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10. Activity was measured in a soundproof chamber (45 by 45 by 28 cm). The floor of the chamber was divided into quadrants, and an index of gross activity was obtained from the number of crossovers each animal made from one quadrant to another. The data were automatically recorded.
11. Although the time course of behavioral activation during long-term reserpine treatment had been demonstrated previously, female rats were used as subjects and activity was measured in a circular activity maze. Because female rats exhibit activity fluctuations corresponding to estrous cycling, and because activity measures are notorious for their lack of agreement, our behavioral study was undertaken in order to examine the generality of the reserpine-induced hyperactivity and in order to determine the optimal times for enzyme determination under our particular experimental conditions.
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15. It is possible that a negative feedback loop exists between postsynaptic neurons and adrenergic cell bodies. In addition, the tyrosine hydroxylase activity in the central nervous system may be influenced by adrenergic stimulation in a manner similar to that reported in peripheral sympathetic structures (*7*). Thus the initial decrease in central adrenergic activity produced by reserpine-induced CA depletion would be expected to reduce negative feedback, subsequently increasing the levels of tyrosine hydroxylase.
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17. Also examined was the possibility that reserpine and starvation interact to produce the increase in behavioral activity and tyrosine hydroxylase activity, that is, reserpine-induced starvation may alter the pattern of metabolites of subsequently administered reserpine. Results indicate that rats that were starved and then injected with reserpine (0.5 mg/kg, for two consecutive days) exhibited neither the behavioral nor enzymatic changes produced by long-term reserpine treatment. Whereas behavior was further depressed by the injection of reserpine, midbrain tyrosine hydroxylase activity was unaltered.
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Microdroplets and Water Drop Freezing

In his report Cheng (*1*) referred to the appearance of numerous microdroplets in the vicinity of a freezing water drop as a "newly observed phenomenon." In fact, microdroplets of this kind have been observed and reported previously (*2, 3*). Dye and Hobbs (*3*) showed that they occur by ejection from the freezing water drop and also by the condensation of water vapor in regions of comparatively high supersaturations in the vicinity of the freezing drop.

Cheng suggested that this phenomenon might provide a mechanism for charge generation in thunderstorms. The same theory was postulated by Mason (*4*). However, considerable care must be taken in extrapolating observations and measurements made on large water drops freezing in the laboratory to the behavior of small droplets in natural clouds. In particular, it has been shown (*3, 5*) that it is important to ensure that the water drops are in thermal and solution equilibrium with the environmental air before they are nucleated. Drops that are nucleated before attaining these conditions are more likely to eject both ice particles and microdroplets during freezing, thereby separating electric charges, than are cloud droplets that are generally very close to equilibrium with their environment. Cheng does not give any information on the condition of the water drops in his experiments prior to their nucleation. However, it is unlikely that they were in equilibrium with the environmental air since they probably nucleated at their surfaces before their interiors had fallen to the temperature of the environment. Moreover, the freezing behavior of cloud droplets is certainly not simulated in the laboratory by the freezing of water drops on glass slides. It is essential that the drops be either freely suspended or in free fall, so that they are ventilated in the proper manner (*6*). It has yet to be shown that drops freezing under conditions similar to those in natural clouds eject microdroplets.

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Several investigators (*1–3*) have reported the appearance of the particles, the formation of spicules, and the occurrence of fragmentation during the freezing of a water drop. The new observations and measurements that I made (*4*) while freezing a supercooled water drop, under the condition of thermal equilibrium with the environment, are as follows: (i) photomicrographic evidence (Fig. 1) of numerous droplets, ranging from less than 1 to 20 μm, ejected from the surface of a freezing water drop; (ii) the duration of ejection of the microdroplets, in this case, about 50 seconds for a 1-mm water drop; (iii) the time-temperature relationship of the freezing water drop; (iv) reversals of the vapor pressure gradient during the freezing period; (v) the electrical properties of the ejected microdroplets; (vi) in addition to one or a few large spicules as mentioned by others (*1–3*), a large number of miniature spicules (Fig. 1) forming between cracks on the ice surface during the freezing period; and (vii) photomicrographic evidence (Fig. 1)

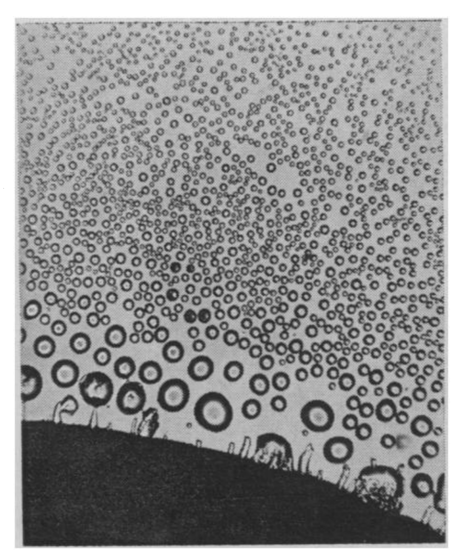

Fig. 1. Microdroplets ejected from the surface of a freezing supercooled water drop.

revealing that a large percentage of the total mass of water in the form of numerous microdroplets was separated from a water drop by freezing. On the basis of these new observations and measurements with the support of photomicrographic evidence, I suggested (*4*) that the ejection of microdroplets by the freezing of a supercooled water drop may be important in studies of thundercloud dynamics and in the generation of thunderstorm electricity (*5*).

