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THE EFFECT OF VARIOUS DRUGS ON EXPERIMENTALLY INDUCED ULCERS IN IMMOBILIZED RATS

H. Schramm

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16. Abstract Experiments related to the importance of functional disorders in the central nervous system in connection with stomach diseases were performed on Wistar rats. Assuming that severe mental strains may be triggering factors for such disorders, testing of the effects of different drugs on experimentally induced ulcers in these rats was done. The immobilization method described by Bonfils and co-workers was used. Particular importance was placed on the sex-related difference which appeared.					
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THE EFFECT OF VARIOUS DRUGS ON EXPERIMENTALLY
INDUCED ULCERS IN IMMOBILIZED RATS

H. Schramm

Medical Polyclinic, Friedrich Schiller University, Jena

Attention has been drawn to the importance of functional disorders in the central nervous system in connection with stomach diseases by bedside observations and animal experiments [3, 6, 8, 9, 13, 17, 18, 20]. Several mental strains may be triggering factors for such disorders. Proceeding from this assumption we tested the effect of different drugs on experimentally induced ulcers in Wistar rats. We used the immobilization method described by Bonfils and co-workers to produce the ulcer [3]. Our variation of the method is described below. We placed particular importance on the sex-related difference which appeared. /305*

Procédure

Wistar rats were immobilized in a wire mesh corset (Fig. 1). The protruding feet were bound together and this apparatus was rigidly suspended above the floor. One day prior to being immobilized the rats received only water. During the immobilization period they received neither food nor water. Twenty four hours after the start of the constraint situation the rats were killed with ether.

In addition, during the 24-hour experiment bell and light signals were given at certain intervals. These were intended to startle the rats out of their quiet state which they attained after a few hours of hyperactivity.

Groups of female and male Wistar rats were used for the experiments. The average weight for the individual groups ranged between 140 and a maximum of 340 grams, with the ages ranging between 5 and 15 months.

*Numbers in the margin indicate pagination in the foreign text.

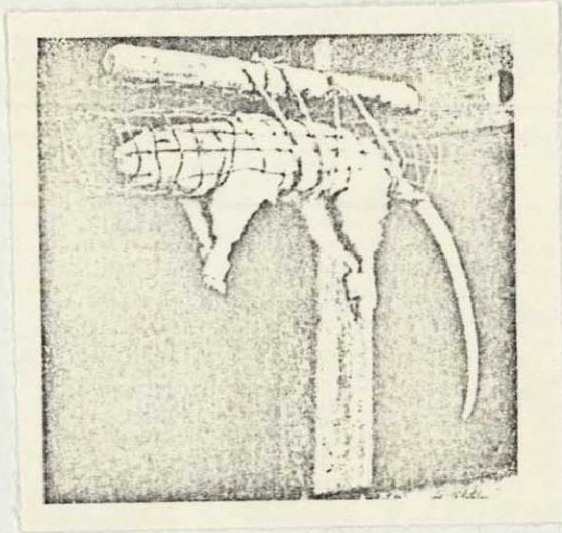


Fig. 1. Rat in wire mesh corset.

On the female rats we tested /306 the effect of propaphenine, protha-ine zine, eustigmine, atropine, depot-pholedrine, depot-padutine and papaverine (Table 1), on the male rats we tested the effect of oestraside with and without mobilization, the effect of propaphenine on rats pretreated with oestraside and then immobilized, as well as the effect of prothazine and the influence of cold during immobilization.

The arrangements and results of the individual test groups are summarized in Tables 1 and 2 [sic].

Experimental Results

Mucous membrane lesions were found for the most part in the glandular portion of the stomach, a few in the omasum. By far the majority of these had a round shape, otherwise elongated, and rarely irregular in shape. Their size varied between the size of a pin prick to several millimeters in diameter (Fig. 2). The lesions of the glandular stomach were, for the most part, uniformly distributed over the anterior and posterior wall and were often symmetrically arranged. On rare occasions they appeared on the lesser curvature or in the pylorus region. No ulcers were ever observed in the duodenum. In evaluating the results only the lesions of the glandular stomach were considered.

Histological Examinations

The defects in the mucous membrane of the omasum extended over the muscularis mucosae. For the most part they were

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Table 1. Test groups of female rats.

