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REDUCTION OF THE DURATION OF RESTRAINT FOR
THE PRODUCTION OF EXPERIMENTAL ULCERS IN RATS
APPLICATION TO THE STUDY OF PROTECTIVE SUB-
STANCES

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REDUCTION OF THE DURATION OF RESTRAINT FOR
THE PRODUCTION OF EXPERIMENTAL ULCERS IN RATS.
APPLICATION TO THE STUDY OF PROTECTIVE SUBSTANCES

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The production of gastric ulcers in rats by means of restraint, proposed by Rossi, Bonfils and their collaborators since 1956 [1], has been applied to the study of the protective activity of either psychotropic substances or cholinolytic substances, although the mechanism conditioning the appearance of these lesions is not yet completely elucidated.

The technique generally employed consists of subjecting some rats to an immobilization lasting 7 to 25 hours, at the conclusion of which the number of rats presenting ulcers varies from 58 to 100% [2]. A long duration of restraint constitutes an inconvenience in the study of protective substances, notably in the examination of rapidly eliminated substances. In order to obtain a re-1226duction in the restraint time, Hanson and Brodie [3] subjected young rats to a previous 48 hour fast; under these conditions, 69% of the animals developed ulcers after 4 hours of restraint.

We studied the experimental conditions which permit reduction of the duration of restraint to a minimum, yet not prolonging the fast beyond 24 hours. To this end, we varied the source of the rats, their age, the time of restraint, in fasting and non-fasting animals, but keeping the method of immobilization constant. After preliminary experiments performed on rats of different origins, we chose Wistar rats, bred at the Gif-sur-Yvette Selection Center, male, about 50 days old, weighing from 120 to 140 gm. The animals subjected to fasting were maintained in lots of 10 in cages with

*Numbers in margins indicate foreign pagination.

wood shavings on the floor, deprived of food, but not of drink (water).

TABLE I

| Number of rats | Duration of fast hours | Duration of restraint hours | Ulcerogenic action | |
|--|------------------------|-----------------------------|--------------------------------------|---------------|
| | | | Percentage of rats developing ulcers | Average index |
| 1. Rats without prior fast subjected to restraint. | | | | |
| 20 | 0 | 1 | 0 | 0 |
| 50 | 0 | 2 | 40 | 0.7 |
| 35 | 0 | 4 | 29 | 0.7 |
| 21 | 0 | 5 | 43 | 0.9 |
| 20 | 0 | 7 | 55 | 1.4 |
| 2. Rats subjected only to fast. | | | | |
| 20 | 2½ | 0 | 5 | 0.1 |
| 20 | 7 | 0 | 0 | 0 |
| 20 | 24 | 0 | 10 | 0.2 |
| 3. Rats subjected to fast followed by restraint. | | | | |
| 20 | 24 | 2 | 70 | 1.9 |
| 20 | 24 | 2 1/2 | 85 | 2.8 * |
| 39 | 24 | 2 1/2 | 82 | 2.8 * |
| 140 | 24 | 2 1/2 | 83 | 2.5 * |

*The maximum number, if the index was 4 for all the rats afflicted, would be 3.4.

(3) H. Hanson and D. Brodie, J. Appl. Physiol., 1960, vol. 15 p. 291.

1. METHOD OF IMMOBILIZATION - After light ether anesthesia, the animals are immobilized by means of a flexible wire gauze pierced with 4 holes for passage of the feet. The feet are tied together in pairs with a strip of adhesive tape; the wire gauze is pressed down on the animals' backs, tailored to the circumference of its body, and also secured in the middle with adhesive tape. The animals are suspended horizontally on a stand; thus they remain immobilized for the duration of the restraint, the ambient temperature being maintained at 22°C, and receiving no food or drink.

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2. Expression of the results. The animals having been sacrificed by decapitation, the stomachs were immediately opened and examined after a light water rinsing. All the ulcers observed are located in the glandular portion of the stomach.

Comparative experiments were performed on groups of at least 20 rats. The percentage of ulcerated stomachs has been noted, as most authors have done. However, Levis and Beersaerts (1960) measured in addition, the degree of severity of the lesions, by employing a special gradation. Following their example, we adopted a system of grading, taking into account the number of ulcers per animal: 0 - normal stomach; 1 - one ulcer; 2 - two ulcers; 3 - three ulcers; 4 - four or more ulcers. For each group of rats, we calculated an average index.

3. PRODUCTION OF ULCERS. Table 1 summarizes the results obtained: 1) from rats without prior fast, subjected to a restraint varying from 1 to 7 hours; 2) from rats subjected only to a fast of 2 1/2 to 24 hours; 3) from rats subjected to a 24 hour fast and to a restraint of 2 or 2 1/2 hours.

It appears in Table I that: 1) without prior fast, a 2 1/2 hour restraint is capable of provoking an irregular percentage of ulcers which reaches 55% (average index: 1.4) with a restraint of 7 hours; 2) with a prior fast of 24 hours, 2 1/2 hour restraint regularly gives rise in 20, 39 and 140 animals to ulcer formation in 82 to 85% of the rats (average index: 2.5 to 2.8).

TABLE II.

| Substance administered | Dose mg/kg | Number of rats | Percentage of rats developing ulcers | P | average index |
|------------------------|------------|----------------|--------------------------------------|--------|---------------|
| Controls | - | 140 | 83 | | 2.5 |
| Atropine sulfate | 1.25 | 20 | 20 | < 0.01 | 0.2 |
| Dihexyverine | 25 | 40 | 60 | < 0.01 | 1.4 |
| | 50 | 20 | 25 | < 0.01 | 0.3 |
| | 10 | 20 | 45 | < 0.01 | 0.7 |
| | 20 | 20 | 25 | < 0.01 | 0.5 |
| Chlorpromazine | 20 | 20 | 25 | < 0.01 | 0.5 |

4. PROTECTION FROM ULCERS. We experimented on rats subjected to a prior 24 hour fast and to a 2 1/2 hour restraint.

We used two cholinolytics, atropine (sulfate) and dihexyverine (hydrochloride of cyclohexyl-1-cyclohexane carboxylate of piperidino-2-ethyl) and a neuroleptic, chlorpromazine (hydrochloride) which we administered by the intraperitoneal route, immediately after immobilization of the animals, or 2 1/2 hours before their sacrifice. /1228

The results obtained are shown in Table II: 1) the dose of atropine, effective in our experimental conditions, is less than that (6 mg/kg) determined by Hanson and Brodie (1960) who utilize a 4 hour restraint preceded by a 48 hour fast; 2) with dihexyverine and chlorpromazine, the degree of protection is a function of the dose utilized. This regularity of results has not been observed by Bonfils et al (1963) with chlorpromazine after restraints of 7 to 24 hours.

CONCLUSIONS - 1. In young Wistar rats, about 50 days old, a 2 1/2 hour restraint following a prior 24 hour fast, provokes ulcers in a constant percentage of animals.

2. We recommend this technique for the study of protective cholinolytic or psychotropic substances.

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