The Mast Cell Reaction in Mouse Skin to Some Organic Chemicals*†

III. The Early Effect of Aromatic Hydrocarbons

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(Received for publication August 19, 1947)

In a previous paper (31) the temporary depletion of the granular substance of the dermal mast cells was reported, following the application of benzene to the skin of mice. This reaction failed in response to alcohol, ether, and acetone. Continued studies indicate that a similar reaction on the part of the tissue mast cells can be elicited by some other aromatic hydrocarbons, and is herein described. The subject is limited to the early pre-neoplastic response of skin to single applications of a series of aromatic hydrocarbons.

These hydrocarbons are known to induce a multitude of intermingling reactions on the part of intracellular constituents. Also, they may evoke chemical reactions resulting in the elimination of the original substances or metabolites. Our results draw particular attention to such protective reactions and to the possible role of the granular substance of the mast cells in local detoxication reactions. Our present knowledge of protective reactions to common aromatic hydrocarbons is based chiefly upon feeding experiments (2, 16, 43), and consequently, the part played by different tissue constituents is little known.

Considering the detoxication of aromatic hydrocarbons particular interest is focussed on certain organic sulfur compounds. Cysteine is used for the synthesis of mercapturic acids in response to halogenated benzenes (54) and naphthalenes (7). The glutathione content was found to decrease in the tissue of animals fed naphthalene (37, 42). Phenols, aromatic alcohols and aldehydes conjugate with sulfuric acid to form ester sulfates. The origin of the sulfuric acid is not known (2). Conjugation occurs also in eviscerated and hepatectomized animals (3, 35). Furthermore, glucuronic acid of unknown origin conjugates with a number of compounds, among them hydroxy groups, benzoate, menthols, and naphthalene. Judging from feeding experiments, benzene, phenols, naphthalene, and phenanthrene are partially excreted in conjugation with ethereal sulfates and/or glucuronic acid, and partially converted to mercapturates (2, 7, 16, 37, 42, 43). In vitro, the production of phenol sulfate was found to be achieved to a larger extent by rat intestine than by liver, muscle, and kidney slices (1). The interpretation of these findings is hampered mainly by the lack of additional data as to the site of conjugation, the origin of sulfate and glucuronic acid, and the morphology of such tissue reactions.

Pertinent studies by Crabtree on the anti-carcinogenic effect of chemical agents indicate that local protective reactions interfere with the process of skin carcinogenesis. Following the application of naphthalene, phenanthrene, anthracene, and benzene a temporary decrease in the glutathione (G.S.H) content of the skin was demonstrated (8-10). This was considered indicative of a local detoxication of the hydrocarbons during the first hours after painting. The G.S.H level was restored within 4 hours. Two carcinogenic hydrocarbons did not induce this effect, however (12, 15). The urinary excretion of conjugated ethereal sulfates was increased during the first to fourth days after the local application of benzene, phenanthrene, and naphthalene (10). Attention was paid neither to the morphological tissue changes, nor to the excretion of conjugated glucuronates.

Thus, according to previous investigations, certain sulfur compounds, particularly sulfuric acid, and glucuronic acid play a prominent role in the detoxication of aromatic hydrocarbons, and the origin of these acids is unknown. Now, the point is that the granular substance of the mast cell contains, among other elements, heparin, which after disn-
integration yields considerable amounts of sulfuric acid (sulfur up to 13.6 per cent dry weight; see Jorpes [23]), and hexuronic acid (about 26 to 29 per cent; probably glucuronic acid). This is described in detail by Jorpes (23, 29) and Wolfrom and Rice (53). Evidently, the composition of the heparin molecule has extensive bearing on several types of protective reactions. It would therefore be of interest to study the morphological and histochemical reactions of the mast cells to different chemical agents. The present paper will perhaps elucidate one aspect of the functional significance of the mast cell's granular substance.