* Drugs 7-13 should be read with e's
at the end of the words.

Nr. A	Immo- bilis. B in h	Hunger- tage C	Gew. in g D	Anz. d. Ratten		%	Signifikanz G zu Gruppe mit Sicherheit
				E im Vers.	F mit Ulzera		
1	ohne H	2 ¹	Ohne Klingel- und Licht- zeichen	190	30	0	
2	24	2 J	Gr. 1-5: Injekt. von Physiolog. NaCl-Lösg. vor der Immob.	166	30	26	85 ^M zu 1 mit 99,9% ^N
3	24	2	15 Monate alt	240	25	17	65 zu 2 nicht signifikant
4	24	2 ² K	ohne Klingel- und Licht- zeichen	256	20	8	40 zu 2 mit 99,9%
5	24	2 L	Propaphenin	160	15	15	100 zu 2 nicht signifikant
6	24	2	Prothazin	150	30	30	15 zu 2 mit 99,9%
7	24	2	Eustigmin	136	30	30	100 zu 2 mit 95% ^N
8	24	2	Atropin	133	31	29	95 zu 2 nicht signifikant
9	24	2	Depot- Pholedrin	182	30	13	45 zu 2 mit 99,9%
10	24	2	Depot- Padurin	153	40	33	80 zu 2 nicht signifikant
11	24	2	Papaverin 30 mg/kg	195	30	25	80 zu 2 nicht signifikant
12	24	2	Papaverin 15 mg/kg	280	15	3	20 zu 3 mit 99% ^N
13	24	2		190	30	24	80 zu 2 nicht signifikant

- Key:
- A. Number
 - B. Hours of immobilization
 - C. Number of fasting days
 - D. Weight in grams
 - E. Number of rats in the experiment
 - F. Rats with ulcers
 - G. Significance to group with certainty
 - H. None
 - I. Without bell and light signals
 - J. Groups 1-5: injection of physiological NaCl solution prior to immobilization,
 - K. 15 months old
 - L. No bell and light signals

Key continued on next page.

- M. To
- N. With
- O. Not significant
- 1 In the groups for which light and bell signals are not mentioned, these were given.
- 2 The average age was about 5-7 months for the remaining groups.

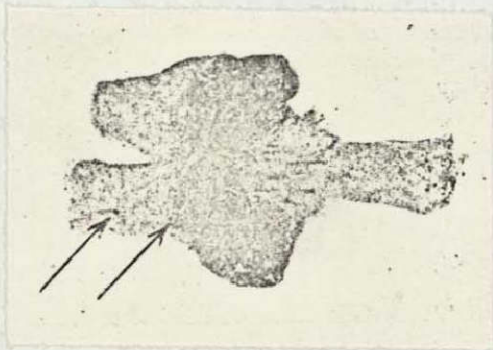


Fig. 2. Rat stomach with ulcers, opened on the greater curvature. The lighter portion is the omasum, the other the glandular stomach and duodenum.

observed almost exclusively.

Following a layer of homogeneous, brownish-black material was a strongly eosinophilically stained region with only very vaguely perceptible nuclear staining. It showed similarities to the layer of fibrinoid swelling of a human ulcer, which is regarded as the typical result of acidic action (Fig. 3 and 4).

The capillaries of the mucous membrane were often dilated /308 in the more immediate vicinity of the defects, also the veins of the submucosa. Arteries appeared constricted.

