The present status of the “two-stage mechanism” of carcinogenesis (3, 4) is largely based on experimental studies on skin (6, 12, 14), though some evidence is already available for its applicability to the thyroid gland (8, 11) and the liver (10). The extension of the problem to gastric carcinogenesis is of particular interest (a) because of the clinical importance of cancer of the stomach and the total lack of information about its etiology in man and (b) because of the wealth of information available about the normal functioning of the gastric mucosa, which might provide a more physiological approach to the problem than was possible in the case of the skin.

The failure to induce tumors of the glandular mucosa of the stomach in mice by feeding carcinogens, even after many attempts to improve the technic (5), led to a shift in emphasis from the glandular mucosa to the squamous epithelium of the forestomach. Unfortunately, the experimental procedure designed for the two-stage mechanism of the glandular mucosa was not ideally suited for that of the squamous epithelium. The use of high concentrations of carcinogen given on an empty stomach, intended to encourage the development of the initiating stage of carcinogenesis in the glandular mucosa, was more than adequate to complete the entire carcinogenic process in the squamous epithelium of the forestomach. For the study of the two-stage mechanism in the latter, these doses were obviously too high for a clear-cut demonstration of promoting effects by agents administered subsequently.

Nevertheless, the results obtained were sufficiently interesting and unexpected to justify their publication in their own right, apart from any light they might throw on the two-stage mechanism.

MATERIALS AND METHODS

The methods were as described in the preceding communication (5), except that the one, two, or three weekly feedings of carcinogen (referred to as “primary treatment”) were followed, after a 5-week interval, by the “secondary treatment,” which consisted of 30 weekly feedings of 0.5 ml. of 1 or 3 per cent croton oil in polyethylene glycol-400, or of the solvent alone, with additional control groups as described in the relevant sections.

As before (5), the animals were male mice, about 3 months old at the start of the experiments, of CSH or Swiss strain, bred in this laboratory by brother-to-sister matings. The normal diet consisted of Purina Laboratory Chow and water ad libitum. Prior to each primary or secondary treatment, the Purina was removed for 18 hours, to be returned to the cages 2 hours after the treatment. During this starvation period, water was given ad libitum. In some of the experiments, for 3 days prior to the primary treatment, milk was substituted for Purina (followed again by 18 hours on water alone) to render the stomach virtually free of food (5). The various test substances were given by polyethylene stomach tube (1-mm. bore, with closed lower end and lateral opening). All other procedures were as described in the preceding communication.

The following abbreviations will be used: DMBA = 9,10-dimethyl-1,2-benzanthracene; BP = 3,4-benzpyrene; MCA = 30-methylcholanthrene; DBA = 1,2,5,6-dibenzanthracene; and PEG solvent = polyethylene glycol-400.

RESULTS

EXPERIMENT 1 (Table 1)

Male CSH mice received the following by stomach tube:

Primary treatment.—0.3 ml. of 1 per cent DMBA or 0.5 per cent BP in PEG solvent, twice, at a 1-week interval.

Secondary treatment.—0.3 ml. of 1 per cent croton oil in PEG solvent, repeated weekly for 30 weeks.

Controls.—(a) Carcinogen twice, followed by solvent alone, weekly, for 30 weeks; (b) solvent alone twice, followed by croton oil in PEG solvent, weekly, for 30 weeks.

The original objective in this experiment was, by analogy with the known promoting action of croton oil on the skin, to elicit a similar effect on the glandular mucosa of the stomach; failing this, it was hoped that a promoting effect by croton oil would be demonstrable in the squamous epithelium of the forestomach. Tumors did not arise in the glandular mucosa; and even in the squamous epithelium of the forestomach the results were ambiguous, because though tumors did develop...
there when the primary treatment with the carcinogenic hydrocarbon was followed by secondary treatment with croton oil, they also appeared in the carcinogenic hydrocarbon controls and in the croton oil control (see Table 1).

