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BIOLOGY SECTION OF RESEARCH DIVISION

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THE EFFECTS OF FAST NEUTRONS ON THE ABILITY OF MICE TO TAKE FORCED EXERCISE

G. E. Stapleton and H. J. Curtis

Progressive Report - P. A. BX12-20

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Abstract

In an attempt to gain some insight into the physiological condition of mice surviving massive doses of radiation, a study of their vitality was undertaken. It was assumed that the ability of these animals to do forced work would be a measure of their vitality. Stimulating exposed animals to run in exercise wheels to their fullest capacity, has resulted in a demonstration of a striking vitality loss during a post-irradiative period, when no other effects are demonstrable by gross examination.

Mice subjected to a median-lethal dose of fast neutrons show a continuous vitality loss over a 300 day period following exposure.

Control animals show no appreciable loss of vitality up to about 8 months of age, after which a gradual loss can be noted, probably due to a normal gereologic process.

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THE EFFECTS OF FAST NEUTRONS ON THE ABILITY OF MICE TO TAKE FORCED EXERCISE

1. Introduction

The acute and late effects of single massive doses of radiation have been studied extensively within the past few years and a recent report[1] by members of the staff of this laboratory, summarized many of the findings.

Among the acute effects of large doses of radiation, which have been studied, are those concerned with such destructive changes in the organ systems of the body as:

1. Damage to the hemopoietic system, as evidenced by hematological and histological examination.

2. Damage to other organs such as the liver, intestines, lungs, gonads, etc. as seen in gross and microscopic pathological examination.

3. Changes in the general body features, such as weight loss, emaciation and other effects, noted by gross observation.

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1. Henshaw, P. S., E. F. Riley, R. S. Snider, and G. E. Stapleton - Comparative Delayed Effects of Single Doses of Fission Neutrons and of Gamma Rays - MonH-116 - June 1946.

Following an exposure of a large group of mice to a median-lethal dose (LD-50) of fast neutrons, the chronological order of events as evidenced from gross observation, is somewhat as follows: (1) a latent period of some 4 to 7 days follows the exposure during which few, if any, of the animals die, (2) a general weight loss and emaciation apparently occurs in a large number of the animals, resulting in death to about half of the animals over a period of about three weeks.

Interestingly, the animals which are able to survive the early effects of this damaging agent apparently recover and resume a normal life. Survival data, however, indicates that commencing at about 30 weeks after exposure, the animals die prematurely depending on the magnitude of exposure. This phenomenon is sometimes foretold by manifestations of premature aging, such as graying hair in colored mice, loss of eyesight and general thinning of hair. During the post irradiative period, from 3 weeks up to 30 weeks, most of the surviving animals show little or no manifestation of physical weakness. They appear to be as healthy and normal as the control mice, yet they have received a dose of radiation sufficient to kill half of the animals in the group.

Since these animals have received a large dose of injurious agent, and since there is evidence of damage incurred, as shown by late effects, the question arose as to whether or not some capacity, normally possessed by animals, might be lost as a result of irradiation, not discernable by gross observation. Moreover, such a loss of ability might be demonstrable soon after exposure, if the exposed animals were given the proper tests.

In an effort to ascertain the physical condition of mice which had been subjected to massive doses of radiation, a study of the vitality of these animals has been undertaken by measuring their ability to do work under stress (i.e. their ability to do forced exercise). The chief purpose of this study was to establish a method for measuring vitality, and although the number of animals used was small, some interesting trends were demonstrable.

1.1 Preliminary Considerations:

Several early attempts were made to devise a method of measurement which would be sensitive enough to detect slight differences in the vitality of experimental and control animals, while at the same time producing no deleterious effects in the animals.

Such methods as determining for what length of time a mouse could hang from a wire, or swim in a tank of water, proved to be as unsuccessful as they were simple, attributable chiefly to the remarkable learning ability of these animals. It had been assumed that either of these methods might have given us a measure of the vitality or endurance of mice, in that both consisted of placing them in an unnatural surrounding, which should have been sufficient stimulus to force them to work to their fullest capacity.