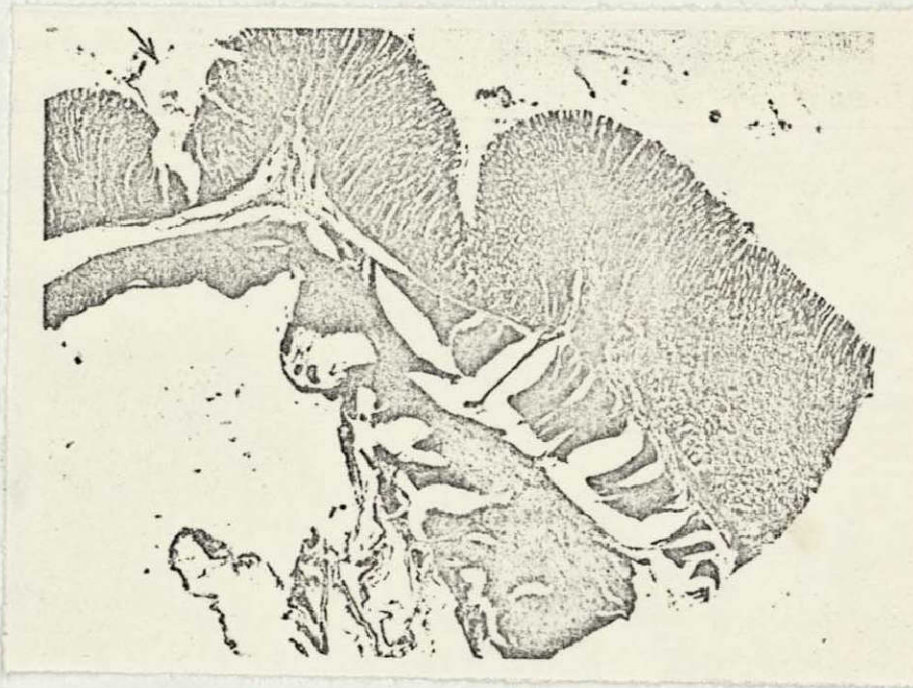


Fig. 3. Ulcer of the glandular stomach,
magnification 25X (H&E stain).

The submucosa was clearly swollen with edema around the ulcer. Leukocytes were found more abundantly on the corresponding places of the omasum than of the glandular stomach. Spontaneous ulcers (ulcers in rats which had not been immobilized) occurred neither in female nor in male rats. Of 30 female and 20 male rats with an average weight of about 180 grams, 26 females (about 85%) and two males (10%) developed ulcers while immobilized. The differences were similar in other weight and age groups (Table 1). The difference in susceptibility of female and male rats with respect to immobilization were also found by Bondils and co-workers and Ader and co-workers [1, 3]. Fasting as well as

weight and age differences had no significant effect in our experiments on ulcer formation, nor did the use of additional light and bell signals increase the ulcer rate.

The difference in frequency of observed ulcers for male rats and female rats is striking.

Experimental Results for Groups /309
of White Rats

In immobilized female rats the number of rats with ulcers decreased significantly as a result of administering the following drugs: Propaphenine (20 mg/kg of body weight, one subcutaneous injection prior to immobilization). Atropine (50 μ /kg of body weight, one subcutaneous injection before and three during the constraint situation at 5-6 hour intervals). Papaverine (30 mg/kg of body weight, one subcutaneous injection before and three during the constraint situation at 5-6 hour intervals). There was not significant decrease in ulcer cases with the administration of depot-pholedrine (1.8 mg/kg of body weight, one subcutaneous injection prior to immobilization) and depot-padutin (2.8 E/kg of body weight, one time prior immobilization).

