STUDIES ON THE MECHANISM OF THE EFFECT OF IONIZING RADIATIONS ON THE OLFACTORY SYSTEM

PROGRESS REPORT

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DISCLAIMER

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Abstract

The effects of x-rays on the olfactory system of rats were examined in 3 experiments, one of which is still in progress. In one experiment the response of single olfactory bulb neurons to x-rays was studied during the perfusion through the nasal cavities of gas containing various concentrations of oxygen. The results show that the response to x-ray is constant for oxygen concentrations above 5 percent, while appreciable response decrement does not occur until concentrations of 2 percent or less are used. The oxygen concentration at which response decrements are first seen (about 2 percent) and the maximum response decrement occurring with 0 percent oxygen (about 30 percent of control values) closely agree with certain other experiments in which the "oxygen effect" has been demonstrated. We concluded that x-rays probably stimulate the olfactory system indirectly by the production of chemical agents and through reactions which are facilitated by oxygen.

In another study it was found that immediate alterations in respiratory rate could be produced in anesthetized rats by x-rays. Further investigations in unanesthetized animals having lesions of the olfactory bulbs or sham lesions of the cerebral cortex revealed that such effects were largely, if not entirely, a consequence of olfactory stimulation by the radiation. Thus, the arousal effect of olfactory stimulation by x-rays is potent enough to produce striking and immediate changes in respiration and such changes may be used as an index of olfactory stimulation.

A study now in progress is aimed at determining the relative responsiveness of rat olfactory bulb neurons to x-ray, ozone, and odor (amyl acetate). Although it is still too early to draw definite conclusions, preliminary results indicate that cells responsive to x-rays are also more responsive to ozone than cells which are not responsive to x-ray. The data obtained thus far indicate that the radiation-produced olfactory stimulus is an oxidizing agent similar to ozone, if not ozone itself.

General Review of Research Progress

Research done before the initiation of this AEC contract had shown that some neurons in the olfactory bulb respond when rats, cats, dogs, and rabbits are exposed to x-rays (Cooper and Kimeldorf, 1966, 1967; Cooper, *et al.*, 1966). Since such responses could be depressed or abolished by the nasal perfusion of pure argon or nitrogen, it was also tentatively concluded that the effects of radiation were exerted on the olfactory mucosa rather than on the olfactory bulb itself. The sensory nature of the response was demonstrated in two experiments presented in a previous progress report. Specifically, it was shown in one experiment that the response to x-rays can be described quantitatively by functions typical of many sensory stimulus-response relationships. In the other experiment beta rays, which had not been employed previously in this type of research, were shown to be effective olfactory stimuli --- but only if the beta source was focussed directly upon the olfactory receptor surface. This material was presented at the annual meeting of the Radiation Research Society in April, 1968 (Cooper, 1968a). Since the results of the two experiments were clearly complementary, they were incorporated into one paper, a reprint of which is included with this report (Cooper, 1968b).

Since the olfactory system is so sensitive to ionizing radiation it might have been supposed that harmful effects on the system would be observed at relatively low doses. But, in another study we have shown that this is not at all the case. Acute abolition of olfactory bulb response to strong odor stimulation in rabbits did not occur until head-only exposure doses in excess of 50 KR had been given. And olfactory receptor responses were not abolished even with doses as great as 95 KR. Therefore, it was concluded that the extreme sensitivity of the olfactory system to x-rays was not a consequence of its being easily damaged by radiation (Cooper, 1969a; reprint enclosed).

During the course of some of the experiments mentioned above it was incidentally observed that changes in respiratory rhythm appeared to occur immediately upon exposure of anesthetized rats to x-rays. During the past year a separate experiment was carried out to investigate this phenomenon. In brief, the results of experiments on both anesthetized and unanesthetized rats show that striking changes in respiratory rate can be recorded well within the first 0.5 seconds after the beginning of irradiation. Furthermore, such responses are a consequence of olfactory stimulation by x-rays rather than of some metabolic effect, since rats with olfactory bulb lesions do not respond. Therefore, respiratory rate measurements represent a very easy and reliable way to assess the olfactory arousal effects of ionizing radiation. Since this work has not been reported previously it is presented in detail below. A manuscript has been submitted for publication.

Much of the data discussed above implicate an effect of ionizing radiation on olfactory receptors. But the question remains of precisely what the radiation-produced stimulus actually is and where it is produced. In another experiment completed within the past year an initial attack on these problems was made. The purpose of the experiment was to determine whether the concentration of oxygen in gas flowing through the nasal cavities influences the strength of response of olfactory bulb neurons to x-rays. The results of the experiment are significant in that they clearly show that the response to radiation is unaffected until the oxygen concentration is decreased to about 2 percent, below which the response decreases dramatically until at 0 percent oxygen it is only 30 percent as large as responses obtained with 10 percent oxygen. The response functions closely resemble the "oxygen effect" curves obtained in a variety of other radiobiological experiments. We concluded that ionizing radiation probably stimulates olfactory receptors by the production of some chemical substance through reactions which require, or are facilitated by, oxygen. This work was presented at the annual meeting of the Radiation Research Society in May, 1969 (Cooper, 1969b) and is described in detail below. A manuscript has been submitted for publication.

