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Activity Pattern and Convulsions in the Abstinence Period after Barbital Treatment in the Rat

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WAHLSTRÖM, G. AND R. LARSSON. *Activity pattern and convulsions in the abstinence period after barbital treatments in the rat.* PHARMAC. BIOCHEM. BEHAV. 6(2) 187–192, 1977. – Barbital solution was given as the only drinking fluid to male rats for 50 weeks (daily dose around 200 mg/kg). During the treatment and in the abstinence period activity and convulsive episodes were recorded with jiggle cages. Sensitivity to hexobarbital was tested with a threshold method. A 12:12 hr L:D schedule was used. During the barbital treatment the activity of the treated rats started earlier (prior to light off) and ended earlier (prior to light on) compared with controls. A clear 24-hr pattern remained and the total activity was the same as in the controls. In the first part of the abstinence period there was a large increase in activity with loss of the 24-hr pattern. Later in the abstinence period the activity was still increased both during light and darkness but a 24-hr pattern influenced by the L:D cycle was re-established. The changes in activity seemed to occur in at least two phases with the second phase lasting between abstinent Days 20–60. A similar two phase pattern was seen also in the changes of the hexobarbital thresholds. The convulsive episodes had several maxima during the abstinence period. The first one occurred around abstinent Days 3–4 and the second one was seen around Day 12. After Day 37 no convulsions were seen. All recorded changes can tentatively be explained by a common increased excitation in the central nervous system.

Barbiturate abstinence Activity Convulsions Tolerance Physical dependence

CONVULSIONS are one of the more serious symptoms of the increased excitability found in the abstinence period after chronic barbiturate administrations [1, 5, 19]. This increased excitability can be quantified in various ways and used to record the intensity of the withdrawal reaction [1, 2, 3, 4, 5]. Increased excitability in the central nervous system (CNS) also increases the tolerance to depressant drugs. This means that the tolerance measured in the CNS during the abstinence period after chronic barbiturate treatments [7, 11, 13] could be due to increased excitation. Such a connection between increased excitation and tolerance has recently been further illustrated and extended when it was found that convulsions in the abstinence period either induced by electrical shocks [16] or occurring spontaneously [15] could decrease tolerance measured with a hexobarbital anesthesia threshold. These results indicate that convulsions could be not only one of the symptoms of increased excitation but also one of the ways in which the increased excitation in the abstinence period is reduced.

Increased excitation is usually observed for only a short time after the end of chronic barbiturate treatments. However, this did not seem to be the case after the rather extended barbital treatment period used to induce spontaneous convulsions in the study mentioned above [15]. The frequency of convulsions was still increasing when recording was ended three days after withdrawal. Since tolerance can be recorded for long times after the end of similar barbital treatments [13] a more detailed study of the time pattern and relation between frequency of convulsions, increased excitation measured as increased activity and tolerance in the abstinence period after extended barbital treatments was warranted. The results of such a study are presented here.

METHOD

Male Sprague-Dawley rats (Nih/Han/Mol, Möllegaard, Li. Skensved, Denmark) were used in the present experiments. Their initial body weight was around 300 g. Three rats were put into each cage at the start of the experiment. Two rats out of the nine rats (three cages) participating in the main activity study died during the barbital treatment. Except for registration of activity during the 20th week of barbital treatment (vide infra) the animals were kept in the original cages during the treatment. The animal room was shielded from all external light. The artificial light darkness schedule was 12 hr of light and 12 hr of darkness with the light being turned off at 08.00 o'clock. The temperature in the animal room was kept at 26°C. Food and drinking fluid were available at all times.

Sodium barbital was given in the drinking water. The concentration was 1.67 mg/ml during the first week and for the remaining 49 weeks was 3.33 mg/ml. During the first 5 weeks of treatment with the higher concentration the animals participating in the main activity study consumed

195 ± 3 mg/kg/day (± SE) of barbital. During Week 25–29 of the treatment the dose had increased to 227 ± 12 mg/kg/day. During the final 5 weeks of the treatment the dose was 223 ± 4 mg/kg/day. These averages are based on the weekly means as statistical units. The average body weight of the 7 animals participating in the activity study was 594 ± 21 g at the termination of the barbital treatment. The three controls that consumed tap water instead of the barbital solution had at the end of the 50 weeks of treatment a body weight of 593 ± 16 g. A more detailed analysis of similar treatments has been given earlier [13].