It seemed then, that a method, to be successful, should entail putting the animal in an almost natural surrounding, the only thing unnatural being the stimulation applied. The device for measuring should be of such a nature that the mouse would be forced to work to its fullest capacity, constantly, for a period of time.

The most suitable of the devices studied were "exercise wheels". Animals, placed in such wheels, could be forced to run by the application of some stimulus, for example, a jet of air playing up on a mouse from beneath the wheel. The number of revolutions run, then, per unit of time should be a measure of the ability of the animals to do forced work.

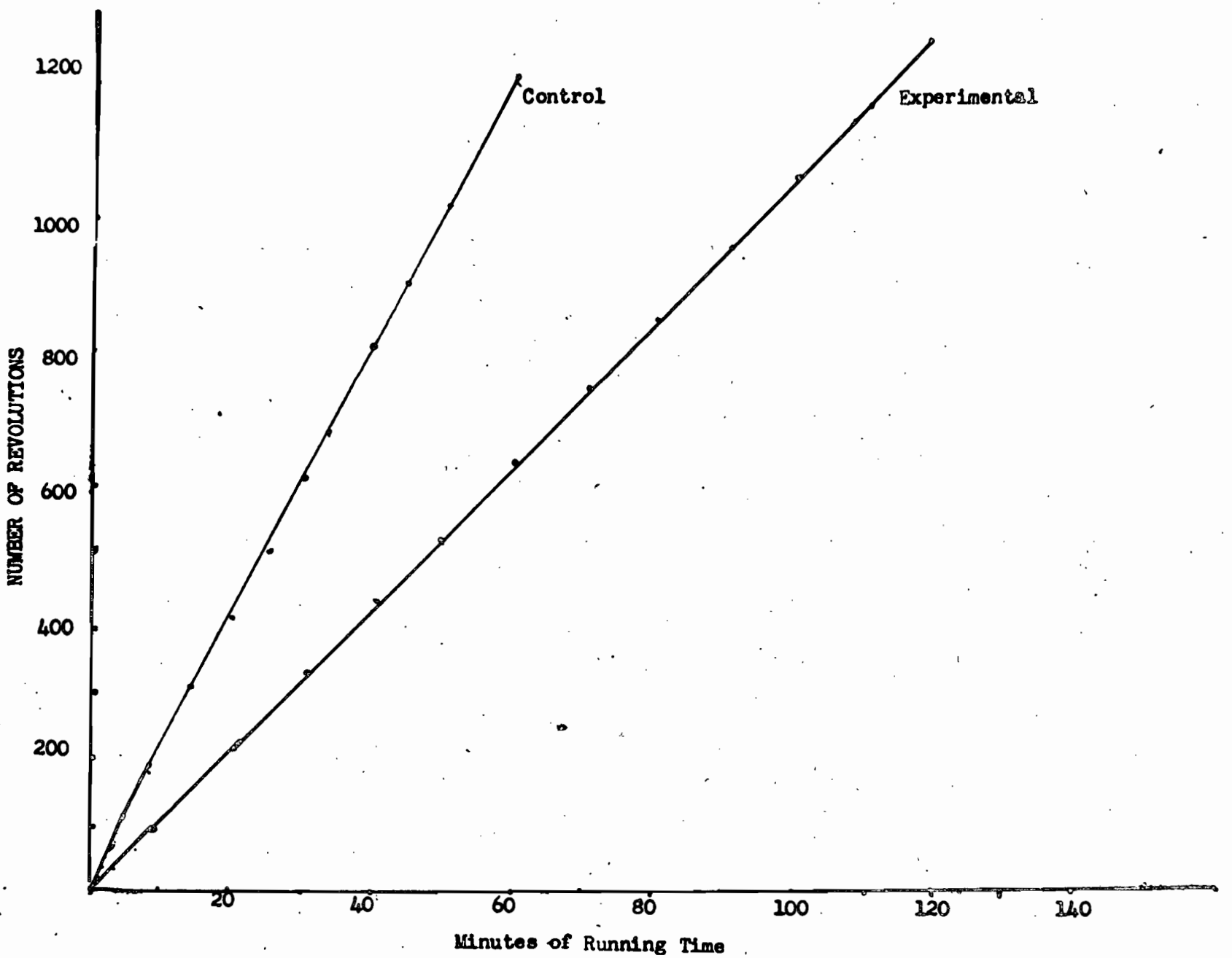
When several animals, chosen at random from a cage of mice which had previously been exposed to the LD-50 of fast neutrons, were placed in the exercise wheels and run individually for a period of several hours, some enlightening trends were observed as shown in Figure 1. The time of running, in minutes, is plotted as abscissae, the average number of revolutions made by three experimental and three control mice, as ordinates.