The outcome of the study described in the preceding paragraph, which establishes the importance of oxygen in the olfactory response to radiation and the finding of Gasteiger and Helling (1966) that ambient ozone selectively masks x-ray detection in rats, led to the design of another experiment intended to further clarify the nature of the radiation-produced olfactory stimulus. The work has not been in progress long enough to yield sufficient data for making firm conclusions, but preliminary results indicate that olfactory bulb neurons which respond to x-rays are also more responsive to ozone than units which do not respond to x-rays. On the other hand, those units which do not respond to x-rays appear to be more responsive to amyl acetate. If these initial results are borne out by future work we will be able to conclude that the stimulus agent produced by ionizing radiation is very probably some oxidizing substance, possibly ozone. From the subjective point of view we can already venture the prediction that the olfactory experience produced by ionizing radiation will prove to have an unpleasant ozone-like quality.

RESPONSE OF OLFACTORY BULB NEURONS TO X-RAYS AS A FUNCTION OF NASAL OXYGEN CONCENTRATION

The olfactory systems of a variety of animal species, including dogs, cats, rabbits (Cooper and Kimeldorf, 1967), rats (Garcia, et al., 1964; Hull, et al., 1965; Cooper and Kimeldorf, 1965; Dinc and Smith, 1966), pigeons (Smith, et al., 1964), and monkeys (Taylor, et al., 1968), have been shown to be responsive to ionizing radiation. Although direct recordings from olfactory receptors have not been undertaken in these studies, several lines of evidence implicate an effect of the radiation on receptors. For example, in tracheotomized rats breathing room air responses of olfactory bulb neurons are abolished or depressed by the nasal perfusion of oxygen-free gas (Cooper, et al., 1966). Also, transection of the olfactory nerves abolishes behavioral responses of pigeons to x-rays (Tucker and Smith, 1969). Finally, localized beta irradiation of the olfactory mucosa in rabbits produces responses of olfactory bulb neurons (Cooper, 1968b).

We have hypothesized that the effects of ionizing radiation on the olfactory system is an indirect one involving the production of some substance such as ozone or hydrogen peroxide (Cooper, et al., 1966). Some support for this was provided by the finding in behavioral experiments that ambient ozone specifically masks x-ray detection in rats (Gasteiger and Helling, 1966). Without trying to further specify the exact nature of the stimulus substance, there is in any case good reason to suppose that oxygen might be importantly involved. Therefore, the purpose of this experiment was to examine the responses of olfactory bulb neurons to x-rays during the nasal perfusion of gas containing various concentrations of oxygen.

Procedures and Equipment

The activity of single olfactory bulb neurons was recorded in adult Wistar rats anesthetized with ethyl carbamate

(Urethan). The trachea of each rat was severed and both ends cannulated. The animal breathed room air through the caudal cannula and the rostral cannula was connected to a gas perfusion system which permitted the nasal perfusion of either odorized or unodorized gas containing any desired concentration of oxygen. Pressurized tanks of nitrogen and oxygen were used, with the desired percentages of the two being obtained through a system of flowmeters and needle valves. For precise and continuous monitoring of oxygen concentrations an oxygen meter was included in the perfusion line. A gas flow rate of 250-300 ml/minute was used. The x-ray dose rate was routinely 90 R/minute measured in air at the skin surface. All exposures were 3 seconds long and were made with a Westinghouse x-ray machine operated at 250 KVP and 15 ma, with 1 mm Al and ½ mm Cu filtration. In preliminary experiments neurons responsive to x-irradiation were tested during the nasal perfusion of gas containing oxygen concentrations ranging from 0 to 100 percent. In later experiments maximum oxygen concentrations of 10 or 20 percent were employed since the preliminary work had shown that neuronal responses were not affected by increases in oxygen concentration above 10 percent. An attempt was made to test all units at oxygen concentrations of 10, 5, 3, 2, 1, and 0 percent, but in many cases the cell could not be held long enough to examine satisfactorily its response at all of these concentrations.

Results and Discussion

Figure 1 shows the responses to x-ray of 4 olfactory bulb units as a function of nasal oxygen concentration. The results are representative of all data collected on 17 different units. In all cases the response to a standard x-ray exposure was constant for all oxygen concentrations above 10 percent. In a few instances there appeared to be a slight depression of response with 5 percent oxygen, but clear response depression occurred only at oxygen concentrations of 2 percent or less. With 2 percent oxygen the mean response was 70 percent of control for 12 neurons studied. At an oxygen concentration of 1 percent the mean response for 13 units was 55 percent of the mean control response for these same units. A mean response amounting to only 30 percent of control values was obtained at 0 percent oxygen (15 units). The curves shown in Fig. 1 closely resemble the "oxygen effect" curves which have been obtained in a variety of other radiobiological experiments (cf. Alper, 1961).