Activity and convulsions were determined by recording the activity of single rats in jiggle cages. Our standard stainless steel cage (25 × 25 × 20 cm) was placed in a metal bow which was suspended from a metal tongue. Movements of the cage were picked up by strain gauges attached to the metal tongue and the upper vertical part of the suspension arrangement. The movements of the cage were dampened by a further fixation of the bow below the cage. Grass polygraphs were used for recording.

The possibility to record convulsions was determined in separate experiments with pentylene-tetrazol. Major convulsive episodes could be picked up with a high degree of certainty by the abrupt start and the amplitude which exceeded normal locomotor activity.

The speed of the Grass polygraph was 5 cm/min which gave a 6 min record on each fold of the recording paper. These 6 min records were used as the basic activity unit. The rat was considered inactive if more than half the unit record consisted of no change in the baseline. This inactivity should occur in not more than two separate periods. A rat with many short bursts of activity was thus considered active even if more than half the unit record was spent in inactivity. Since the periods of activity or inactivity in the rat usually were longer than 6 min the introduction of the convenient 6 min activity unit did not distort the data in any important way.

An anesthesia threshold was determined by infusion of sodium hexobarbital in a tail vein at a constant rate of 0.25 mg/kg/sec (volume rate 0.1 ml/min). The electroencephalogram was recorded during the infusion with stainless steel sutures as electrodes. With these simple electrodes it was easy to pick up the first burst suppression of 1 sec or more (the silent second) which occurred in the EEG. The silent second was used as a threshold criterion and the dose of hexobarbital needed to obtain the criterion was calculated. Since different animals tended to have individual hexobarbital threshold doses the results are given in per cent of a pre-experimental value obtained by determinations prior to any treatment. The average pre-experimental values were in the barbital treated animals 61.3 ± 1.0 mg/kg (± SE N = 10) and in the controls 60.2 ± 1.9 mg/kg (N = 14). All threshold determinations were performed during the first 5 hr of darkness. The anesthesia threshold method is described in detail elsewhere [10].

After 19 weeks of barbital treatment 5 rats were placed into individual activity recording cages for a period of one week. Immediately after the 50 week treatment (designated abstinence day zero) seven rats were placed singly into the activity recording cages, where the barbital solution was replaced with tap water. Except for technical failures the recording was continued up to Day 60. Three controls were also recorded in the same way. The animals used for the threshold determinations were participating in the same barbital treatment but kept in the activity recording cages only between Day 0 and Day 3 of the abstinence. The rest of the abstinence period was spent in their home cages. These short activity records in these rats were part of another study not to be presented here.

The doses of the barbiturates used are given as their sodium salts. Student's t-test was used in the statistical analysis and where not otherwise stated two-sided unpaired tests were carried out.

RESULTS

Activity Pattern During the Barbital Treatment

In the control rats the main activity was restricted to the dark period of the 12:12 light darkness schedule. However, this main activity period could be subdivided into smaller parts by periods of inactivity lasting sometimes for several hours. During the light period there were only short bursts of activity interspaced between long periods of inactivity. This well known pattern has been called polyphasic by Szymanski [8] or polycyclic by Kleitman [6].

In Fig. 1 the pattern of activity in the control rats is compared with the pattern seen during the barbital treatment. There are some distinct differences between the patterns in the two groups. In the control animals the activity was clearly restricted to the dark period with usually less than 20 per cent of time spent in the light being classified as activity. A clear 24 hr rhythm was also seen in the barbital treated animals but the maximum occurred earlier and the activity was not clearly restricted to the dark period. During the light period the most marked difference was seen in the time interval between 04.00 – 08.00 hr (prior to light off). In all panels in Fig. 1 the barbital treated animals showed more activity than the controls. Significant differences ($p<0.05$) were found on Days 4, 6 and 7. Because only two values from the control rats were obtained on Day 5 no t-test was performed on this day. In