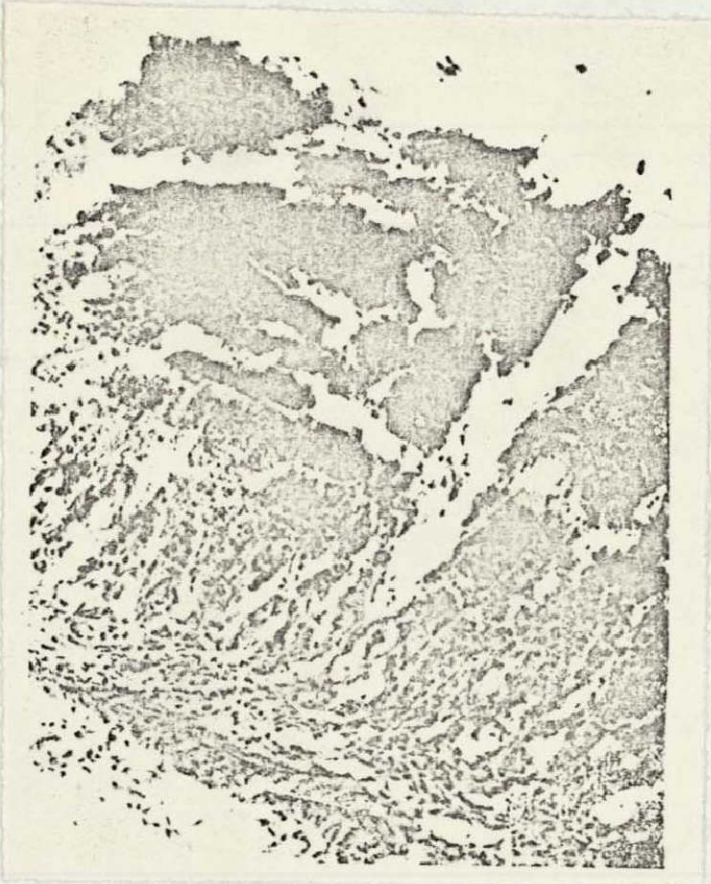


Fig. 4. Section from Fig. 3 magnified 420 times.

A significant increase in ulcer frequency developed with the administration of prothazine (25 mg/kg of body weight, once immediately prior to immobilization). An insignificant increase in

ulcer rate occurred due to Eustigmine (100 λ /kg of body weight, one subcutaneous injection prior to immobilization), but here the lesions in the individual rats were more serious than in the control group.

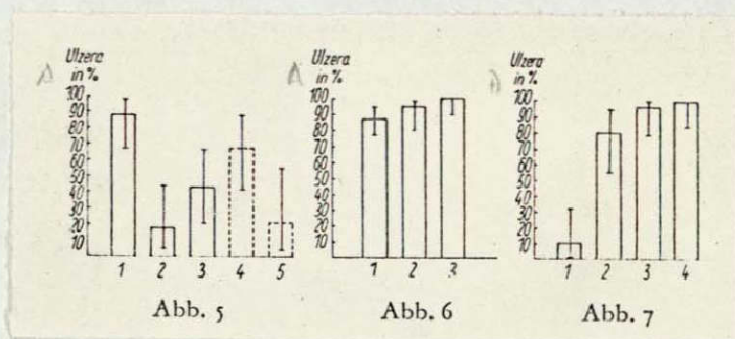


Fig. 5. Decrease in ulcer frequency in immobilized female rats due to propaphenine (2), atropine (3), and papaverine (5). 1 and 4: control groups of different average weights (also see Table 1, nos. 2, 3, 6, 9 and 12). Statistical certainty of the confidence limits 99%.

Fig. 6. Increase in ulcer frequency in immobilized female rats due to eustigmine (2) and prothazine (3). 1: control group (also see Table 1, nos. 2, 7 and 8). Statistical certainty of the confidence limits 95%.

Fig. 7. Increase in ulcer frequency in immobilized male rats due to oestraside (2), due to decreased room temperatures (3) and due to prophazine (4). 1: control group. Statistical certainty of the confidence limits 99%.

Key: A. Ulcers in %

Experimental Results for Groups of Male Rats

The difference in ulcer frequency in female and male rats caused us to perform experiments using sex hormones.

After the administration of oestraside (170 λ /kg of body weight) (for 10 days without immobilization) no stomach lesions appeared. However, a significantly higher ulcer rate occurred /310

if the thus pretreated rats were constrained. Hence the male animals, when treated with oestraside, reacted similar to the females, i.e. substantial ulcer formation as a result of being constrained.

In this experimental arrangement propaphenine had an ulcer-preventing effect just as in the immobilized female rats.

Administration of prothazine (25 mg/kg of body weight once prior to immobilization) and carrying out the experiments at decreased room temperatures (15°C as opposed to 24°C for the other groups) resulted in a significant increase in the number rats with ulcers. Attention is also drawn to the influence of room temperature on ulcer frequency by Senay and Levine [10] and Robert, Philipps and Nezamis [26].

Obviously the main role in ulcer formation is played by central nervous system factors. Among other things, this seems to be substantiated by the dependence of the ulcer rate on the size of the space allotted to the rat, the increasingly smaller susceptibility of the rats with regard to repeated constraint situations [3] and the clear-cut ulcer preventing effect of propaphenine in our experiments.

Sex-related Difference and Oestraside Effect

There is a considerable difference in the ulcer frequency for immobilized female rats (ulcer in about 85%) and immobilized male rats (ulcer in 10%). This was also present in the experiments by Bonfils and co-workers and Ader and co-workers [1, 3]. The difference disappears if the males are treated with oestraside prior to immobilization. Without immobilization no ulcers form after oestraside treatment, but after immobilization they form in almost equal numbers as in immobilized female rats.