With 3 units the x-ray dose rate as well as oxygen concentration was systematically varied. The results obtained

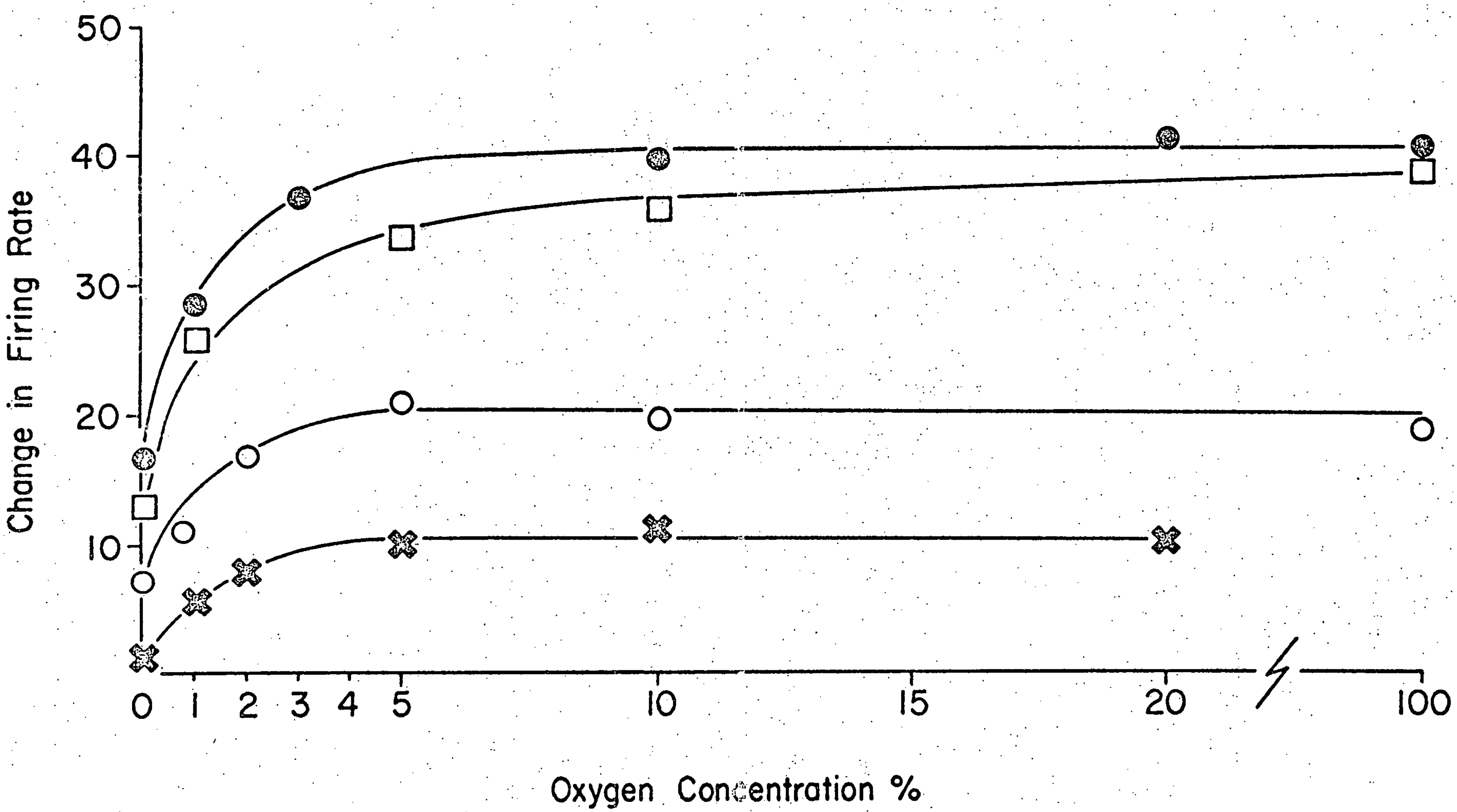

Fig. 1. Change in firing rate of four different olfactory bulb neurons in response to x-ray as a function of nasal oxygen concentration. Each point is the mean of two observations.

from one of these cells is shown in Fig. 2. At any given oxygen concentration the response is approximately a linear function of the logarithm of the dose rate. As the oxygen concentration is reduced the response function shifts to the right with no appreciable change in slope.

Depressions of normal resting activity of olfactory nerve fibers and olfactory bulb neurons as well as very small depressions of olfactory nerve response to odor have been observed with nasal oxygen concentrations of 1 percent or less (Tucker, 1963; Cooper, et al., 1966). Therefore, to control for the effects of lowered oxygen on normal receptor function we examined the response of 10 of the units described above to amyl acetate (10^{-2} of vapor saturation at 30°C). Responses to odor stimulation remained essentially constant at all oxygen concentrations, as shown with 2 units in Fig. 3.

As a working hypothesis we have proposed that ionizing radiation affects the olfactory system through the production of a hypothetical stimulus substance in or near the olfactory mucosa (Cooper, et al., 1966; Cooper, 1968b). If this view is valid then the data of Figs. 1 and 2 suggest, in summary, that the concentration of this substance is, within limits (a) linearly related to the dose rate, since the logarithmic transformations required for the linear functions of Fig. 2 presumably result almost entirely from the nature of the energy transduction process of receptors, and (b) positively related to nasal oxygen concentration at very low concentrations although oxygen is not essential. Of the major chemical products of radiation occurring in air or aqueous solution only ozone is known to be normally odorous. Therefore, it is probable that it or some short-lived oxidizing substance is the agent mediating olfactory stimulation by ionizing radiation.