EXPERIMENTAL

Two series of young and mature male and female Swiss albino mice were used, all on the same basal diet. Standard methods of application and preparations as previously reported were used (30, 31). Painting was done only in the right interscapular skin area, leaving the left side for control. Both methods previously described were used in counting mast cells (30). Following single applications of hydrocarbons to the right interscapular skin of mice of the same age, serial observations were made on the number of mast cells in painted skin flaps and the number of these cells in the symmetrical unpainted control skin areas in the same animals, thus assuring the greatest possible accuracy (30). The following symbols are used:

\[
\begin{align*}
A &= \frac{a}{\text{the average number of mast cells (60 observations) in a volume of superficial dermis measuring 0.01 mm. } \times 0.0044 \text{ sq. mm.}} \\
B &= \frac{b}{\text{the average number of mast cells (60 observations) in an equal volume of deep dermal and hypodermal tissue.}} \\
C &= \frac{c}{\text{the average number of dermal mast cells (40 to 50 observations) per 1.0 mm. of epidermal length, regardless of dermal thickness (height). Sections 10 microns.} }
\end{align*}
\]

The calculated quotients \(A/a\) and \(C/c\) are plotted (Figs. 1 to 3, and Fig. 5). The quotient \(B/b\) proved to be of minor significance and is therefore omitted in the graphs. For statistical evaluations of results the readers are referred to our preceding papers (30, 31).

Single skin paintings were made using the following aromatic hydrocarbons and derivants:

- Benzene (Pure)
- Phenol (Cryst. 1% and 2.7% in ether)
- Naphthalene (Cryst. (Kahlbaum) 2.7% in ether)
- Phenanthrene (Edcan) 0.6% in benzene and acetone
- 20-Methylcholanthrene

The number of brush strokes will be stated for each series of mice. Because the concentrations and amounts of hydrocarbons used in this series have been kept at levels similar to those reported by Crabtree (10), some comparison may be made of the effects on GSH level in the skin, but this is not possible with regard to the partition of sulfur in the urines of experimental mice.

A basis for rough estimation of the different concomitant events in the skin of experimental mice was obtained by observing the following changes: initial epidermal cell injury, edema, hyperemia, inflammatory cell infiltration, and the degree of subsequent epidermal regeneration.

RESULTS

I. MAST CELL REACTION TO SINGLE APPLICATIONS OF NON-CARCINOGENIC HYDROCARBONS

Benzene.—The previously reported depletion of granular substance of mast cells after the application of pure benzene (31) was corroborated (Fig. 4 "a"). Maximum depletion was reached 3 to 5 days after painting, and the normal level was restored after 6 days. Benzene did not cause any significant increase in the number of mast cells during the following 4 weeks. In mature mice, however, the depletion started fairly late (31).

Phenol.—Weak solutions of pure carboxic acid applied to two series of mature mice induced a statistically significant decrease in mast cell quotients (Fig. 1). A moderate drop was observed in response to smaller amounts of phenol (Fig. 1, Series 2), but larger amounts were found to exert a much more pronounced action (Fig. 1, Series 1). Following sublethal doses only about 10 per cent of the normal number of mast cells was observed 3 days later in the superficial dermis. The cor-

DESCRIPTION OF FIGURES 1 AND 2

Fig. 1.—Changes in mast cell quotients after single application of diluted carboxic acid to the right interscapular skin area of mice 6 to 8 weeks old. In series 1 six mice were painted with 4 brush strokes of 2.7% phenol in ether. In series 2 fourteen mice received 2 strokes of 1% phenol in ether.

Fig. 2.—Mast cell quotients after single application of 4 brush strokes of 2.7% naphthalene in ether to the right interscapular skin area of a series of 24 mice 10 to 12 weeks old.
Figs. 1–2
responding quotients were $B/b = 0.32$, and $C/c = 0.28$.

Naphthalene.—In mature mice moderate amounts of naphthalene destroyed about 25 per cent of the dermal mast cells within 24 hours after painting, and approximately 50 per cent of them 48 hours after application (Fig. 2). The normal mast cell level was again reached in 6 days.

Phenanthrene.—No significant decrease in the number of mast cells could be discerned after single paintings with 2.7 per cent phenanthrene in ether (Fig. 3). Thus, further investigation is needed.