It can be seen from the graph (Figure 1) that a constant running rate was established immediately by the animals in both groups. It is also noticeable that the experimental animals were able to run at about one-half the rate of the controls. This trial run was made with animals which had received an exposure 70 days previous to the date of the test.

From these data it could be concluded that about one-half an hour running time would be sufficient to give us the desired information. However, to supply a safety factor, in routine experiments they were run for an hour, revolutions per hour being taken as the standard unit for comparative vitality measurements.

FIGURE 1

MOUSE RUNNING RATES



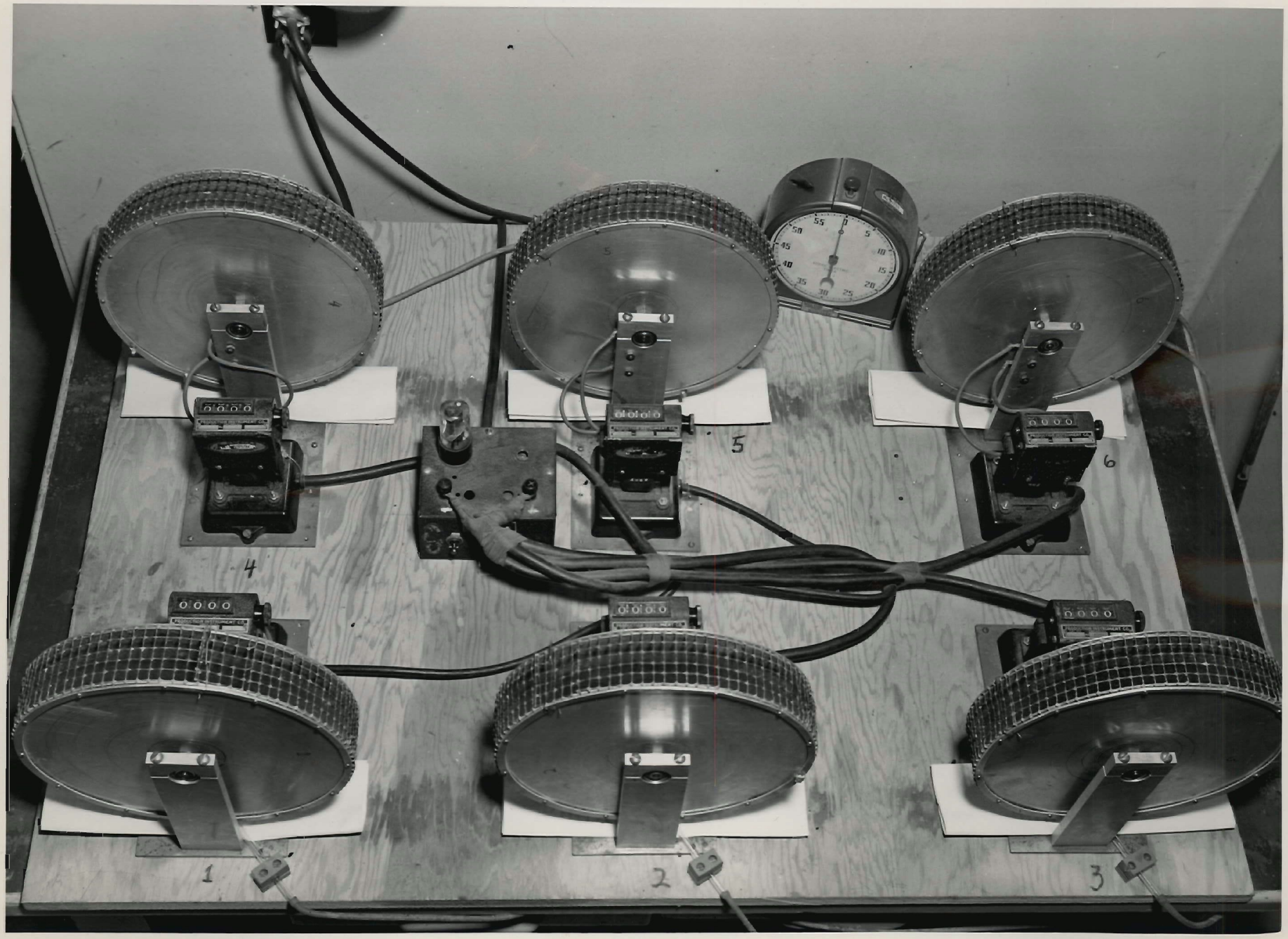
2. Material and Methods

During the course of preliminary experimentation, various qualifications were found to be necessary in a wheel, in order that reproducible results could be obtained. Among these were:

(a) low inertia
(b) ease of operation
(c) accessibility for cleaning and sterilization
(d) uniformity of characteristics between wheels when several were used.