IMMEDIATE RESPIRATORY CHANGES RESULTING FROM OLFACTORY STIMULATION BY X-RAYS

During the course of other experiments it was incidentally observed that changes in respiratory rhythm appeared to occur immediately upon exposure of anesthetized rats to x-rays. These observations were made while recording from olfactory bulb neurons, many of which have activity patterns which are synchronized with respiration. The effect was seldom observed because, as the present research revealed, such changes cannot

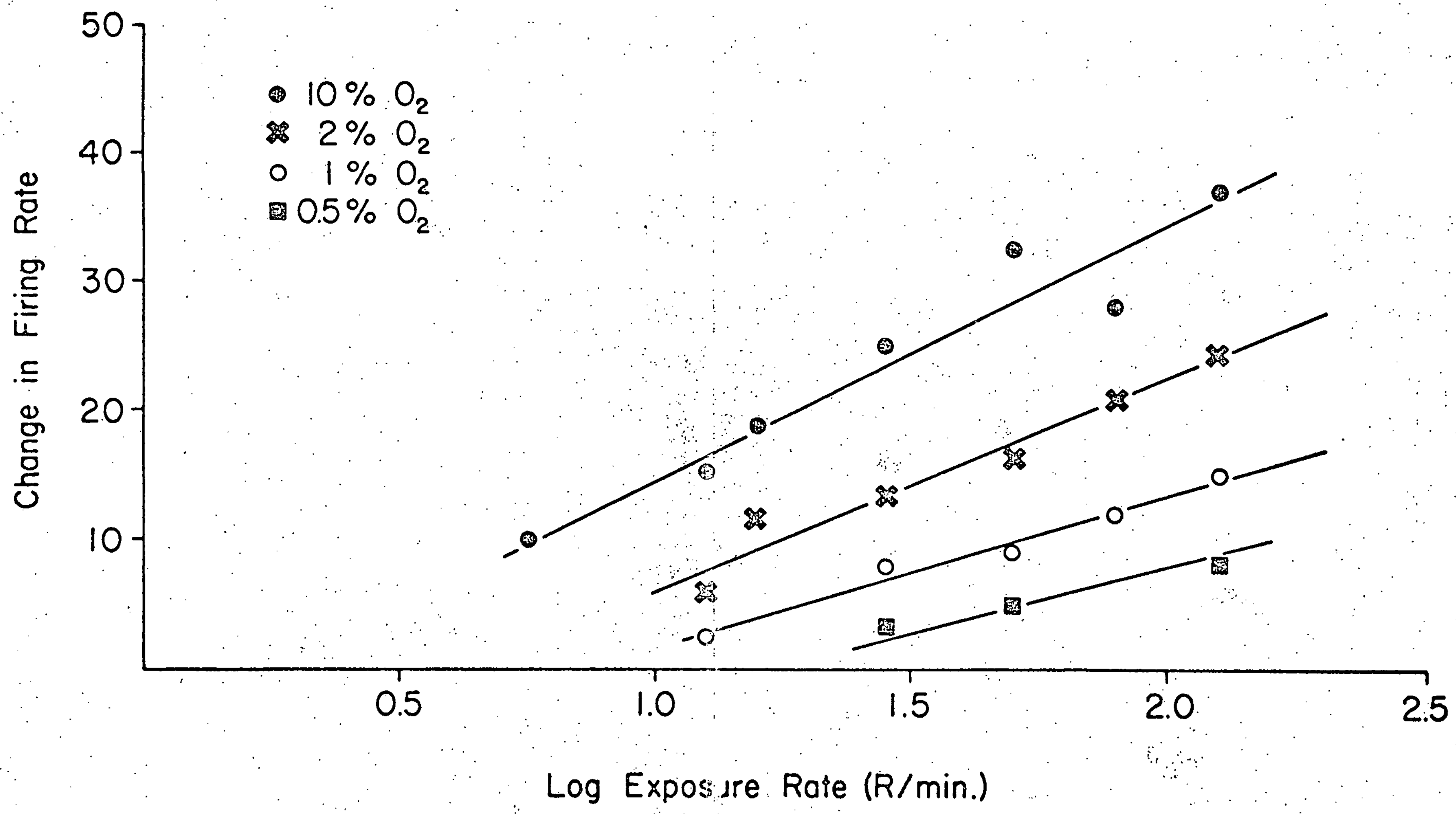

Fig. 2. Change in firing rate of one olfactory bulb neuron as a function of x-ray exposure rate and nasal oxygen concentration. Each point is the mean of two observations.

