an intimate participant in muscle fiber activity.

Injections of potassium chloride hastens the recovery from fatigue.[18] The return of vigor to a fatigued muscle is explained as a result of the restoring the potassium which is lost during muscle activity.

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16 Leon A. Heppel, "The Effect of Age and Diet on Electrolyte Changes in Rat Muscle During Stimulation," American Journal of Physiology, 128:440, 1939-40.

17 R. C. Ingraham and M. B. Vincher, "Further Studies on Intestinal Absorption With the Performance of Osmotic Work," American Journal of Physiology, 121:771, 1938.

18 H. E. Hoff, A. W. Winkler and P. K. Smith, "Recovery of Fatigued Muscle Following Intravenous Injection of Potassium Chloride," American Journal of Physiology, 131:615, 1941.

CHAPTER III

PROCEDURE AND DATA

Statement of experimental procedure and method of obtaining data. During the experiment every attempt was made to make the experimental conditions as closely adaptable to man as possible. The 8% glycine solution used was decided upon because the author felt, after personal experimentation, that this concentration was the maximun that a fatigued man could drink without considerable discomfort. The amount of injection, corresponding to 1% body weight of the animal, would roughly equal a man drinking one quart of fluid. The potassium chloride solution was made to be isomolar with a 0.9% sodium chloride solution and was also given at 1% body weight of the animal. Caffeine sodium benzoate was given at 0.007 mg. per gram body weight of the animal. This concentration was believed to be comparable to an adult human dose.

Ten female white mice, of the Swiss Albino strain from the Larlan Small Animal Farms, weighting between 28-32 grams were used in the experiment. The mice were fed on a diet of Purina Dog Chow Checkers.

The author feels that it is significant to state that the overall metabolism of mice is about ten times that of man.

Each mouse was placed in a tread wheel and run until it was fatigued. Fatigue was determined when the mouse developed its particular characteristic fatigue tracing. The mouse was then rested for ten minutes, at the beginning of which time the various injections were made subcutaneously. At the end of ten minutes the mouse was again placed in the tread wheel and again allowed to run until it developed its fatigue tracing. This was done for each of the ten mice. The percent recovery was obtained by dividing the number of second work period revolutions by the number of first work period revolutions and multiplying the quotient by one hundred. The number of revolutions was recorded by means of a bristle, that projected from the edge of the wheel, which rubbed against a kymograph drum.

Stimulation of the mice to make them run was acheived through two methods. First, the blunted nails projecting from the stimulus plate exerted a mechanical stimulus; second, an electrical stimulus of 30 volts was created when the mouse completed the circuit between the wheel and the stimulus plate. A key switch was incorporated in the circuit to permit stimulation when desired. A regulation 9 inch in diameter hamster wheel wrapped on the outside with screen wire was used as the tread wheel.

For further information concerning the construction of the tread wheel consult the labeled sketch of the stimulus plate or the photograph of the complete apparatus.

TABLE I

PERCENT RECOVERY AFTER TEN MINUTE REST

(CONTROL)

Mouse Number	Weight In Grams	First Work Period Rev.*	Ten Minute Rest	Second Work Period Rev.	Percent Recovery
10	35.6	113		61	53
11	28.0	234		54	23
12	30.5	202		76	32
13	29.0	248		83	33
14	33.1	158		67	42
15	28.2	141		69	41
16	27.1	126		58	48
17	27.0	187		52	28
18	32.2	121		46	37
19	27.4	167		65	39

Average Percent Recovery was 37.8.

*Revolutions of Tread Wheel.

TABLE II

PERCENT RECOVERY FOLLOWING THE SUBCUTANEOUS INJECTION OF 0.2 mg. OF CAFFEINE SODIUM BENZOATE

Mouse Number	First Work Period Rev.*	Ten Minute Rest	Second Work Period Rev.	Percent Recovery
10	120	Caffeine-0.2 mg.	83	69
11	223	"	104	46
12	194	"	98	50
13	243	"	119	49
14	168	"	89	53
15	119	"	72	61
16	94	"	54	57
17	173	"	87	50
18	144	"	89	62
19	184	"	119	65

Average Percent Recovery was 56.2.

*Revolutions of Tread Wheel.