The results were not identical for the two series. In the DMBA series, the tumor incidence with the carcinogenic hydrocarbon alone (2/25 = 8 per cent) plus that of the croton oil control (7/45 = 16 per cent) was approximately that of the group in which the hydrocarbon was followed by croton oil (13/45 = 26 per cent). In the BP series, however, no tumors developed with the carcinogenic hydrocarbon alone, so that the tumor incidence of the group in which the hydrocarbon was followed by croton oil (10/30 = 33 per cent) was higher than that of the combined controls (16 per cent).

A surprising result was that the tumor incidence of the carcinogenic hydrocarbon control was low (e.g., 8 per cent after two weekly doses of 1 per cent DMBA followed by weekly feedings of the PEG solvent) compared with the previously observed tumor yield of 20 per cent when 0.5 per cent DMBA was given once only and was not followed by PEG solvent or any other treatment (5). Whether this difference was due to the PEG solvent, acting as an anticarcinogen, or to the weekly over-night starvation in the present, but not in the previous, series was tested in subsequent control series (see below).

In the next experiment, the procedure was changed in the following ways: (a) The stomachs were virtually emptied prior to the feeding of the carcinogenic hydrocarbon by the substitution of a milk diet for 3 days, followed by water only for 18 hours, instead of merely the water alone for 18 hours. (b) Only one feeding of hydrocarbon was given for the primary treatment. (c) The concentration of croton oil was increased from 1 to 3 per cent. (d) Several more controls were included in the experiment.

### TABLE 1

**TUMOR INDUCTION IN THE FORESTOMACH OF CSH MALE MICE**

(No preliminary milk diet; solid food removed for 18 hours prior to each treatment. Each treatment: 0.3 ml. administered by stomach tube; interval of 3 weeks between primary and secondary treatment.)

<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>SECONDARY TREATMENT</th>
<th>0-10 WEEKS</th>
<th>11-40 WEEKS</th>
<th>41-80 WEEKS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 per cent DMBA in PEG</td>
<td>1 per cent croton oil in PEG</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>1 per cent DMBA in PEG</td>
<td>PEG alone</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0.5 per cent BP in PEG</td>
<td>1 per cent croton oil in PEG</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>0.5 per cent BP in PEG</td>
<td>PEG alone</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PEG alone</td>
<td>1 per cent croton oil in PEG</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

* DMBA = 9,10-dimethyl-1,2-benzanthraene; BP = 3,4-benzpyrene; PEG = polyethylene glycol-400 (solvent). \( \times 2 \) = two doses at 1-week interval; \( \times 50 \) = 50 weekly doses; \( N \) = without tumors; \( P \) = mice bearing papillomas of the forestomach; \( Ca \) = mice bearing carcinomas of the forestomach.

Note: mice bearing both papillomas and carcinomas are listed once only under carcinomas.

### TABLE 2

**TUMOR INDUCTION IN THE FORESTOMACH OF SWISS MALE MICE**

(Milk diet alone for 3 days, followed by water without food for 18 hours, prior to primary treatment; Water alone for 18 hours prior to each secondary treatment.)

<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>SECONDARY TREATMENT</th>
<th>0-10 WEEKS</th>
<th>11-40 WEEKS</th>
<th>41-80 WEEKS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 per cent DMBA in PEG</td>
<td>8 per cent croton oil in PEG</td>
<td>17</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>0.5 per cent DMBA in PEG</td>
<td>PEG (solvent) alone</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>0.5 per cent DMBA in PEG</td>
<td>PEG alone</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Liq. paraffin</td>
<td>8 per cent croton oil in PEG</td>
<td>27</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Liq. paraffin</td>
<td>PEG (solvent)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

* Numbers in parentheses indicate percentage effective tumor incidence (i.e., excluding animals that died during the first 10-week period).

† Water without food for 18 hours once weekly, as in other groups prior to secondary treatment.