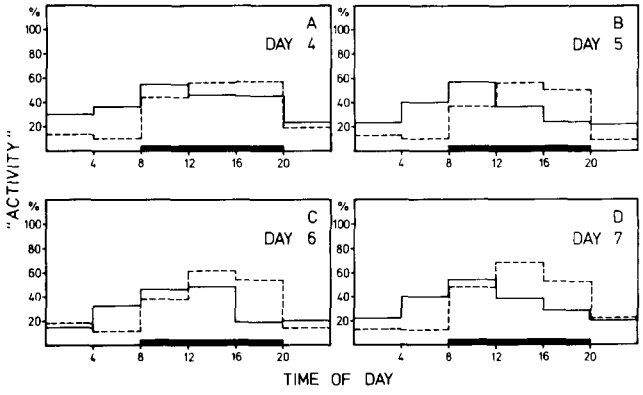

FIG. 1. The activity pattern during the barbital treatment. The activity was calculated as per cent of each 4 hr period. The black bar along the abscissa indicates the dark period in the light darkness schedule. The barbital treated animals (unbroken line) were recorded for one week after 19 weeks of treatment. The controls (broken line) were recorded at the end of the barbital treatment. Days were counted from the day the animals were put into the recording cages and are indicated in each panel. The number of animals which could be evaluated were 4 in the barbital treated group and 3 in the control group except on Day 5 when records were obtained from only 2 control rats. In the barbital treated rats the range of the standard errors were: on Day 4 3–11 per cent, on Day 5 3–5 per cent, on Day 6 2–7 per cent and, on Day 7 2–15 per cent. In the controls the corresponding values were: on Day 4 1–5 per cent, on Day 6 2–7 per cent and on Day 7 3–8 per cent.

the other time intervals during the light period the patterns in the two groups were more similar. During the dark period the control animals always showed more activity in the time interval between 16.00 – 20.00 hr (prior to light on). For this time interval too, there were significant differences ($p<0.05$) between the barbital drinking animals and the controls on Days 6 and 7. On Day 4 the p value (p less than 0.10) pointed in the same direction but did not reach a two-tailed significance. The difference at the end of the light period and at the end of the dark period indicate that the activity in the barbital treated animals was shifted forward and not as strictly regulated by light on and/or off as in the control animals.

The total time of activity (± SE) in the control animals was 7.9 ± 0.2, 7.7 ± 0.3 and 8.6 ± 0.5 hr on Days 4, 6 and 7 respectively. The corresponding total time of activity in the barbital treated animals was 9.4 ± 0.8, 7.2 ± 0.3 and 8.1 ± 0.5 hr respectively. The differences between the controls and the barbital treated animals were not significant ($p>0.05$) on any of the days. Thus during the barbital treatment the pattern but not the total amount of activity seemed to be changed.

Activity Pattern During the Abstinence Period

A comparison of the total time spent in activity during the 12 hr dark period between the controls and the treated rats over the abstinence period is shown in Fig. 2A. In the control animals approximately half the time was spent in activity. In the previously barbital treated animals the activity was consistently increased compared with the controls but only on a few occasions was a significant ($p<0.05$) increase recorded.

Figure 2 B presents similar criteria to Fig. 2 A except that the 12 hr light period is considered. The control animals had very short bursts of activity which in total did not amount to more than 2 hr. Compared with the controls the previously barbital treated animals had a very large increase in activity during the first part of the abstinence. The peak for this activity during the light period occurred around Day 3. On several days around this maximum the differences with the corresponding controls were highly significant ($p<0.01$). On Day 20 only a very small nonsignificant increase remained. A new much smaller peak was seen on Day 29. Later on the activity was still increased in the previously barbital treated animals but only on sporadic occasions was a significant difference seen. On Day 58 the previously barbital treated animals for the first time in the abstinence period showed less activity during light than the corresponding controls.

