than in the granuloma test), followed by hydrocortisone (20 times more active in the
carrageenin than in the granuloma test), while hydrocortisone-bendazac ester is the least specific
drug, with a potency ratio for the two activities of only 10:1.

As the effects of topical application of a drug in the form of ointment may differ from
those seen with injection, our results suggest that in the therapeutic use of topical corti-
costeroids, not only their potency, but also the spectrum of anti-inflammatory activity
should be taken into consideration. Fluorinated corticosteroids, like betamethasone,
should be used in acute inflammatory conditions of the skin, where the vascular component
prevails. On the other hand, non-fluorinated corticosteroids, such as hydrocortisone and
hydrocortisone-bendazac ester, should be given preference in chronic conditions where
cellular proliferation prevails.

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DECREASE IN PAIN THRESHOLD IN SART STRESSED MICE

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We have turned our attention to the so-called vegetative “Stigmatisierte” occurring in
early spring or early autumn when there is a rapid change in temperature within one day,
and we attempted to induce these states in experimental animals. When mice and rats had
been reared under the conditions of alternating rhythm in temperature from 24°C to 8°C
(or −3°C), all animals displayed symptoms usually seen with disturbances in the autonomic
nervous system. The abnormal state is termed “SART stress” (specific stress state caused
by alternating rhythm in temperature) (1). Physiological changes were as follows: a) decrease of increasing rate in body weights, b) decrease of ACh response in the isolated duodenum, c) a slight increase in respiration, d) increase of heart rate and prolongation of QRS-time on ECG and e) decrease in electric resistance of the skin, increase of reactivity with external stimuli and shortening of the recovery time on GSR (the galvanic skin response) in rats. These symptoms resemble those seen in vegetative “Stigmatisierte” so-called by physicians. We have reported the inhibitory effects (2) of Neurotropin (NSP), a neurosedative, some tranquilizers and other drugs on the abnormal states in SART stressed animals. We found that analgesic effects of NSP and other drugs were more potent in SART stressed mice than in non-stressed mice (3). We assumed that the pain threshold in SART stressed mice must be lower than that in non-stressed mice.

In the present work, pain sensation in SART stressed mice was investigated and compared to that in non-stressed mice. Table 1 shows the comparison of pain sensation between in SART stressed and the non-stressed mice. Experimental animals were male ddY-strain mice, weighing 18–20 g. In Table 1, a) the number of writhing syndromes induced by both acetic acid and phenylquinone was significantly increased in SART stressed mice, that is, these animals were more sensitive to acetic acid or phenylquinone-induced pain than were the non-stressed mice. b) Latency of response to thermal stimulation (D’Amour-Smith method) was significantly shortened, and even a slight weight applied to the tail of

<table>
<thead>
<tr>
<th>Methods</th>
<th>Mean±S.D.</th>
<th>Normal</th>
<th>SART stressed</th>
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</table>
| No. of writhing syndromes induced by acetic acid
d<sup>a</sup> |                               | 29.6±1.4                | 39.8±1.8***             |
| No. of writhing syndromes induced by phenylquinone
d<sup>b</sup> |                               | 56.2±2.8                | 75.4±4.3***             |
| Response time (sec) to thermal stimulation
d<sup>c</sup> (D’Amour-Smith method) |                               | 14.5±1.2                | 8.1±0.9***              |
| Weights (g) causing pain
d<sup>e</sup> (modified Randall-Selitto method) | 128 ±9                       | 76 ±6***                |
| Normal abnormal environmental temperature
d<sup>f</sup> | 33.2±3.9                     | 33.2±4.9                | 22.4±6.9***             |
| high<sup>e</sup> |                                |                         |                         |
| No. of writhing syndromes induced by acetic acid | 132±18                      | 179±22***                | 176±22***               |