The sex-related difference and the effectiveness of the hormone in our experiments indicated a hormonal influence in the formation of ulcers caused by immobilization. However, there does not appear to be a direct effect here, since, for example, administrations of oestradiol alone did not lead to the formation of ulcers.

The Effect of Phenothiazines

Propaphenine significantly decreased the ulcer rate both in immobilized female rats and in male rats pretreated with oestradiol and then immobilized. Similar results were obtained in experiments by Hanson and Brodie [11] on immobilized rats and by Bornmann on the Shay rat [5].

Triflupromazine and chlorpromazine [5] and thiazinamium and pascatal [15] had the same effect.

The pharmacological effect of propaphenine is complex, and the change in ulcer frequency due to propaphenine with immobilization must be regarded as the sum of various factors. According to Kleinsorge and Rosner [12], the inhibition of nerve conductions to chlorpromazine is supposed to take place primarily in the central synapses and to a lesser extent in the peripheral ganglia. From this standpoint, the results obtained with propaphenine would argue for ulcer formation of a central nervous system origin during immobilization. /311

With female and male rats treated with prothazine and then immobilized, all of them developed stomach ulcers. The quantitative differences of different factors of the two phenothiazine preparations do not explain the so different results after their administration. Perhaps another result can be expected with another dosage of prothazine.

The ulcer-preventing effect of imipramine on the constrained rat is also attributed by Bonfills and co-workers to a central nervous system along with a peripheral nervous system effect of the drug [4].

The Effect of Vasoactive Drugs

Depot-padutine and depot-pholedrine showed no significant effect on ulcer formation in immobilized white rats. No decisive conclusions can be drawn from this. It may be that an insufficient amount of depot-padutine was administered. No important changes can be expected of depot-pholedrine if we already assume vasoconstriction due to spasm of the vessel musculature or of the muscularis propria. In the case of immobilized rats, Guth and Hall attribute the mucous membrane lesions to a disorder in the microcirculation of the mucosa, which is said to be triggered by the release of vasoactive substances from the mast cells [10].

The Effect of Papaverine

Above all, the spasmolytic action on the stomach musculature should be regarded as the reason for the significant decrease in the number of ulcers, to a lesser extent the vasodilating action which occurs primarily as a result of intravenous administration and greater dosage.

The Effect of Parasympathetic Drugs

Atropine: Its ulcer-preventing effect is statistically certain. The spasmolytic effect on the stomach musculature and secretion inhibition are potentially effective factors.

The secretion change in the immobilized rats is not uniformly indicated, but there does not seem to be a clear-cut

increase in secretion, although in most cases the acid concentration is higher than in the control rats [3, 7, 14].

Vagotomy is said to offer partial protection against mucous membrane lesions caused by immobilization in rats [3, 14].

Eustigmine increases the ulcer frequency, but not significantly. The lesions in the individual rats, however, were severe. Secretion stimulation and an increase in tonus of the stomach musculature may be involved here. The latter possibility was assumed by Mallik [2] for ulcer formation caused by pilocarpine.

Summary

In this study on male and female Wistar rats, gastric ulcers were produced by means of a constraint situation (binding in a wire mesh corset using the method described by Serge Bonfils and co-workers). The constraint situation is explained as psychological stress.

Without immobilization no ulcers were observed in 30 female rats nor in 30 male rats.

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Fasting, weight differences and additional disturbance due to bell and light signals had no effect on ulcer formation.

The ulcer frequency was significantly higher among female rats than male rats.

With immobilized male rats pretreated with oestraside the ulcer rate turned out to be almost as high as for immobilized female rats, but oestraside treatments alone did not influence ulcer formation. With the administration of propaphenine, papaverine and atropine there was a significant decrease in

ulcer frequency among female rats.

As a result of prothazine administration and also due to decreased room temperatures all of the rats developed ulcers of the glandular stomach. With eustigmine the increase was not significant.

The considerable effect of propaphenine seems to indicate that ulcer formation is strongly dependent on central nervous system activity.

The changes in ulcer rate caused by atropine and papaverine indicate disorders in stomach functions, motoricity and secretion which can be triggered by immobilization via the central nervous system..

Sex-related differences and the oestraside effect suggest an hormonal influence in ulcer formation due to immobilization.

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