Note: Otherwise as in Table 1.
Male Swiss mice received milk diet for 3 days, and then the following:

**Primary treatment.**—0.3 ml. of 0.5 per cent DMBA in PEG solvent, once only.

**Secondary treatment.**—0.3 ml. of 3 per cent croton oil in PEG solvent, repeated weekly for 30 weeks.

**Controls.**—(a) DMBA once, followed by PEG solvent alone for 30 weeks; (b) DMBA once, followed by overnight starvation (18 hr.) weekly, for 30 weeks; (c) PEG solvent once, followed by 3 per cent croton oil in PEG solvent, weekly, for 30 weeks; (d) 0.3 ml. liquid paraffin once, followed by 3 per cent croton oil in liquid paraffin, weekly, was administered weekly for 30 weeks. Here, the effect could not be attributed to the weekly repeated (18 hr.) starvation, since this was instituted in both groups.

**Experiment 3 (Table 3)**

In Exp. 1, a difference was noted between the croton oil effect in relation to DMBA and BP, and a further check on this point was made in the following experiment, with two other carcinogens—MCA and DBA—and with pretreatment with milk, as in Exp. 2.

Male Swiss mice received milk diet for 3 days, and then the following:

**Primary treatment.**—0.3 ml. of 0.5 per cent DMBA or DBA in PEG solvent, once only.

**Secondary treatment.**—0.3 ml. of 3 per cent croton oil in PEG solvent, repeated weekly for 30 weeks.

**Controls.**—(a) MCA once, followed by PEG solvent alone for 30 weeks; (b) MCA once, followed by overnight starvation only, weekly, for 30 weeks; (c) and (d) as (a) and (b), but with DBA as carcinogen; (e) PEG solvent once, followed by croton oil, weekly, for 30 weeks (taken from Exp. 2).

The results with MCA (see Table 3) were more akin to those with BP (Table 1) than to those with DMBA (Tables 1 and 2), in that the tumor incidence of MCA followed by croton oil was higher than the combined incidences of MCA alone and croton oil alone.

With MCA, the tumor incidence of the carcinogen control was again much higher when no subsequent treatment was given (80 per cent) than when the carcigen treatment was followed by

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**TABLE 3**

**TUMOR INDUCTION IN THE FORESTOMACH OF SWISS MALE MICE**

(Milk diet alone for 3 days, etc., as in Table 2)

<table>
<thead>
<tr>
<th>Primary Treatment (X1)</th>
<th>Secondary Treatment (X30)</th>
<th>0–10 Weeks</th>
<th>11–20 Weeks</th>
<th>21–30 Weeks</th>
<th>Total</th>
<th>Per cent *</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 per cent MCA in PEG</td>
<td>3 per cent croton oil in PEG</td>
<td>8 4 0 3</td>
<td>3 9 0 14</td>
<td>23 0</td>
<td>25 30 0 50/55</td>
<td>55 (60)</td>
</tr>
<tr>
<td>0.5 per cent MCA in PEG</td>
<td>PEG alone</td>
<td>4 0 0 0</td>
<td>0 0 0 7</td>
<td>2 0</td>
<td>11 2 0 2/13</td>
<td>15 (22)</td>
</tr>
<tr>
<td>0.5 per cent MCA in PEG</td>
<td>PEG alone</td>
<td>4 0 0 0 0 1</td>
<td>1 1 18 1 5 18 2 20/25</td>
<td>80 (90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG alone</td>
<td>3 per cent croton oil in PEG</td>
<td>27 1 0 2 1 0</td>
<td>14 5 0</td>
<td>42 7 0 34/29</td>
<td>14 (27)</td>
<td></td>
</tr>
<tr>
<td>0.5 per cent DBA in PEG</td>
<td>3 per cent croton oil in PEG</td>
<td>12 1 0 2 0 0</td>
<td>15 6 0</td>
<td>27 7 0 34/29</td>
<td>21 (28)</td>
<td></td>
</tr>
<tr>
<td>0.5 per cent DBA in PEG</td>
<td>PEG alone</td>
<td>2 0 0 1 0 0</td>
<td>15 2 0</td>
<td>18 2 0 2/20</td>
<td>10 (11)</td>
<td></td>
</tr>
<tr>
<td>0.5 per cent DBA in PEG</td>
<td>PEG alone</td>
<td>0 0 0 1 0 0</td>
<td>21 0 0</td>
<td>22 0 0 0/22</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

*See footnote for Table 2.