A spectacular photograph of microscopic particles of water bursting from the drop in the process of rupture appeared in Kachurin and Bekryaev's paper (*2*). Unfortunately, the water drop was cooled in an environment consisting of a high concentration of carbon dioxide (*6*). No experimental data and no photomicrographic evidence concerning the ejected microdroplets were presented in the paper by Dye and Hobbs (*3*).

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Cloud Seeding Experiments: Possible Bias

In recent months, *Science* has devoted much attention to weather modification experiments; I refer in particular to the articles on the effects of cloud seeding in Florida by W. L. Woodley (*1*) and J. Simpson and W. L. Woodley (*2*). The purpose of this comment is to call attention to a possible source of bias that may have been overlooked in the design of these experiments, or might be overlooked in future experiments.

I refer to what I shall call "selection bias," or bias introduced into an experiment by the manner in which the experimental subjects are selected. In any experiment (such as cloud seeding) in which two treatments are to be compared, it is well known that the results of the experiment may be biased if the experimental subjects (clouds) are selected with the knowledge of the treatment they are to receive. Simpson and Woodley have recognized this difficulty. They wrote (*2*), "The delivery racks were armed or disarmed in the rear of the aircraft by a 'randomizer,' who opened in secret the sealed envelopes containing the decisions. The envelopes were prepared by a statistician to say 'seed' or 'no seed' according to a procedure roughly similar to tossing a coin (but where long strings of successive identical instructions were precluded)."

Precautions such as these may not be sufficient, however, to prevent the (usually subconscious) introduction of selection bias into the experiment. This possibility always exists for experiments such as cloud seeding, in which the potential subjects arrive sequentially and are judged "suitable" or "not suitable" by the same scientists who are performing the experiment. This was first studied by Blackwell and Hodges (*3*), and I have discussed it further elsewhere (*4*).

Nonmathematically, the potential difficulty can be described by the following example. Suppose the scientist knows (after all, it is his experiment) that the experiment will consist of approximately equal numbers of seeded and unseeded clouds. Envelopes containing instructions are prepared "at random" by a statistician. The scientist then judges a cloud "suitable" or "not suitable" and proceeds with the experiment as if he were seeding. *After* the plane alights, he is told whether the cloud was seeded or not seeded. It is this "post-trial" information that permits the introduction of bias. Indeed, at each stage of the experiment the scientist can "guess" on the basis of his past information what the next trial will be, which allows him to bias the experiment through his judgment of the suitability of the next cloud for seeding. Even though his "guesses" would not always be correct and this bias would usually operate subconsciously, Blackwell and Hodges have shown that there is no randomization that can eliminate the possibility of bias; in fact, selection bias can significantly distort the results of the experiment regardless of the number of clouds seeded. It *is* true that the effect of this bias can be reduced by a suitable design when the bias *is* operating subconsciously (and even made negligible if the experiment is sufficiently large) (*4*).

There are three ways in which the possibility of selection bias can be eliminated entirely: (i) Do not inform the scientist of the result of a trial until the *entire* experiment is complete. (ii) Perform a true coin flip at each trial (not "roughly similar to tossing a coin"). (iii) Have the judgment of suitability made by a third party, not informed about any other aspect of the experiment. Unfortunately all these alternatives have drawbacks. The first is often impractical as the scientist wants to know the results of the trials in order to decide when to terminate the experiment (actually, it is better to have the statistician make the decision). The second has the unpleasant possibility of providing a very unbalanced experiment (for instance, almost all clouds are unseeded), which makes a meaningful statistical analysis impossible. The third is often impractical because only those closest to the experiment may be entirely sure what is meant by "suitable." Other ways of eliminating bias are given by Hodges and Blackwell (*3*).

It is not my intention to imply that the results of the Florida experiment are suspect because of the possibility of bias [particularly since the description of the design given in *Science* is incomplete (*2*)]. I only wish to alert future experimenters to the dangers of bias associated with this type of experiment (similar difficulties are involved in some clinical trials), so that they may avoid controversy as to the validity of their conclusions. Hammond (*5*) points out that "even well-documented and randomized early experiments, such as the Whitetop trials . . ., produced ambiguous and disputed results." Weather modification is too important a field to allow even the possibility that large and expensive experiments will be disputed or incorrectly interpreted because of a faulty experimental design.

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