The graphs obtained for benzene, phenol, and naphthalene show a certain uniformity in type and time relationship, and this would seem to indicate the unspecificity in the mast cell response. Roughly, according to the dosage of hydrocarbons a declining order of response is noted, as follows: Phenol, naphthalene, and benzene. Quantitative correlations between dosage of and the depletion of mast cell granular substance could be obtained only for the phenol series. Large amounts of benzene elicit an earlier mast cell reaction than smaller amounts (31), but the level of maximum response remains the same. All graphs indicate the restoration of mast cell balance in a few days without over-compensation, in other words, the primary decrease in granular content did not induce a subsequent increase in the number of dermal mast cells.

II. MAST CELL REACTION TO SINGLE APPLICATIONS OF METHYLCHOLANTHRENE

The early effects of single paintings with 20-methylcholanthrene dissolved in benzene and in acetone were studied in three series of mice (Figs. 4 and 5). When applied to the skin in benzene solution (Fig. 4 "A") a similar response is elicited on the part of the dermal mast cells as to the solvent itself (Fig. 4 "a"). A temporary granular depletion during the first week after painting is followed by a rapid granular regeneration (cp. 31). Three weeks after painting the mast cell level showed a considerable increase in the methylcholanthrene-painted area.

Acetone, it was found, does not induce changes in the mast cell granular content (31), whereas methylcholanthrene applied to young mouse skin in acetone solutions elicits an insignificant decrease in the number of dermal mast cells (Fig. 5), not exceeding twice the standard deviation of quotients (30). No clear-cut correlation was noted.

![Fig. 3](https://example.com/fig3.png)

**Fig. 3.**—Mast cell quotients after single application of 4 brush strokes of 2.7% phenanthrene in ether to a series of 6 mice 6 to 8 weeks old.
for moderate and large doses of the hydrocarbon, as shown in Fig. 5, C/c. A slight decrease in the number of superficial mast cells (Fig. 5, A/a) was interpreted to be as an artefact, due to concomitant edema.

Thus, the mast cell depletion following the application of methylcholanthrene in benzene seems to be attributable to the benzene itself. The carcinogen has so far not induced any apparent early granular decrease in the number of dermal mast cells, nor was a gradient obtained with reference to different dosage. Further investigation with other carcinogenic hydrocarbons is going on. The subsequent increase in the number of dermal mast cells and the cytological changes induced by the carcinogen will be discussed elsewhere.

III. MORPHOLOGY OF THE MAST CELL REACTION

Following phenol, naphthalene, and benzene paintings the loss of metachromatic granular substance was gradual until the complete depletion of granules, when the cells became indistinguishable from other connective tissue cell elements. The rate and degree of this reaction varied in different series. During this process both nuclei and cytoplasm increased in size, and a gradual decrease in basophilic affinity of the nuclei was seen. Mast cells deficient in granules had fairly large nuclei with subnormal amounts of chromatin, and pale-staining nucleoli. No abnormal mitoses such as colchicine mitoses, or other degenerative nuclear changes were observed.

The fate of the metachromatic granular substance during this stage could not be clearly explained. Unusual spreading of granules did not occur, nor were mast cells found to move towards the vessels. The usual technical procedures for fixation and staining were employed, but no metachromatic material was immediately discerned in the intercellular fluid of the surrounding connective tissue. Later on, however, small amounts of metachromatic material was demonstrated in the intercellular fluid by means of the "freezing-drying" technic of fixation. This was found after heavy painting with phenol, and seems to be of particular interest. Dissolution of granular material in the mast cell cytoplasm was not seen.

During recovery gradually increasing amounts of small dust-like metachromatic granules were noted in mast cells otherwise quite similar to those just vanished. The nuclei and nucleoli showed an increasing basophilia.

To sum up, we received the impression that the hydrocarbons mentioned above cause a temporary damage to the mast cell cytoplasm and the nuclei resulting in a depletion of cytoplasmic granules, and intranuclear disturbance of chromatin production. To all appearances, these changes are followed by simple recovery of the same cells; resynthesis of cytoplasmic granules, and re-established nuclear functions. The findings do not support the suggestion that the mast cells have been killed or irreversibly damaged during these events. The unusual appearance of metachromatic material in the intercellular tissue fluid indicates that at least a certain amount of granular substance is transferred to this fluid.