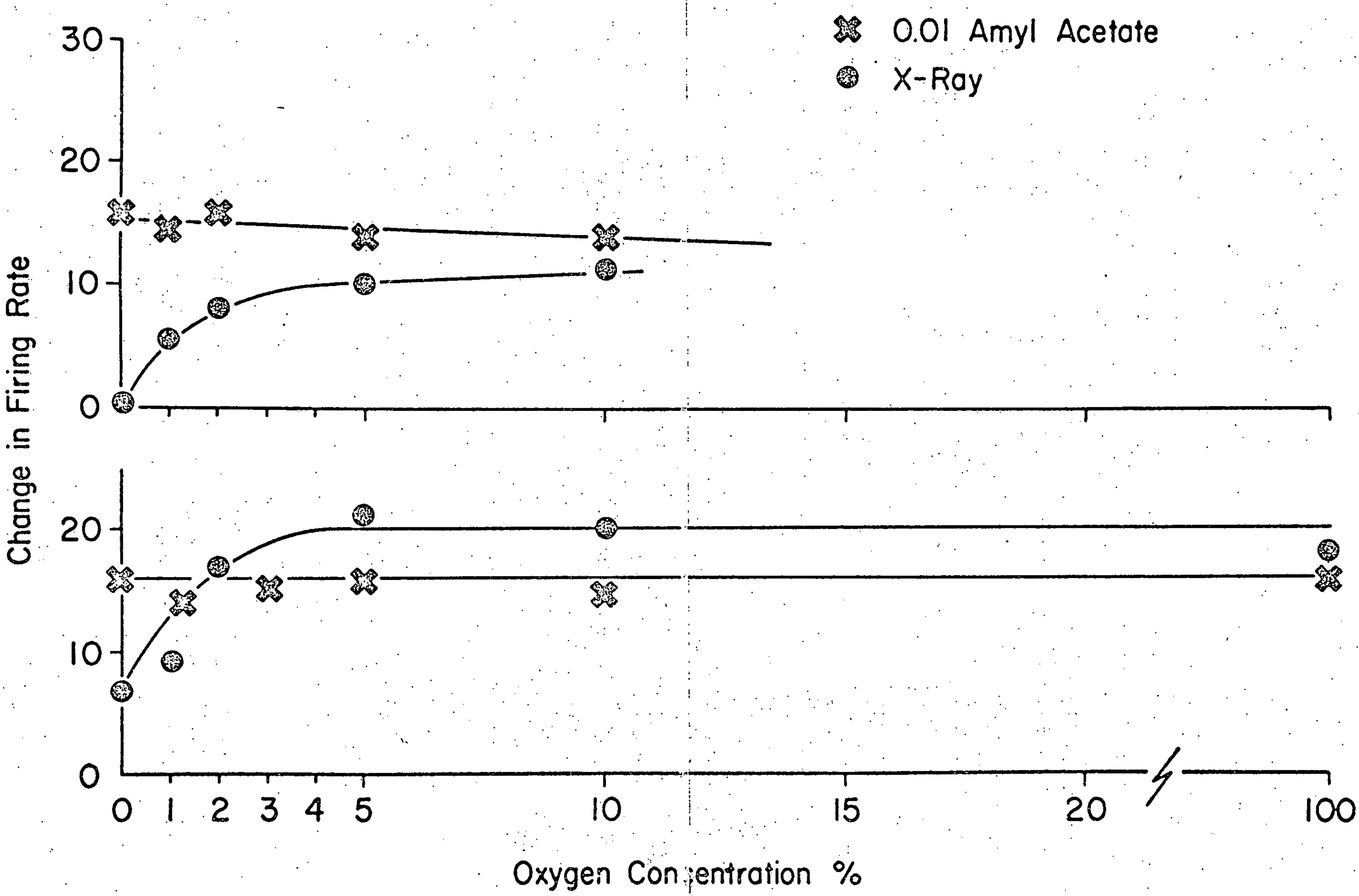

Fig. 3. Response of two different olfactory bulb neurons to x-ray and amyl acetate as a function of nasal oxygen concentration. Each point is the mean of two observations.

be obtained with animals under deep anesthesia.

Other workers have studied the effects of ionizing radiation on various parameters of respiration but insofar as we can determine the effects that have been observed on respiratory rate and depth, and on oxygen utilization have occurred only after relatively long periods of time and high doses (Kimeldorf and Hunt, 1965). In the normal animal changes in respiratory rhythm may be a consequence of either metabolic requirements or of changes, often sudden, of stimulating conditions not directly associated with metabolic need --- such as the arousal effect of a loud noise. The respiratory changes appearing during and after large doses of radiation are probably of the former class, while the immediate changes seen in the present experiment are almost certainly of the latter type.

Following the completion of this experiment it was learned that Hunt (1969) had made similar observations using "hypnotized" rabbits. This work will be given deserved further consideration below.

Procedures and Equipment

Thirty adult male Wistar rats were used. In the first part of the experiment, in which 16 rats were employed, each animal was given a 1 gm/kg intraperitoneal injection of ethyl carbamate (Urethan). Within 30 minutes after anesthetization electrodes were attached to the thorax for recording respiratory movements with an impedance pneumograph (E and M Instrument Co.). The animal was then placed in a prone position on a table and arranged so that it would be within a vertically-oriented x-ray beam generated by a Westinghouse x-ray machine operated at 250 KVP and 15 ma, with 1 mm Al and $\frac{1}{2}$ mm Cu filtration. All exposures were 3 seconds long and the dose rate was 3 R/second, measured in air. Sham exposures were made before and after each x-ray exposure and consisted of either exposing the whole animal to 30 KVP x-rays or shielding the whole animal with a 1 cm-thick sheet of lead and operating the x-ray machine as usual. A positive response to x-ray was recorded only if the respiratory rate changed by at least 1 cycle per second within 3 seconds after the beginning of irradiation on at least two trials, and with no changes on sham trials preceding and following the x-ray test.