Note: Method of presentation as in Table 2.

---

for 30 weeks; and (e) no initial treatment, followed by PEG solvent, weekly, for 30 weeks.

Once again, no tumors of the glandular mucosa were observed in any of the animals. In the squamous epithelium of the forestomach, the tumor yields were as shown in Table 2. Croton oil alone once again elicited a few tumors of the squamous epithelium of the forestomach, and the tumor incidence of the group receiving DMBA followed by croton oil was again approximately the same as the combined incidences of the group with the carcigenic hydrocarbon alone and that of croton oil alone.

Other results arising from this experiment were: (a) that the PEG solvent alone was noncarcigenic; (b) that the nature of the solvent did not significantly influence the weak carcigenic action of croton oil; and (c) that the tumor incidence in the carcigenic hydrocarbon control was considerably higher when no subsequent treatment was given than when the PEG solvent...
PEG solvent for 30 weeks (15 per cent). With DBA, the relationship was reversed, however, the tumor yield being 10 per cent when followed by PEG solvent and 0 per cent without.

**Experiment 4 (Table 4)**

The above experiment was repeated with BP as carcinogen but with two changes from the original BP experiment (see Table 1): (a) milk diet for 3 days prior to the carcinogen treatment and (b) the experiment performed in duplicate, with one dose and three daily doses of 0.3 ml. of 0.5 per cent BP, respectively, in PEG solvent. Otherwise, the procedure was as in the previous experiments, and the croton oil control was the same one that served in Exp. 3.

No significant differences were obtained in tumor yield between the single dose and the triple dose of BP. In both series, the tumor yield of carcinogenic hydrocarbon followed by croton oil was approximately the same as the combined incidences of hydrocarbon alone (followed by PEG solvent) and croton oil alone. This is contrary to the results of the original BP series (Table 1). The relatively high tumor yield in the BP controls, in contrast to the absence of tumors in the first experiment, is attributable to the influence of the emptying of the stomach by virtue of the 3-day milk diet (5).

Once again, a difference in tumor yield was noted between the carcinogen control followed by PEG solvent for 30 weeks (46 per cent) and the carcinogen control without such treatment (85 per cent). Table 5 gives the combined results of the carcinogen controls of all the experiments, in which this anticarcinogen effect of PEG is clearly evident.

**TABLE 4**

**Tumor Induction in the Foregut of Swiss Male Mice**

(Milk diet alone for 3 days, etc., as in Table 2)

<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>SECONDARY TREATMENT</th>
<th>0-10 Weeks</th>
<th>11-30 Weeks</th>
<th>31-50 Weeks</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 per cent BP</td>
<td>S per cent croton</td>
<td>14</td>
<td>4</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>PEG in PEG</td>
<td>oil in PEG</td>
<td>7</td>
<td>11</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>0.5 per cent BP</td>
<td>PEG (solvent)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>0.5 per cent BP</td>
<td>S per cent croton</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>PEG in PEG</td>
<td>oil in PEG</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>0.5 per cent BP</td>
<td>S per cent croton</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>PEG in PEG</td>
<td>oil in PEG</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>PEG (solvent)</td>
<td>S per cent croton</td>
<td>27</td>
<td>1</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>alone</td>
<td>oil in PEG</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

*See footnote for Table 2.
†The three feedings of BP were at 24-hour intervals; otherwise, as in Tables 2 and 3.