Since the activity in the previously barbital treated animals was increased in comparison with the controls both during the dark (Fig. 2 A) and during the light (Fig. 2 B) period of the 24 hr light darkness schedule, the total activity per 24 hr is of interest. This is given in Table 1. As expected from the values presented in Fig. 2 A and B the total activity was much greater for the barbital treated animals. Of the days included in Table 1 a nonsignificant difference was obtained only on Days 20 and 60. The first peak in the total activity found in the abstinence period was mainly due to the large increase found in the light period. After that there seemed to be a more general increased level of activity which was not restricted to any particular time of the 24 hr light darkness schedule.

This conclusion is illustrated in Fig. 3 where some examples of the activity pattern are given. On Day 4 there

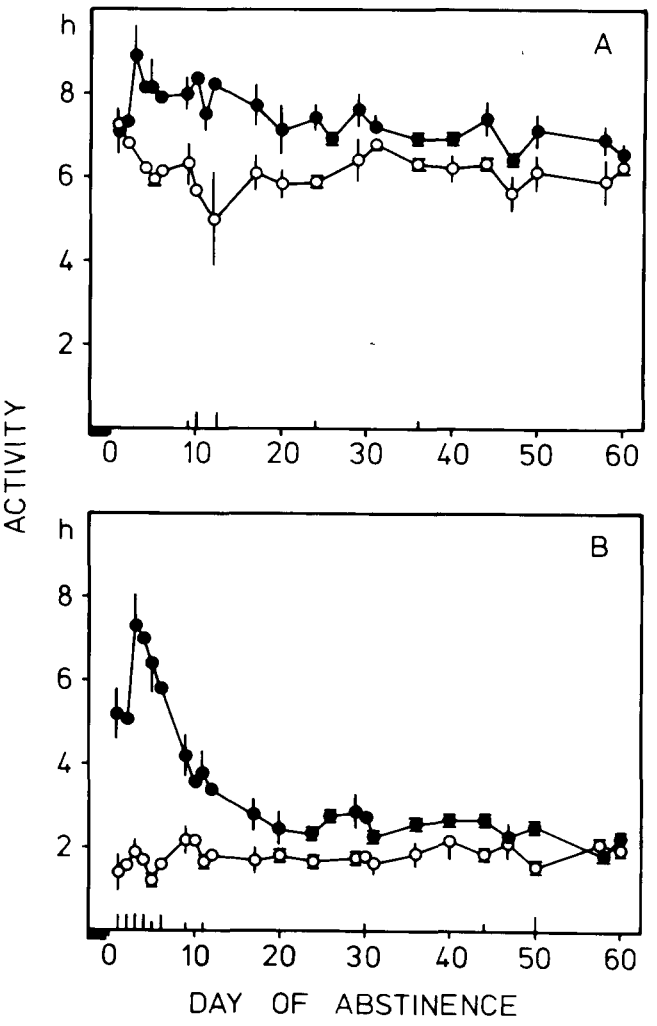

FIG. 2. Time spent in activity during the 12 hours of darkness (panel A) and 12 hours of light (panel B) in the 24 hr darkness-light schedule. The bar along the abscissa to the left indicates the last part of the barbital treatment. The standard error of the mean sometimes plotted only in one direction is indicated by the vertical line, or, if covered by the symbol indicated by a short horizontal line. Filled symbols indicate barbital treated animals (N = 7) and unfilled symbols indicate controls (N = 3). Differences with a p value less than 0.01 are indicated by the longest vertical line on the abscissa, differences with a p value larger than 0.01 but less than 0.05 are indicated by the shorter vertical line on the abscissa.

was a consistent high activity at every time of day in the previously barbital treated animals. No activity rhythm with a 24 hr period could be seen. On Day 12 the activity in the previously barbital treated animals was more confined to the dark period, indicating a return to a 24 hr rhythm regulated by light. The activity was still, at all time intervals, greater than the controls. The pattern is similar but the increases less marked on Day 30. On Day 60 there is essentially no difference between the two groups of animals although the previously barbital treated animals do still tend to be slightly more active.