IV. EVALUATION OF SECONDARY PHENOMENA

The account of concomitant changes in the skin is of fundamental importance for our interpretations. We must emphasize, however, that our results refer only to single paintings. Approximate evaluation of the secondary changes are listed below.

Evidently, no direct correlation could be established between the varying degrees of mast cell response and the subsequent and synchronous secondary changes in painted skin. Neither the initial cell damage, nor the other enumerated secondary changes, such as edema, hyperemia, inflammatory cell reaction, and epithelial regeneration, can be regarded as causative factors per se.

V. POSSIBLE INTERPRETATIONS OF RESULTS

The results indicate the existence of a non-specific reaction on the part of the mast cell granular substance, induced by the intracellular uptake of some aromatic hydrocarbons and derivatives. After painting the hydrocarbons spread in the intercellular medium and in the cells of the skin according to their ratios of solubility. A good deal of the lower hydrocarbons is rapidly transferred to

<table>
<thead>
<tr>
<th>Hydrocarbon</th>
<th>Initial cell damage</th>
<th>Edema and hyperemia</th>
<th>Inflamm. cell infiltration</th>
<th>Epidermal regeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene, pure</td>
<td>Slight</td>
<td>Moderate</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td>Phenol, 1% in ether</td>
<td>Pronounced</td>
<td>Pronounced</td>
<td>Pronounced</td>
<td>&quot;</td>
</tr>
<tr>
<td>Naphthalene, 2.7% in ether</td>
<td>Slight</td>
<td>Slight</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Phenanthrene, 2.7% in ether</td>
<td>Pronounced</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Mcha, 0.6% in benzene</td>
<td>&quot;</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Pronounced</td>
</tr>
<tr>
<td>Mcha, 0.6% in acetone</td>
<td>&quot;</td>
<td>&quot;</td>
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<td>&quot;</td>
</tr>
</tbody>
</table>
the blood,1 and a part is left in the skin to constitute the active portion. What is taken up by the blood is detoxified elsewhere, and appears in conjugated form or otherwise in the urine.

Regarding the operating mechanisms we must consider the following possibilities.

Cell damage.—Following single applications of the hydrocarbons in this series transitory changes were observed in the nuclei and cytoplasm of the mast cells. These changes might be comparable to those displayed by so-called “mitotic poisons” (32, 33, 34, 39, 40, 41). Our gradation is in accordance with that of Gavaudan (13, 14), who found the mitotic changes to be more specific and intense in response to phenol than to naphthalene and benzene. However, we obtained no reaction with ethyl alcohol, ethyl ether, and acetone, which are known to exert colchicine mitotic efficiency (41). Further, it would be reasonable to assume a marked effect with methylcholanthrene, but the mast cell response failed to appear. In view of these facts it seems to us hardly likely that the mast cell granular reaction should be due primarily to cell damage, but it will be admitted that this mechanism probably is only partially operative.

Chemical effects.—In our opinion the order of hydrocarbon activity with reference to the mast cell granular system, and also the gradients obtained with different dosage of hydrocarbons (phenol and benzene), indicate that the chemical reactivity could be the chief operative factor. The hydrocarbons must induce chemical reactions of protective nature, and the different hydrocarbons in our series demand various chemical groups for their detoxication.

According to investigations by Crabtree (10) a local depletion of G.SH is rapidly induced and restored in the skin. This effect was graded in the following quantitative order: naphthalene, phenanthrene, benzene. This was considered to indicate local mercapturate formation in the skin. Two carcinogenic hydrocarbons (dibenzanthracene and benzpyrene) did not affect the G.SH level. With reference to the present results, this temporary G.SH depletion demonstrated by Crabtree can hardly be regarded as a causative factor.