**TABLE 5**

**Effect of Polychlorofyl Glycol 400, Fed Weekly by Stomach Tube for 30 Weeks, Following a Single Feeding of Carcinogen**

<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>SECONDARY TREATMENT*</th>
<th>TUMOR YIELD</th>
<th>PERCENTAGE TUMOR YIELD</th>
<th>PERCENTAGE INHIBITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PEG (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinogen</td>
<td>or no treatment (−)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BP</td>
<td>−</td>
<td>17/20</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>DMBA</td>
<td>+</td>
<td>41.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>MCA</td>
<td>+</td>
<td>2/13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>DBA</td>
<td>+</td>
<td>0.2</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

*Starvation for 18 hours once weekly prior to PEG feeding (+series) and also in untreated (−) controls.
DISCUSSION

Croton oil is the most powerful known purgative for man, and the fact that the mouse can tolerate large doses by mouth without any evidence of purgative action is of considerable pharmacological interest. The doses used in the present investigation (0.3 ml. of a 1 or 3 per cent solution) were slightly lower than the therapeutic dose for man, though relatively enormous if estimated/100 gm of body weight. From preliminary trial tests, it appears that even much higher doses, well within the toxic range for man, could have been given to the mice without any noticeably harmful effects. Croton oil is also a vesicant on human skin and, because of this, was originally used in dilute solutions, in the study of the mechanism of skin carcinogenesis in the mouse (1, 2, 6, 18). It seemed reasonable, therefore, to choose it also as the first substance for test as a potential promoting agent for gastric carcinogenesis.

Though the glandular mucosa did not respond to the carcinogenic action of polycyclic aromatic hydrocarbons when these were administered orally (5), the possibility existed that initiating action alone might occur in that tissue from such treatment, and that this would be demonstrable by the subsequent administration of a suitable promoting agent. However, no such promoting effect was demonstrable in the present investigation.

Tumors did arise in the squamous epithelium of the forestomach, but evidence of a two-stage mechanism, analogous to that arising in the skin, was ambiguous, for two reasons: (a) because the dose of carcinogenic hydrocarbon as primary treatment (chosen with an eye to the glandular mucosa) was too high, so that many tumors arose in the hydrocarbon control, and (b) because croton oil alone proved to be carcinogenic. In some of the experiments, the results were compatible with a simple summation of action by the hydrocarbon and the croton oil; but in others (BP and MC, see Tables 1 and 3), the results were suggestive of a promoting action by the croton oil over and above that attributable to the independent effects of the two agents.

The only previous study of croton oil in connection with gastric carcinogenesis was by Beck (7), but the small number of animals used and the absence of any controls prevent any conclusions to be drawn from these experiments.

The development of squamous papillomas in fourteen out of 95 mice (Tables 1 and 3), after 30 weekly feedings of croton oil, was unexpected. Though this brings croton oil within the class of carcinogens and thus complicates the problem of the two-stage mechanism, the following should be taken into account in the over-all assessment of the problem.

1. The tumors which developed in the forestomach of the mouse in the present experiments resulted from prolonged treatment (30 weeks) with a high concentration of croton oil. The incidence of 14 or 16 per cent papillomas (and no carcinomas) represents a very weak action compared, for instance, with the incidence of 71 per cent papillomas after a single feeding of DMBA, and of many carcinomas as well when DMBA was fed for 6 weeks (5).

2. Tumors have been observed only rarely in croton oil control experiments on the skin, and then only in isolated cases (1), though Rusch et al. (15) recently found a strain of mice in which such tumors developed more frequently. Perhaps in such a strain the initiating stage occurs spontaneously, so that the "tumor induction" by the croton oil might still represent only promoting action.

3. In the case of the skin, tumor production by means of a single dose of carcinogenic hydrocarbon, followed by repeated treatment with croton oil, could not possibly be attributed to a summation of carcinogenic action by the two agents, even when the croton oil alone did induce a solitary papilloma. Furthermore, promoting action by other agents (e.g., wound healing or applications of turpentine, in the case of rabbit skin), which are not themselves carcinogenic, supports the promoting effect of croton oil which might have borderline carcinogenic activity.

4. The noncarcinogenicity of a substance is becoming harder and harder to define. Provided that the test organ is sensitive enough (e.g., the subcutaneous tissues of the rat), even olive oil is slightly carcinogenic (9). Perhaps the squamous epithelium of the forestomach of the mouse is an equally sensitive test organ.