Convulsive Activity and Tolerance to Hexobarbital During the Abstinence Period

The spontaneous convulsions recorded during the absti-

TABLE 1

TOTAL OF RECORDED ACTIVITY IN HOURS ON DIFFERENT DAYS AFTER THE RATS WERE PUT INTO THE RECORDING CAGES*

Day*	Barbital Treated Animals Mean	SE	N	Control Animals Mean	SE	N	Difference t	p
4	15.2	1.1	7	7.9	0.2	3	4.06	<0.005
10	12.0	0.8	7	8.0	0.4	3	3.23	<0.02
12	11.6	0.8	7	6.9	0.9	3	3.48	<0.01
20	9.6	0.9	7	7.7	0.3	3	1.34	NS
24	9.8	0.5	7	7.6	0.3	3	2.75	<0.05
30	10.3	0.5	7	8.2	0.4	3	2.83	<0.025
40	9.6	0.2	7	8.3	0.4	3	2.94	<0.02
50	9.6	0.5	6	7.7	0.5	3	2.48	<0.05
60	8.8	0.4	7	8.3	0.2	3	0.71	NS

*The number of the day corresponds to the time the barbital treated animals have been abstinent.

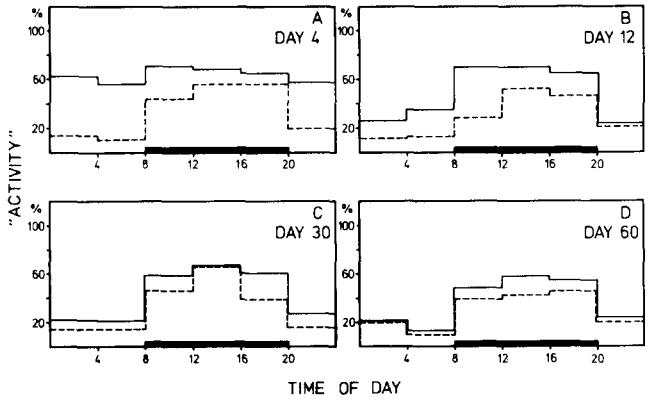

FIG. 3. The activity pattern after the barbital treatment. The activity was calculated as per cent of each 4 hr period. The black bar along the abscissa indicates the dark period in the light-darkness schedule. The previously barbital treated animals (N = 7, unbroken line) and the controls (N = 3, broken line) were recorded from the end of the barbital treatment. Days were counted from the day the animals were put in the recording cages and corresponds to days of abstinence. Day No. 0 was the one in which the recording and the abstinence started. In the previously barbital treated animals the range of the standard errors were: on Day 4 4–7 per cent, on Day 12 3–6 per cent, on Day 30 2–5 per cent and on Day 60 2–4 per cent. In the controls the corresponding values were: on Day 4 1–5 per cent, on Day 12 2–14 per cent, on Day 30 1–5 per cent and on Day 60 2–7 per cent.

nence period are shown in Fig. 4 A. The total frequency over time has several similarities with a dampened oscillation. The first maximum was seen on Days 3–4 and is easily recognizable. The second maximum is also distinct and occurred on Day 12. Maxima may occur later but are harder to identify. If three smaller values are required on both sides to define a maximum (disregarding the late sporadic convulsions) another maximum on Day 25 can be noted. No convulsions were observed after Day 37 and no convulsive episodes at all were seen in the controls.

Between Day zero and Day 9 (the first maximum) 44 per cent of a total of 98 convulsions occurred during the light period. Between Day 10 and Day 21 and for the recorded time after Day 21 the corresponding figures were 18 per cent out of a total of 68 convulsions and 17 per cent out of a total of 17 convulsions respectively.

The changes in sensitivity to hexobarbital were recorded with the threshold method. These threshold determinations were not performed on the animals used to obtain the long activity record. They were kept singly in the activity recording cages only up to Day 3 when the first threshold determination in the abstinence period was performed. Figure 4 B shows that there was a decrease in sensitivity to hexobarbital in the abstinence period after the barbital treatment. This tolerance had a first maximum on Days 7–8 and a second maximum on Days 28 – 29. On Days 59 – 60 there was still a small but significant ($p<0.05$) difference between the controls and the previously barbital treated animals. The next threshold determination was performed on Days 73–74. At that time no significant difference was recorded.