For the second part of the experiment, olfactory bulb ablations were made by aspiration in 10 rats,and ablations of the parietal cerebral cortex were made in another 10 animals. After surgery the animals were placed at random in individual cages by a technician. The animals were not marked in any way to indicate the type of lesion which had been sustained so that this knowledge could not prejudice the outcome of subsequent x-ray trials. The rats were allowed one month for recovery after which time 14 of them were used in the experiment. The experimental procedure was identical in most respects to that described above, except that these lesioned rats were not anesthetized and were therefore placed in cylindrical lucite restraining cages during testing. All rats which responded to whole-animal x-irradiation were given body-only exposures by shielding the head and neck with a 1 cm-thick sheet of lead. After examining the effects of x-irradiation on respiration the rats were killed and the location and extent of the lesions determined.

Results and Discussion

Fig. 4 shows the results of a series of x-ray exposures in an anesthetized rat. Striking changes in respiration occurred within 0.5 seconds in most rats and probably occurred within 250 milliseconds in many. These changes usually consisted of a pronounced increase in rate, usually associated with some decrease in depth of inspiration. In Fig. 4 are shown the 1st, 2nd, 4th, 6th, and 8th x-ray exposures (records A through E, respectively) given to the whole animal. Exposures were made at 5 minute intervals. As can readily be seen the respiratory response diminishes with successive exposures until there is little or no alteration on the 8th trial. This habituation occurred in all 6 animals which were given such a series of exposures.

Table I shows the data for the first x-ray exposure for each of the 16 anesthetized preparations. Respiratory rates were determined by counting the total number of respiratory cycles occurring in the 10 seconds preceding the onset of irradiation, and for the periods 1 to 3, 5 to 10, and 20 to 30 seconds after the beginning of irradiation; the numbers obtained were divided by the number of seconds involved for each of the 4 periods. Two of the rats (numbers 3 and 15) failed to respond but the remaining 14 animals showed substantial increases in respiratory frequency during the 3-second period of irradiation. The mean rate changed from 2.1 per second in the 10 seconds prior to irradiation to 3.8 per second in the 2-second interval beginning 1 second after the start of irradiation. It is surprising that for most animals the respiratory rate is already approximately at control levels in the 5 to 10 second interval after the beginning of irradiation.