a): Number of writhing syndromes observed for a 15 min period from 15 min after i.p. administration of 0.1 ml/10 g of 0.7% acetic acid in saline. b): Number of writhing syndromes observed for a 20 min period from 5 min after i.p. administration of 0.1 ml/10g of 0.075% phenylquinone in 5% ethanol. c): Thermal stimulation of 70°C was given to the tail of mice within 30 sec. d): Mice were exposed to −5°C for 30 min. e): Mice were exposed to 38°C for 15 min. ***: p<0.001, significant differences from normal mice. No. of mice: 20-30/group.
mice to induce pain (modified Randall-Selitto method) produced a significant result in SART stressed mice. Thus, the pain threshold in SART stressed mice was evidently lower than that in the non-stressed mice. To determine the difference between SART stress and other so-called "stress", the following experiments were carried out. Pain threshold was examined in acutely stressed mice exposed to low (−5°C) or high (38°C) environmental temperatures.

As can be seen in Table 1, results in such acutely stressed mice were contrary to those observed in SART stressed mice. That is, the number of writhing syndromes induced by acetic acid was decreased or unchanged, and a greater weight applied to mice to induce pain (modified Randall-Selitto method) was required as compared with the controls. Akil et al. (4) reported that acute stress caused by inescapable electric foot shock produced analgesia in rats (tail flick test), and Madden et al. (5) found decrease in pain responsiveness after chronic stress. They suggested that endorphins, opioid peptides, took part in this stress-induced increase of pain threshold. Aonuma et al. (6) found that in SART stressed rats, adrenal corticosterone levels remained unchanged despite evident increase of plasma corticosterone levels, increase in weight of adrenals and evident decrease of thymus weights as compared with non-stressed rats, that total cholesterol in plasma was increased by approximately double, and that ascorbic acid levels in the adrenals were slightly decreased as compared to normal levels. From these results they emphasized that SART stressed rats were indeed in a severe state of stress. If SART stress is so-called "stress" due to a rise in adrenal cortex function, an increase of pain threshold can be expected. How then is the adrenal cortex function related to decrease in pain threshold in SART stressed mice? The influence of consecutive administrations of spironolactone (Sigma), metopirone (CIBA-

### Table 2. Comparison of pain threshold in SART stressed and non-stressed mice using the modified Randall-Selitto method

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Weights (g) causing pain (mean ± S.D.)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Non-stressed</td>
</tr>
<tr>
<td>(Control)</td>
<td>112 ± 8</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>113 ± 5</td>
</tr>
<tr>
<td>5 mg/kg/day × 5</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>112 ± 8</td>
</tr>
<tr>
<td>Metopirone</td>
<td>75 ± 9</td>
</tr>
<tr>
<td>25</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>114 ± 7</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>118 ± 8</td>
</tr>
<tr>
<td>1</td>
<td>76 ± 6</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(Control)</td>
<td>124 ± 2</td>
</tr>
<tr>
<td>Sham-operated</td>
<td>111 ± 9</td>
</tr>
<tr>
<td>Adrenalectomized</td>
<td>104 ± 11</td>
</tr>
</tbody>
</table>

*: p < 0.05, **: p < 0.01, ***: p < 0.001, significant differences from non-stressed, respectively. No. of mice: 8–12/group. Drugs were administered intraperitoneally once daily × 5. Tests were carried out 60 min after the last administration. Adrenalectomized mice were loaded with SART stress 2 days after operation.
Geigy) and dexamethasone phosphate (Banyu, “Decadron”) on pain threshold was examined using a modified Randall-Selitto method (Table 2). Spironolactone and metopirone are considered to produce secondary effects in increase of pituitary-adrenal cortex function, as a result of inhibition of biosynthesis of adrenal cortical hormones. As shown in Table 2, weights applied to induce pain did not differ among non-stressed groups, and decrease of pain threshold was clearly observed in all SART stressed groups. No significant differences were observed among all SART stressed groups, even when spironolactone, metopirone or dexamethasone was given to mice as a pretreatment. Even in adrenalectomized mice, by the method of Koyama (7), decrease of pain threshold was observed in the SART stressed group.

From the above-mentioned results, pain threshold was apparently decreased in SART stressed mice. It is suggested that the evident decrease is not related to adrenal cortex function, and that SART stress differs from what is usually alluded to as “stress”.

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