DISCUSSION

In the present study the variables which were followed during the abstinence period only slowly returned to the control level. Convulsions had disappeared around Day 30. More than 60 days were needed for the changes in activity and in sensitivity to hexobarbital to reach the control values. With regard to changes in sensitivity to hexobarbital the duration of the changes exceeded the durations found in an earlier study [13]. The duration of the present barbital treatment was also 8 weeks longer than the maximum treatment in the experiments reported earlier. Since the barbital doses in the present experiment was well within the range of doses obtained in the earlier experiments [13] the increase in the duration of the treatment is the most probable cause of the increase in the duration of the abstinence period.

In the data obtained with the hexobarbital threshold (Fig. 4 B) there was recorded a clear biphasic pattern in the tolerance. After a first maximum the thresholds almost returned to the control level on Day 21. Later on a new maximum was seen. Such a biphasic pattern has earlier been recorded in the tolerance to hexobarbital after barbital treatments [12, 13, 18]. In the present experiments the data on the increase in total activity (Table 1) had the same biphasic pattern as the tolerance data. In fact the change over time was very similar in the two variables. With regard to convulsions (Fig. 4 A) the pattern is not equally clear since the total frequency is declining three weeks after the

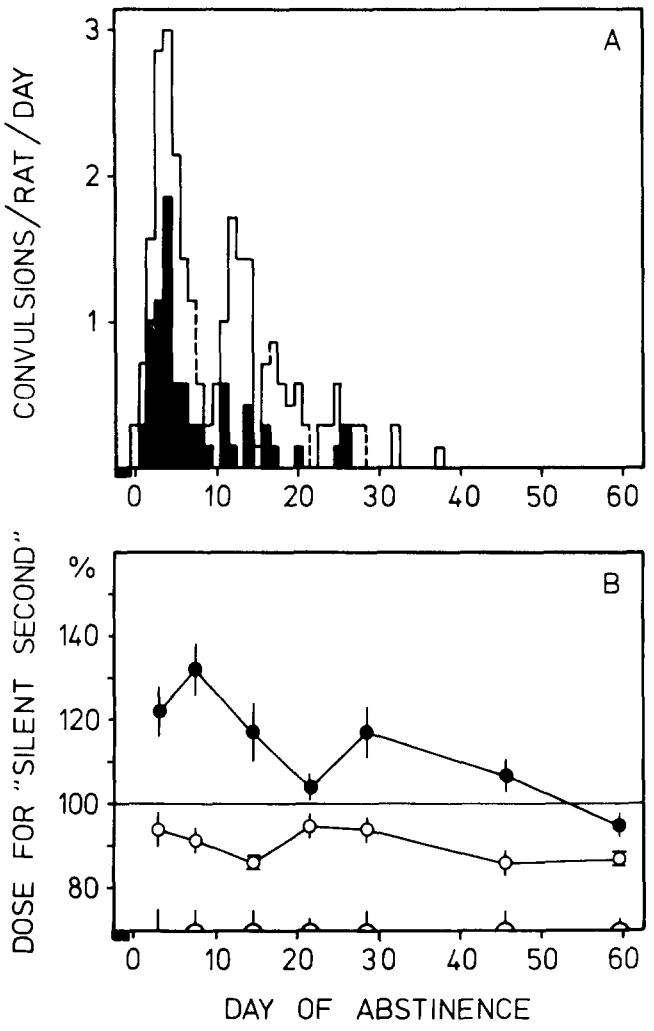

FIG. 4. Number of convulsions per rat per day (panel A) and hexobarbital thresholds (panel B) in the abstinence after the chronic barbital treatment. In panel A the unfilled bars represent the total number of convulsions recorded, the filled bars represent the number of convulsions which occurred during light. A broken vertical line indicated no record for some hours due to technical troubles. The number of rats participating in the recording of convulsions were 7. No convulsions were seen in the records from 3 control animals. In panel B the hexobarbital thresholds are given in percent of a preexperimental average. The vertical lines at the symbols indicate the standard error of the mean, the short horizontal lines indicate a standard error smaller than the symbol. Previously barbital treated animals (N = 8–11) are indicated by the filled symbol, controls (N = 12–14) by the unfilled symbol. A half circle on the abscissa indicate recording on two different days, if combined with the larger vertical line the difference between previously barbital treated animals and controls had a p value less than 0.01, if combined with the shorter vertical line the p value was larger than 0.01 but less than 0.05.

end of the barbital treatment. A late maximum can probably be defined around Day 25 (see Results).