After studying, to some extent, the commercial models of exercise wheels, it was found that by having the experimental wheels built to our specifications, more of the necessary features could be included.

Six aluminum wheels were fabricated and are shown in Figures 2 and 3. Two disks, 10 inches in diameter, were cut from 1/16 inch aluminum plate. To these, the tread surface of the wheel ($\frac{1}{4}$ inch wire mesh, $1\frac{1}{2}$ inches in width), was attached with two superimposed aluminum rings. The wheels were fitted with precision ball-bearings, which made them almost frictionless in their motion. The number of revolutions of the wheels was recorded on Wizard-type electric recorders, controlled by micro-switches attached to the wheel standards. These micro-switches were 'tripped' by small cams attached to the axles of the wheels. The cams and switches were so designed, that a revolution in either forward or backward direction was recorded.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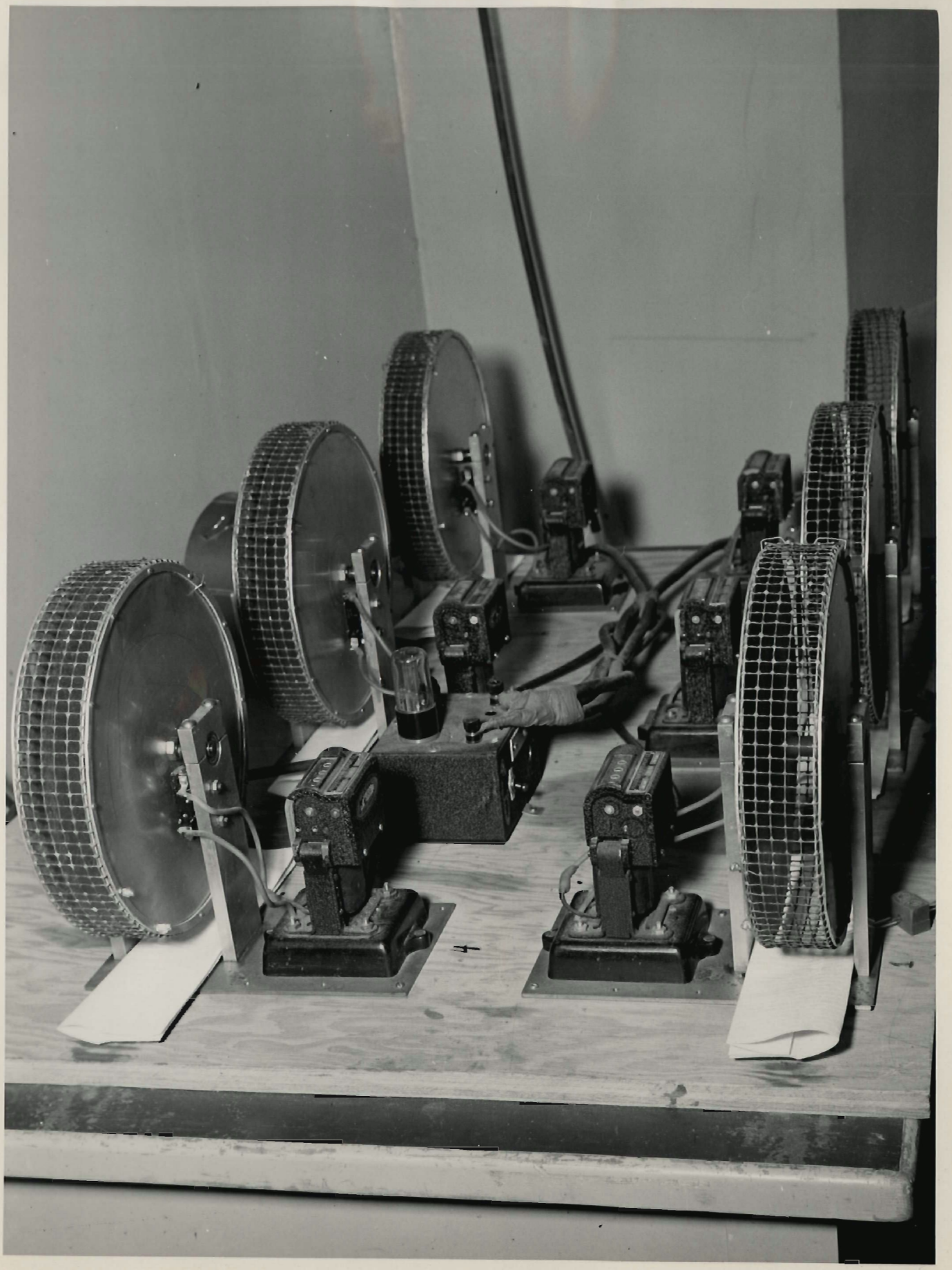