TABLE III

PERCENT RECOVERY FOLLOWING SUBCUTANEOUS INJECTION OF 8% GLYCINE

(DOSE: 1% BODY WEIGHT)

Mouse Number	First Work Period Rev.*	Ten Minute Rest	Second Work Period Rev.*	Percent Recovery
10	92	Glycine-0.3 cc	64	69
11	233	"	167	72
12	160	"	88	55
13	202	"	159	78
14	135	"	123	91
15	130	"	62	47
16	122	"	57	46
17	157	"	92	58
18	139	"	71	61
19	164	"	81	49

Average Percent Recovery was 62.6.

*Revolutions of Tread Wheel.

TABLE IV

PERCENT RECOVERY FOLLOWING THE SUBCUTANEOUS INJECTION OF 1.16% POTASSIUM CHLORIDE (DOSE: 1% BODY WEIGHT)

Mouse Number	First Work Period Rev.*	Ten Minute Rest	Second Work Period Rev.*	Percent Recovery
10	127	0.3 cc 1.16% KCl	46	36
11	174	"	62	35
12	216	"	71	32
13	221	"	64	29
14	142	"	58	42
15	135	"	65	48
16	110	"	34	31
17	167	"	89	53
18	101	"	39	39
19	87	"	38	43

Average Percent Recovery was 38.8.

*Revolutions of Tread Wheel.

TABLE V

PERCENT RECOVERY FOLLOWING THE SUBCUTANEOUS INJECTION OF CAFFEINE SODIUM BENZOATE AND POTASSIUM CHLORIDE

CONCENTRATION: CAFFEINE SODIUM BENZOATE 0.3 cc = 0.2 mg.; KCl 1.16%

DOSE: 1% BODY WEIGHT

Mouse Number	First Work Period Rev.*	Ten Minute Rest	Second Work Period Rev.*	Percent Recovery
10	105	0.3 cc Caffeine-KCl	99	94
11	197	"	174	88
12	179	"	163	91
13	226	"	192	82
14	123	"	110	97
15	138	"	143	103
16	113	"	77	68
17	221	"	158	71
18	99	"	102	103
19	101	"	73	72

Average Percent Recovery was 86.9.

*Revolutions of Tread Wheel.

TABLE VI

PERCENT RECOVERY FOLLOWING THE SUBCUTANEOUS INJECTION OF GLYCINE POTASSIUM CHLORIDE

CONCENTRATION: GLYCINE 8%; KCl 1.16%

DOSE: 1% BODY WEIGHT

Mouse Number	First Work Period Rev.*	Ten Minute Rest	Second Work Period Rev.*	Percent Recovery
10	98	0.3 cc glycine & KCl	85	86
11	135	"	109	80
12	119	"	96	81
13	210	"	191	90
14	112	"	98	87
15	123	"	91	74
16	122	"	103	84
17	201	"	194	96
18	83	"	68	81
19	117	"	96	82

Average Percent Recovery was 84.1.

*Revolutions of Tread Wheel.