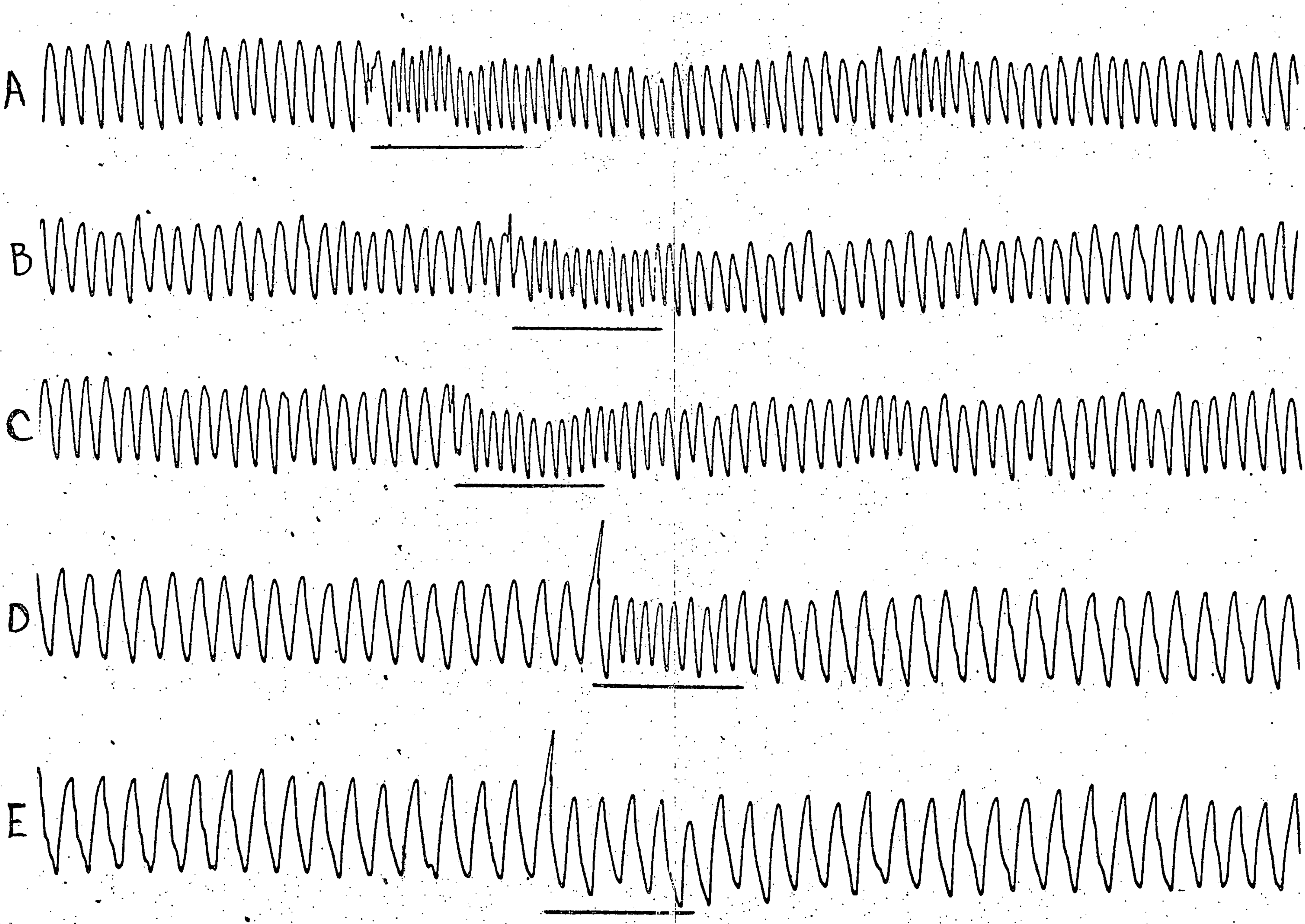

Fig. 4. Respiratory responses of an anesthetized rat to 3 R/sec. X-irradiation. A, B, C, D, and E were respectively the 1st, 2nd, 4th, 6th, and 8th exposures of a series made at 5-minute intervals.

TABLE I

Respiratory Rate In Cycles Per Second Of Anesthetized Rats Before And After The First 3-Second X-Ray Exposure

Rat	Time in seconds relative to beginning of irradiation (time 0)			
	-10-0	1-3	5-10	20-30
1	2.9	4.5	2.6	2.8
2	1.8	3.5	1.8	1.7
3	1.2	1.0	1.3	1.2
4	1.6	4.5	1.7	1.6
5	2.7	5.0	2.9	2.8
6	2.8	5.5	3.1	3.0
7	3.1	5.0	3.0	3.2
8	1.6	3.0	1.8	1.6
9	2.1	4.5	2.4	2.2
10	2.8	4.5	2.9	2.4
11	1.4	2.5	1.5	1.4
12	2.1	3.5	2.0	2.2
13	1.7	3.5	1.8	1.7
14	1.3	4.0	1.4	1.3
15	1.9	2.0	1.9	2.0
16	2.6	4.0	2.6	2.6
Mean	2.1	3.8	2.2	2.1

All the values in Table I were derived from recordings made 30 to 60 minutes after the rats were anesthetized with 1 gm/kg of Urethan. The level of anesthesia under these conditions is "light". The animal usually lies quietly and without moving unless he is stimulated although an apparently spontaneous movement occasionally is seen. Minor surgery can be performed but not ordinarily without some reflex pain response. Four rats were given an additional 0.5 gm/kg injection of Urethan after first having observed good respiratory responses to x-rays on two separate trials. Fifteen minutes after administering the additional anesthetic respiratory responses to x-ray could not be evoked. These results explain why the respiratory response to x-ray was seldom noticed in our previous experiments with anesthetized animals: in those experiments we attempted to maintain a state of deep anesthesia at all times.

Fig. 5 shows records taken from unanesthetized rats, 2 with lesions of the cerebral cortex (records A and B) and 2 with olfactory bulb ablations (records C and D). These records are representative and they show, in summary, that olfactory stimulation is responsible for the respiratory changes produced by irradiation in this experiment. Table II shows the results obtained from the 14 rats involved in this part of the experiment. Following the x-ray testing an examination of the brains revealed that 6 of the 14 rats had ablations of the cerebral cortex. On the basis of the respiratory changes evoked by x-rays we had correctly predicted the type of lesion involved for 5 of these animals. Rat 23 failed to respond to x-ray and we therefore predicted incorrectly in this instance. As can be seen from the table, the response to radiation is less dramatic than those of the anesthetized rats. In this series all animals which responded to irradiation of the whole animal were given sham trials consisting of body-only irradiation. No responses were observed. Of 8 rats which later proved to have olfactory bulb ablations, 7 were correctly identified through their failure to respond to x-ray. However, one of the animals (number 26) responded dramatically even though the olfactory bulbs appeared to have been completely destroyed.

In his work with rabbits which were in a sleep-like or "hypnotized" state Hunt (1969) found that brief exposures to 250 KVP x-rays (1.9 or 3.6 R/sec.) produced immediate changes in respiratory rhythm when exposures of the whole animal were made. But, significantly, he also found that exposures of the body only or separate areas of the body such as the abdominal region also produced such respiratory effects, although the incidence of response under these conditions was considerably