A small jet of air, playing up from underneath, through the wire mesh, provided sufficient stimulation to keep a mouse moving, while at the same time having no apparent deleterious effects on the animal. A normal non-irradiated control mouse was able to run approximately one thousand revolutions per hour, with the above described experimental device.

2.1 Biological Material:

Carworth CF-1 female mice, the standard strain of mice for this laboratory, were used in all of the determinations. The animals used were from groups which had received a median-lethal dose of fast neutrons previous to the vitality determinations.

2.2 Biological Method:

The standard procedure was to pick, at random, three animals from a group of previously exposed mice. The control mice were picked, similarly, from groups of mice which have become known as Specific Controls, in other words, animals which received the identical mechanical treatment as the experimental animals, except, of course, the actual irradiation. The six animals chosen for running were marked, either with stain, or toe-clipped, in order that they could be distinguished from the rest of the animals in a particular cage.

Once a week, six animals, three experimentals and three controls, were placed in the wheels, and with the air turned through the small jets, the run was started. The animals were rotated from wheel to wheel, week after week, in order to determine the uniformity of the wheels, and also to average out any non-uniformity which might have existed. Using this method, it was found that the six wheels differed by 10 per cent or less.

3. Results and Discussion

The running rates of three groups of mice, which had been exposed to the LD-50 (90 n) of fast neutrons, previous to the time determinations began, are shown in Figure 4. The number of revolutions per hour made by the experimental and control mice are shown as ordinates; the number of days the experiment had been in progress is plotted as abscissae.

The curves, indicated as Experimental A and B, demonstrate the occurrence of a continuous loss of vitality of those animals which had received a dose of radiation, as compared with the controls (Control A and B curves).

Although each of these curves represents the average running rates of only three mice, their validity as a true representation of the occurring events following irradiation, is substantiated by the fact that, the curves Experimental C and Control C, which are based on the average running rates of 18 and 6 animals respectively, are already showing the same general trend. At present (130 days after exposure) the experimental animals are, on the average, only 70 percent as efficient as the controls.