TABLE VII

PERCENT RECOVERY FOLLOWING THE SUBCUTANEOUS INJECTION OF CAFFEINE SODIUM BENZOATE, GLYCINE AND POTASSIUM CHLORIDE

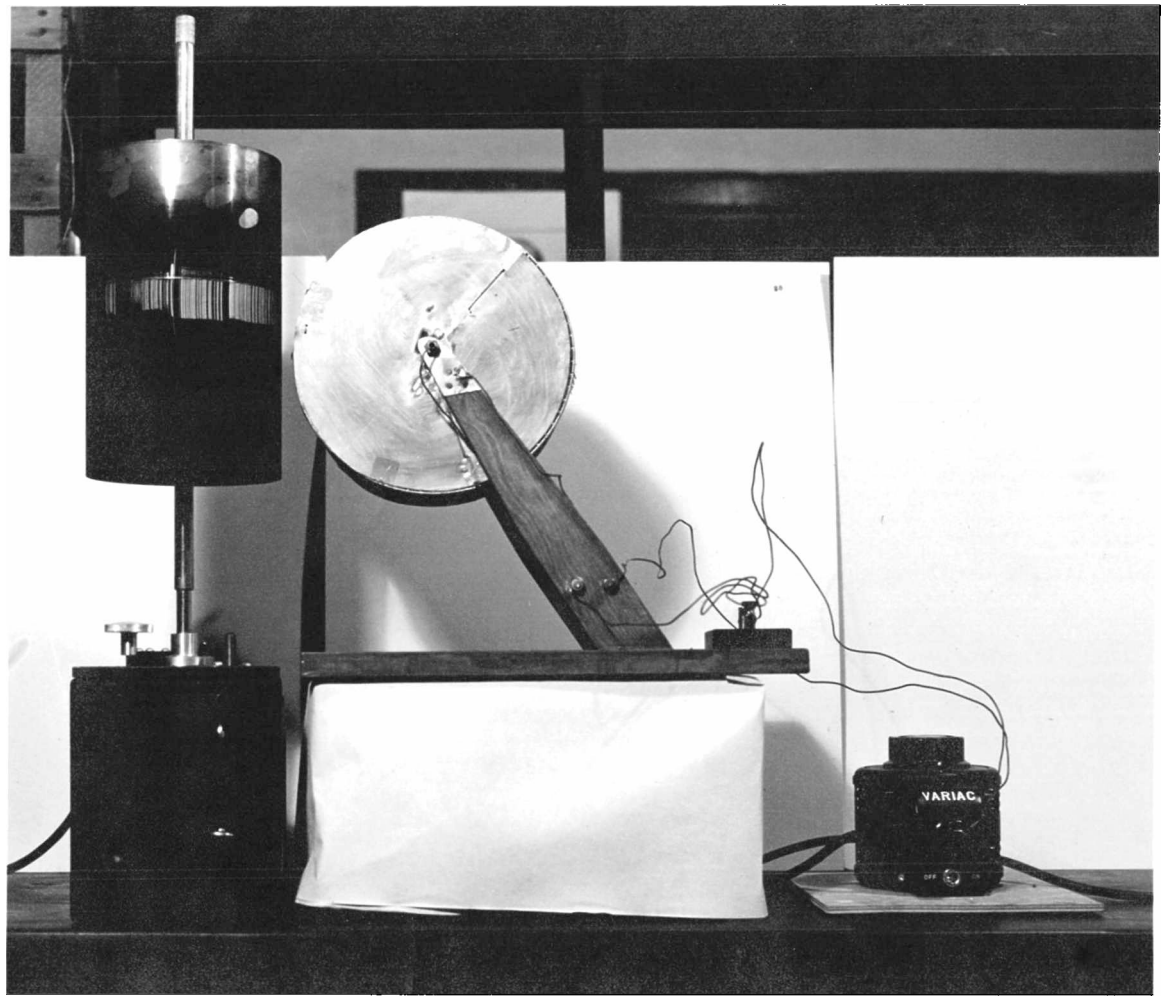
CONCENTRATION: CAFFEINE SODIUM BENZOATE, 0.3 cc = 0.2 mg.; GLYCINE 8%; KCl 1.16%

DOSE: 1% BODY WEIGHT

Mouse Number	First Work Period Rev.*	Ten Minute Rest	Second Work Period Rev.*	Percent Recovery
10	80	0.3 cc caffeine, glycine & KCl	70	87
11	67	"	69	103
12	141	"	124	88
13	197	"	184	93
14	121	"	112	92
15	146	"	131	89
16	108	"	82	80
17	139	"	125	89
18	105	"	100	95
19	78	"	69	99

Average Percent Recovery was 91.5.