Croton oil is, nevertheless, a substance of unusual biological properties. It displays pronounced promoting action on the skin of the mouse (6), but not of the rat, rabbit, or guinea pig (18). It is noncarcinogenic to the skin in most strains of mice, but apparently not in all. It shows slight carcinogenic activity in the forestomach of the mouse. Pharmacologically, it is a violently strong purgative for man but not for the mouse. Its active constituent—croton resin—is a highly complex substance, the constitution of which has not yet been elucidated.

It is evident, therefore, that for the study of the two-stage mechanism of carcinogenesis in the stomach some other, preferably simpler, promot-
Polyethylene glycol-400 (a carbowax possessing both lipophilic and hydrophilic properties) was used as solvent throughout these experiments, proved to be anticarcinogenic. This necessitates some qualifications: As solvent for the carcinogens themselves, it failed to display any anticarcinogenic action; on the contrary, the tumor yield was, if anything, higher for DMBA in this solvent than in liquid paraffin. However, following a single feeding of carcinogenic hydrocarbon, tumor production was considerably greater when no further treatment was given than when polyethylene glycol-400 was fed weekly thereafter compared with control mice, or 61 per cent. In other words, its anticarcinogenic action is restricted to the promoting phase of carcinogenesis. This is all the more surprising in view of the recent report by Setal (17) that, on mouse skin, many detergent solvents act as promoting agents.

It is interesting to note that three daily doses of 3,4-benzpyrene (0.5 ml. of a 0.5 per cent in PEG solvent per dose), by mouth, yielded no more tumors of the forestomach than a single dose. Since it was previously shown (5) that multiple doses at weekly intervals lead to an increase in tumors, the present results may be due to a saturation of the tissues lasting at least 24 hours, or possibly to a more complex mechanism connected with a temporary refractory phase.

The previous conclusion that emptying the stomach prior to the feeding of the carcinogen augments tumor production in the forestomach of the mouse is confirmed in the present investigations: whereas two weekly feedings of benzpyrene, followed by PEG for 30 weeks, yielded no tumors at all when tested on mice without prior emptying of the stomach (Table 1), a single feeding of this carcinogen on an empty stomach yielded 46 per cent tumors (Table 4). (Though different strains were used in these two groups, there is no indication from previous tests [5] that this could have accounted for the striking difference.)

SUMMARY

1. Swiss and C57 male mice received one, two, or three feedings by stomach tube of 3,10-dimethyl-1,2-benzanthracene, 3,4-benzpyrene, 20-methylcholanthrene, or 1,2,5,6-dibenzanthracene, and then weekly feedings of croton oil for 30 weeks. The tumor yield in the forestomach was consistently higher than when the carcinogen treatment was followed by 30 weekly feedings of the solvent alone.

2. In the control series, in which croton oil was fed weekly for 30 weeks without previous carcinogenic hydrocarbon feeding, papillomas of the forestomach also developed in 14–16 per cent of the animals.

3. The increased tumor yield in the series in which the carcinogenic hydrocarbon treatment was followed by croton oil could be attributed in most cases to a summation of carcinogenic action of the hydrocarbon and the croton oil, though, in one case, there was a suggestion of a true promoting action on the part of the croton oil over and above that attributable to their combined carcinogenic activities.

4. The need for different promoting agents, in place of croton oil, and for other changes in technic for the study of the two-stage mechanism of carcinogenesis in the stomach is discussed.

5. Polyethylene glycol-400 (a carbowax possessing both lipophilic and hydrophilic properties), which was used throughout as solvent for the various agents, was found to produce a decided anticarcinogenic effect at the promoting phase (i.e., when given repeatedly after cessation of the feeding of the carcinogen), though not when serving as solvent for the carcinogenic hydrocarbons (i.e., when acting concurrently with the carcinogen).

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The Influence of Croton Oil and of Polyethylene Glycol-400 on Carcinogenesis in the Forestomach of the Mouse

I. Berenblum and Nechama Haran


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