It has also become evident that the non-irradiated control mice show a decrease in running rate at about 180 days after the beginning of the experiment which may be an indication of a normal aging effect on vitality. Since it was a general practice to use, for exposure purposes, mice which were about 8 weeks old, the normal age effect became apparent at about 240 days. It should be noted that at about the same time, a striking vitality loss occurs in the experimental animals, which may be attributed to a radiation effect markedly

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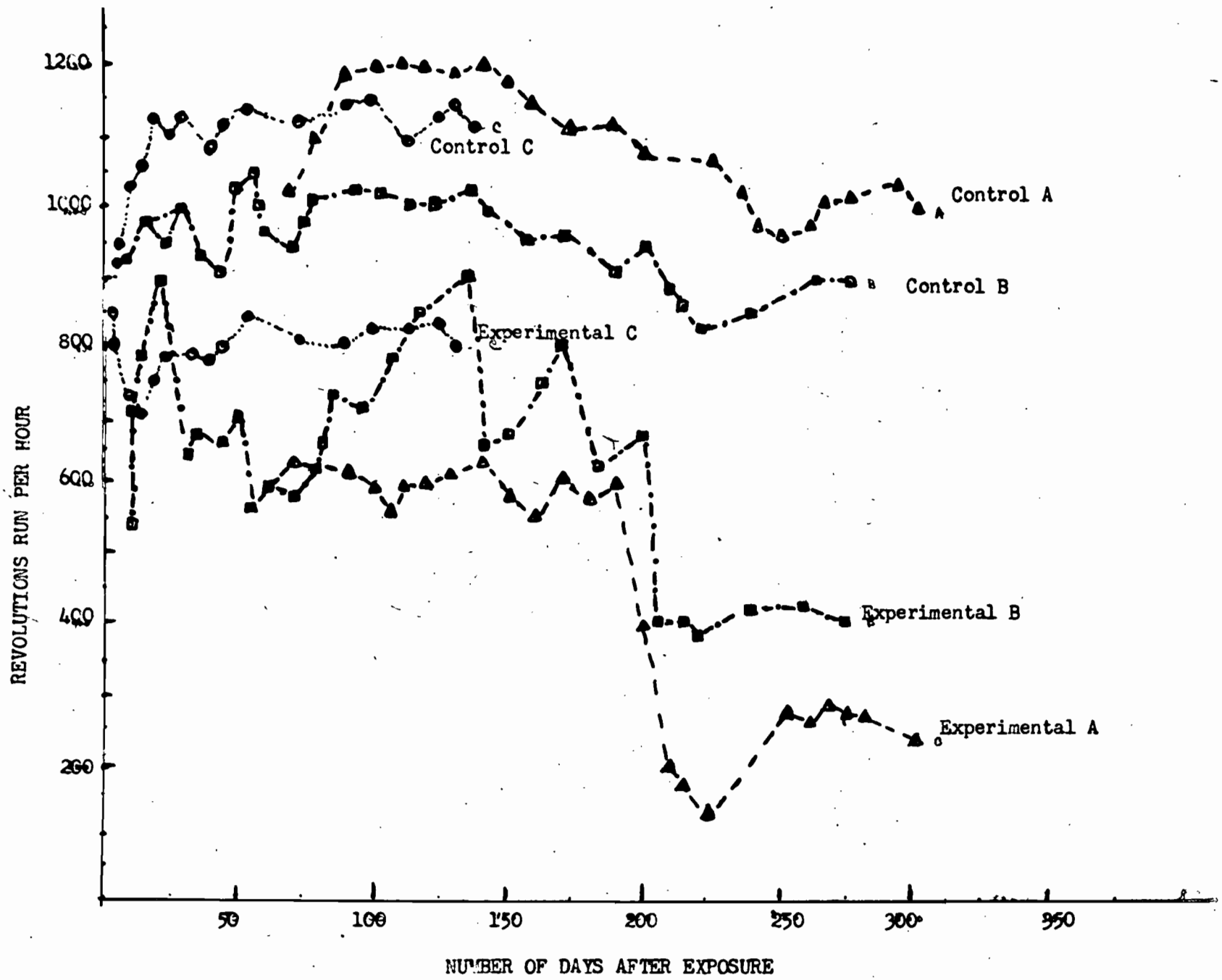
FIGURE 6

RUNNING RECORD OF UNTRAINED MICE



enhancing the normal aging effect. The two, occurring simultaneously, result in a loss of from 60 to 75 percent of the normal vitality of a mouse at about 30 weeks after exposure. It is interesting to note that at this time the animals became emaciated and the phenomenon of pre-mature death set in.