*Revolutions of Tread Wheel.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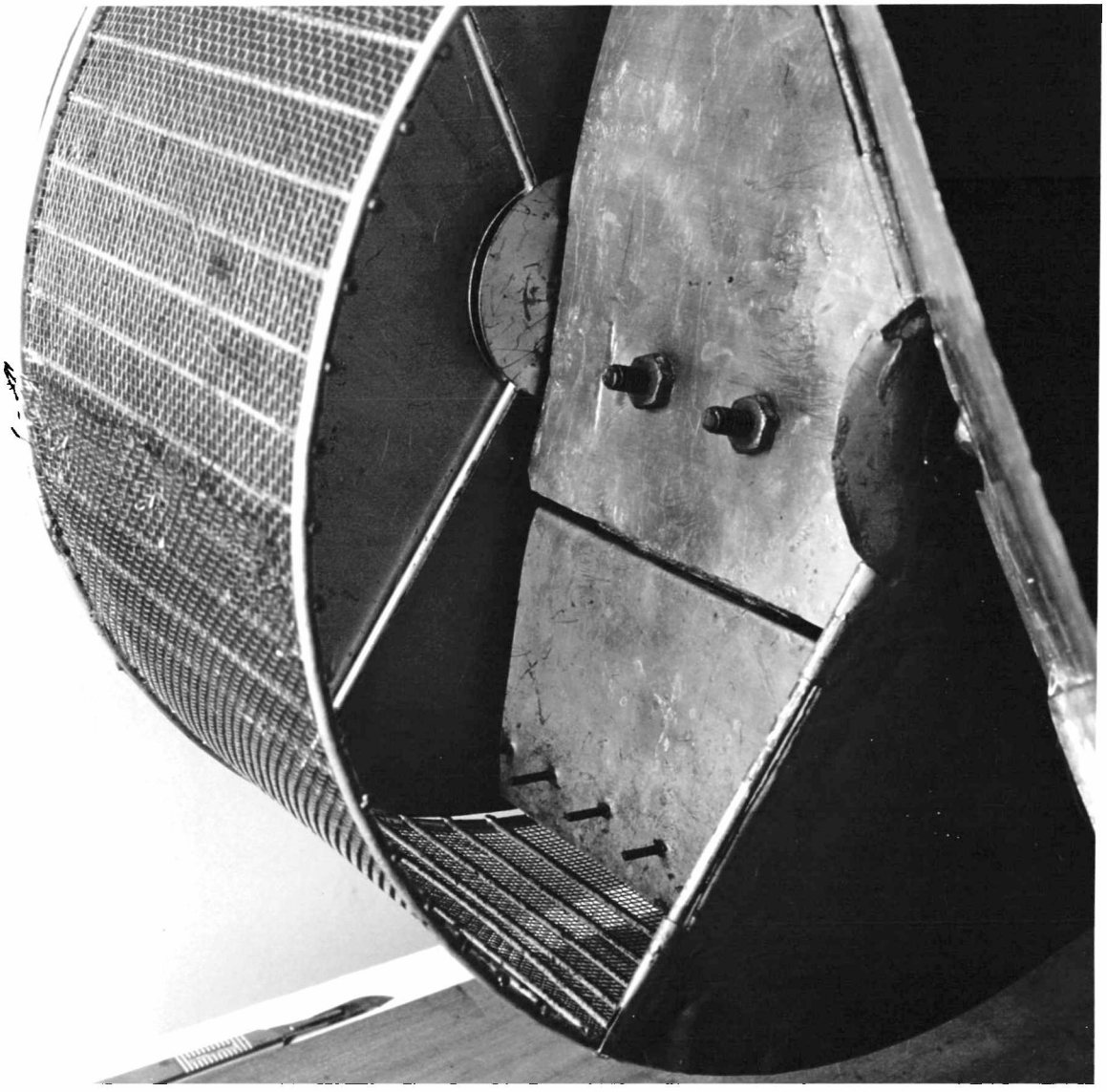