The biphasic pattern can be used to divide the abstinence period into two parts. In the first phase up to Day 20 the more dramatic changes were seen. The changes of activity mainly occurred in the light part of the 24 hr light darkness schedule (Fig. 2B). The rats were for a short time very active and no 24 hr activity rest pattern could be found (Fig. 3A). This could mean either that the mechanism regulating the time pattern of activity and rest (the basal clock) did not work during abstinence or that the clock is working all right but some other overriding control system has taken hold of the variable used to record the function of the clock. Such a disruption of recording but with a basal clock probably still running has been seen after treatment with reserpine in canaries [9]. In the present case there is no possibility to choose between these alternatives. The earlier start of the activity found during the barbital treatment (Fig. 1) which also can be recorded if running wheel activity is used [14] does not specifically favour either of the hypotheses. The only definite conclusion which at this moment can be drawn from the activity pattern found during phase one is that light-darkness schedules cannot be relied upon to regulate the time of activity during this phase of the abstinence period.

Earlier studies have shown that there is a relationship between convulsions and sensitivity to hexobarbital during the first four days of abstinence. The tolerance to hexobarbital is reduced by spontaneous convulsions [15], pilocarpine induced convulsions [17] and electrically induced convulsions [16]. Since two different groups of animals were used in the present experiment no detailed comparison between the frequency of convulsions (Fig. 4A) and sensitivity to hexobarbital (Fig. 4B) can be made. It is nevertheless obvious that during phase one there was a parallel decrease in the frequency of convulsions and in the tolerance to hexobarbital.

There is also during phase one a parallel decrease in frequency of convulsions during the light (Fig. 4A) and in activity during light (Fig. 2B). It is possible that convulsions could occur only during activity. A decrease in activity would then mean a concomittant decrease in convulsions if there was no change in the number of convulsions per activity time unit. If such a connection exists the 6 min time period prior to all convulsions should consist of activity. This was however not the case: 60 per cent of the 98 convulsions which occurred between day zero and Day 9 were preceded by at least one 6 min period of activity. Around Day 4 when most of the convulsions in the time period between Day zero and Day 9 occurred (Fig. 4A) the animals spent slightly more than 60 per cent of the total time as activity (Fig. 3A). Thus the percentage of convulsions preceded by activity is very close to the value expected if convulsions occurred without any direct relation to either activity or rest. The parallel changes in activity and in frequency of convulsions seen between day zero and Day 9 of the abstinence period must be regarded as not directly related. However, they could still be different expressions of the same basic change in the animal.

After Day 9 the large increase in activity (Table 1) seen mainly during the light (Fig. 2B) has passed. There is now also a change in the distribution of the convulsions. Between Days 10 and 21 the percentage of convulsions preceded by at least one 6 min period of activity was increased to 76 per cent out of 68 convulsions. In the time period after Day 21 the figure was 82 per cent out of 17 convulsions. Thus at later stages of the abstinence period the convulsive episodes tended to occur at a time period when the animal was active, which also means that they now occur predominantly during darkness (see Results). It is only during the early part of the abstinence period when

no 24 hr regulated pattern of activity can be found that such a pattern in the convulsions also is absent.

In phase two there is a maximum on Day 30 of increase in activity (Table 1) and tolerance to hexobarbital (Fig. 4B), followed by a gradual decrease in both variables. The increase in spontaneous activity has no distinct 24 hr pattern (Fig. 3C) and the light darkness regulated activity rhythm is retained. It is highly probable that both variables in different ways measure an increased excitation in the central nervous system. The hexobarbital threshold is evidently at least as good a way to pick out these changes as the activity measurements. Such a long lasting excitation could of course be of importance for the relapse rate when depressant drugs have been abused. Whether the loss of the 24 hr light darkness regulation of the pattern of activity and to some extent also convulsions during the first part of phase one is due only to quantitative differences in the intensity of the abstinence reaction or if qualitative differences are involved is an open question.

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