It is apparent from Figure 4 that a vitality loss is demonstrable in irradiated mice almost immediately after exposure. During the same period of time the control mice, because they are learning to run the wheels more efficiently week after week, increase their running rates. After about 3 or 4 weeks, the control animals reach a maximum efficiency which they maintain for about 180 days, after which time normal aging begins to have an effect on their vitality.

Although there are some indications of periodic temporary recoveries, the general trend of the running rate of irradiated animals is downward.

The results just presented demonstrate that a loss of vitality occurs in animals subjected to a median-lethal dose of fast neutrons. This loss is not manifested when animals are observed in the standard experimental environment (i.e. in cages in the animal farm), but is readily observable when they are forced to expend their energy in doing work.

Moreover, these results give us an insight into the physical condition of the irradiated animals during a period of their lives (21 to 200 days) when no other method is able to demonstrate a damaging effect of radiation.

The loss of vitality has been shown to be a continuous process in that it progresses with time, and does not consist merely in an animal's being impaired to such an extent that a lower level of activity is assumed and maintained. This

seems to indicate that when a large dose of ionizing radiation is administered to some animals, a process of slow physical degeneration is initiated, which is probably enhanced at a later date by the normal gereological processes.

3.1 Influence of Training on Vitality of Mice:

It became obvious as the experiment progressed that some effects might have occurred during the first three weeks after irradiation, which may not be demonstrable by the method used. As indicated above there is evidence that during the first three weeks after the determinations began, the control mice improved their running record. If a similar process occurs in the irradiated mice, the radiation effects might be masked or confused by the training process.

In an attempt to eliminate this possible complication, several groups of mice were trained before exposure. The mice were run every third day for a three weeks' period, or until they reached a maximum. At this time certain mice in a group were found to be consistent in their running rates for several runs. Three of these mice, whose running rates compared within a few percent consistently, were chosen for running. The entire group was exposed to an LD-50 of fast neutrons, and the running rates of these animals and their controls were recorded once a week up to the present time.

The results obtained when determinations were made with three such groups are shown in Figure 5. It will be noted that there was no striking difference between the running rates of the irradiated and non-irradiated mice. In one group there was a difference of 12 percent, 270 days following exposure. In contrast, the groups which were exposed before

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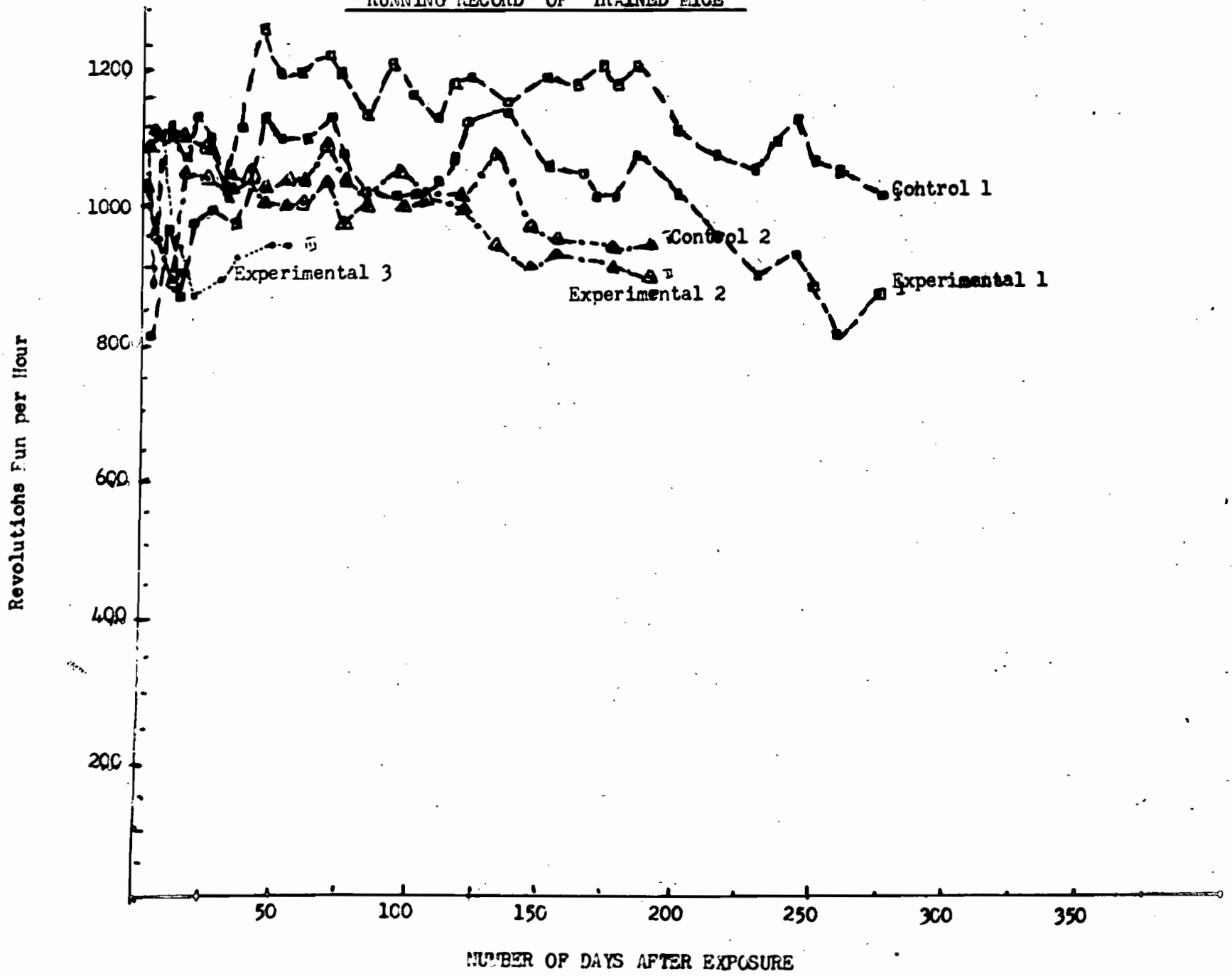
FIGURE 5