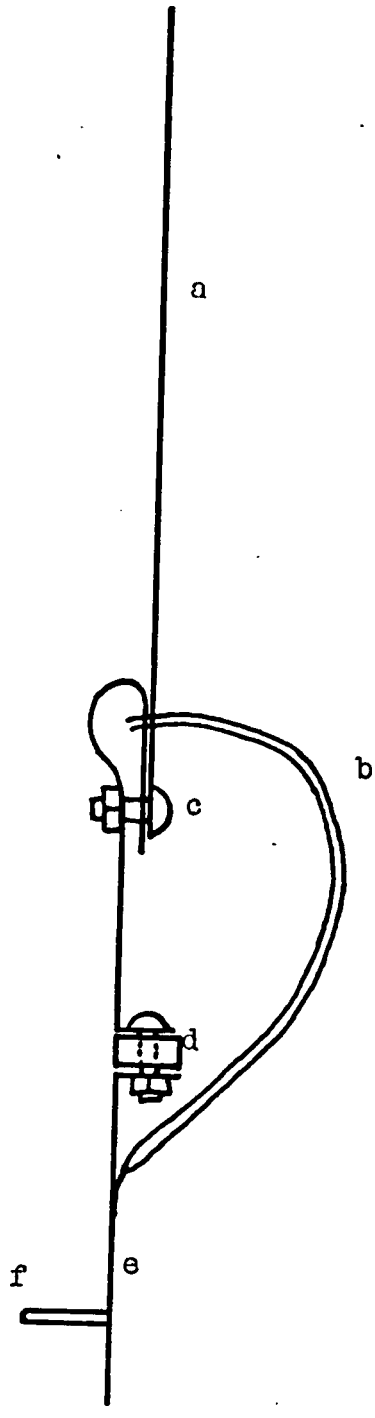

Cross Section of Stimulus Plate. a,guard plate; b,wire from axle to stimulus plate; c,nut and bolt to tighten plate to axle; d,insulation; e,stimulus plate; f,blunt nails.

CHAPTER IV

SUMMARY AND CONCLUSIONS

1. The percent recovery from fatigue under normal conditions (control) of a mouse after ten minutes rest was found to be thirty-eight percent.

2. Caffeine sodium benzoate was found to be beneficial in the recovery from fatigue. The percent recovery following fatigue and the administration of caffeine sodium benzoate was found to be fifty-six percent. This was twenty percent above the normal.

3. Glycine was found to be beneficial in the recovery from fatigue. The percent recovery following fatigue and the administration of glycine was found to be sixty-two percent. This was twenty-two percent above normal.

4. The administration of potassium chloride had no effect upon the normal percent recovery from fatigue.

5. The administration of potassium chloride with caffeine sodium benzoate increased the percent recovery of caffeine sodium benzoate to forty-six percent. This was an increase of twenty-six percent over caffeine sodium benzoate by itself. Total percent recovery using potassium chloride with caffeine sodium benzoate was eighty-six percent.

6. The administration of potassium chloride with glycine increased the percent recovery of glycine to forty-four percent. This was an increase of twenty-two percent over glycine by itself. Total percent recovery using potassium chloride with glycine was eighty-four percent.

7. The administration of caffeine sodium benzoate, glycine and potassium chloride increased the percent recovery fifty-one percent above the normal. Total percent recovery was ninety-one percent.

8. The author feels that it is significant to mention that following the injection of caffeine sodium benzoate and potassium chloride and the injection of glycine and potassium chloride the experimental animal ran with more vigor and at a more steady rate.

9. It is concluded that potassium chloride has considerable effect upon increasing the percent recovery following the administration of caffeine sodium benzoate and glycine.

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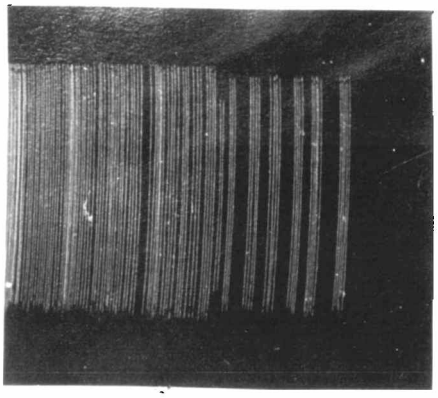
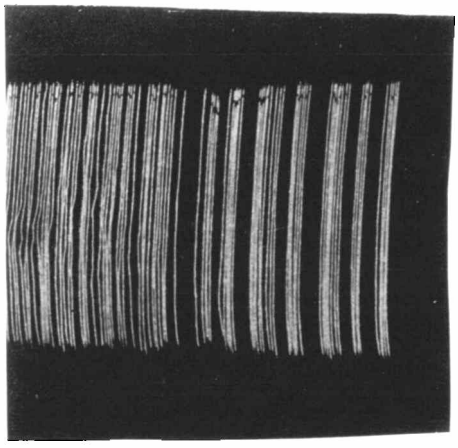
APPENDIX





Fatigue tracings showing the characteristic space intervals between similar reoccurring revolutions.