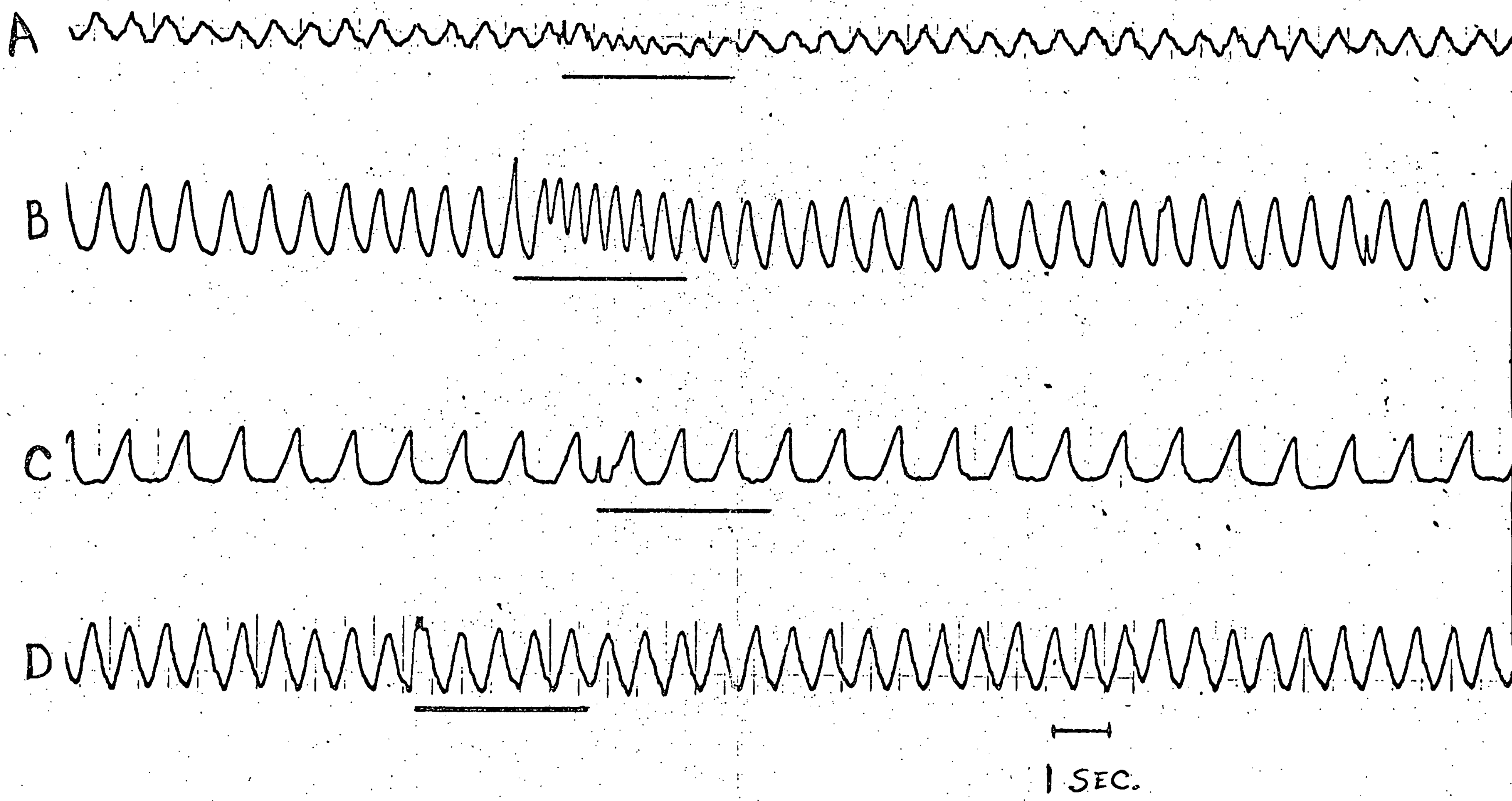

Fig. 5. A and B: respiratory response of two different unanesthetized rats to 3 R/ sec. x-irradiation. C and D: absence of respiratory response in two unanesthetized rats with olfactory bulb ablations to 3 R/sec. x-irradiation.

TABLE II

Respiratory Rate In Cycles Per Second Of Unanesthetized Rats With Ablations Of The Olfactory Bulb or Ablations Of The Cerebral Cortex Before And After The First 3-Second X-Ray Exposure

Rats with ablations of the cerebral cortex

	Time in seconds relative to beginning of irradiation			
Rat	-10-0	1-3	5-10	20-30
17	1.5	3.0	1.7	1.6
22	2.0	3.0	2.1	1.8
23	1.4	1.6	1.5	1.6
24	1.6	3.0	1.8	1.5
25	1.8	3.5	1.8	1.7
28	1.7	2.8	1.7	1.7
Mean	1.7	2.8	1.8	1.7

Rats with olfactory bulb ablations

	Time in seconds relative to beginning of irradiation			
Rat	-10-0	1-3	5-10	20-30
18	1.3	1.3	1.4	1.3
19	1.4	1.4	1.4	1.4
20	1.8	1.8	1.9	1.8
21	1.5	1.5	1.5	1.6
26	2.1	6.5	2.6	2.4
27	1.7	1.7	1.8	1.7
29	2.2	2.2	2.2	2.2
30	2.0	2.1	2.0	2.2
	1.8	2.3	1.9	1.8

less and the latency greater than when head-only or whole-animal exposures were made. In previous work with sleeping rats Hunt and Kimeldorf (1963) and Cooper and Kimeldorf (1964) had observed behavioral and electroencephalographic arousal responses resulting from body-only x-irradiation. In the present experiment the absence of response to body-only irradiation may very well be attributable to the non-habituated state of the animals. This experiment, however, does make it quite clear that short-latency respiratory responses to radiation are due predominantly to olfactory stimulation and are so strong that they can be used as an index of radiation-produced arousal even in anesthetized or non-habituated animals.

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