RUNNING RECORD OF TRAINED MICE



determinations began, at a similar time after exposure, showed that the experimental mice were able to do only 50 percent as much work as the controls, per unit of time.

Control mice showed a downward trend in vitality at 180 days, similar to that demonstrated in all previous groups.

One might conclude from the results obtained, that running the mice before exposure made them more physically fit, and thereby more radio-resistant. A more plausible explanation, however, is that picking the mice which reached a consistent maximum first, was, in a true sense, a process of selection. In other words, picking the mice as we did probably resulted in choosing the best and healthiest mice in a lot.

It is accepted by most investigators that the extent of damage incurred by the use of an injurious agent is dependent on the physical condition of the test animals at the time of administration. Since a selected group of mice was used for determinations, we might expect that they would be more radio-resistant than the average, or poorer than average, animals. To compare the results of these two experiments is in all probability not valid, since the procedure was altered in the second experiment.

It is thus apparent that the 'training' procedure as utilized does not go far in demonstrating the history of events occurring during the days immediately following irradiation. Since much is already known concerning the acute effects during this period, as evidenced by other types of examination mentioned before, it was not considered pertinent at this time to delve deeper into the vitality history.

From a different viewpoint, however, the training experiment is interesting in that it suggests a possible method for differentiation of animals in a group according to their physical condition. This leads one to ponder the possibility of using a similar method to study the relationship of physical condition to radio-sensitivity. Some experiments are now under way to test quantitatively this assumed relationship.

4. Summary

1. The effect of fast neutron irradiation on the ability of mice to do forced exercise has been studied, using several groups of CF-1 female mice. The experiments, performed with relatively small numbers of animals, do not allow us to make strong statistical analysis, but nevertheless, do show interesting trends, which suggest further experimentation using this method with minor improvements.

2. This method has made it possible to study the damaging effects of radiation on mice during a period when no effects were manifested by gross examination.

3. A continuous loss of vitality has been demonstrated in animals over a 300-day period following exposure to a median-lethal dose of fast neutrons.

4. Control mice have been found to demonstrate a vitality loss beginning at an age of about 8 months, which is probably a normal effect of aging. At the same time, irradiated mice show a striking loss of vitality, probably due to a compound effect brought about by normal aging occurring simultaneously with one of the late effects of radiation.

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