On the other hand, we must emphasize that all three substances displaying marked activity in our series, namely phenol, naphthalene, and benzene, are known to be rapidly detoxified by conjugation with ethereal sulfates and/or glucuronic acid. Methylcholanthrene does not primarily require any of these compounds, and it may be the reason why this substance does not affect the mast cell granular substance. Two other carcinogens (10) did not affect the G.SH level, nor are they detoxified by simple conjugation (11). Thus, we believe that the reaction of the mast cell granular substance is induced by such hydrocarbons and derivants as require ethereal sulfate and/or glucuronic acid for their elimination. Consequently, the granular substance of mast cells is supposed to participate in protective reactions.

Mode of reaction.—The active substances in this series evidently evoke parallel phenomena, such as changes in the physico-chemical state of intracellular structures, and chemical reactions with intracellular constituents. Complex series of events impossible to distinguish in details is predicted. The governing factors can not even be approached because additional data on the local concentrations, solubility, and chemical reactivity, are lacking. Present results indicate, however, that the intracellular uptake of active hydrocarbons is followed by heavy changes of the mast cell granular substance leading to a loss of metachromatic staining reaction. This indicates that the native granular substance either is transferred, or disintegrated with subsequent loss of ester sulfate bonds. The liberation of ester sulfate radicals and hexuronic acid (glucuronic acid) would then constitute prerequisites for detoxication reactions.

We have as yet no direct evidence favoring the hypothesis that the actual conjugation should occur in the skin. Most of the granular material seems to have disappeared in the cell cytoplasm. A small amount was demonstrated in the surrounding tissue fluid. The conjugation reaction may take place in the mast cells, in the tissue fluid, in the blood, or elsewhere in the body. If, however, the report by

DESCRIPTION OF FIGURES 4 AND 5

Fig. 4.—The numerical changes in dermal mast cells following single painting with 3 brush strokes of 0.6% methylcholanthrene in benzene to the right interscapular region of 22 mice 10 weeks old. For comparison the left interscapular areas in the same mice were at the same time painted with 3 brush strokes of pure benzene.

Fig. 5.—Mast cell quotients following single application of 0.6% methylcholanthrene in acetone. In series 1 six mice (2 weeks old litter mates) were painted with 12 brush strokes. In series 2 fourteen mice 3 weeks old received 3 brush strokes.
Methylcholanthrene in benzene
Pure benzene

Days after painting

Figs. 4-5.
Arnolt and de Meio concerning the conjugation of phenol and ethereal sulfate in vitro is recalled, the actual conjugation may occur in the skin as well as in the intestine or liver.

**DISCUSSION**

This reaction of the granular system of mast cells in response to some hydrocarbons and phenol seems to be the expression of local detoxication procedures in the skin. It provides a basis for further studies in this field, and may explain the origin of considerable amounts of ester sulfate and hexuronic acid (glucuronic acid?) not previously understood. This interpretation was touched upon by earlier authors. Webb (51) found various stages of mast cell granular "dissolution" following intraperitoneal injections of carbon and egg white. The latter substance apparently requires detoxication, but this was not stressed by Webb. The transfer of granular substance (heparin) from hepatic mast cells to the blood during peptone shock in dogs was described by Wilander (52, cp. also 22), and serves as a guide to physiological mast cell function. In this respect, however, his observation seems to be of limited value, although it may indicate a similar detoxication process such as described here.

The present investigations also have a bearing on skin carcinogenesis in general and on the particular line of research dealing with the retardation of experimental carcinogenesis (Crabtree and his associates). It would probably be worthwhile in future discussions on "labile" sulfurous compounds to include not only G.SH, but also the ester sulfates of the mast cell granular system, which to all appearances belong to labile sulfur constituents of connective tissue in general, and may be mobilized in response to different stimuli (10, 13, 45, 48, 50-52).

Regarding the physiological significance of the mast cell granular substance the present situation is rather puzzling and a matter of much controversy (36). As a corollary to the discovery of some chemical components of the isolated heparin molecule (23, 24, 28; cp. also 4-6, 25, 27, 29), Jorpes, Holmgren, and Wilander assume that the tissue mast cells under normal physiological conditions supply heparin to the blood whereas the coagulation of normal blood should be prevented (17-19, 21, 26, 29). They base their hypothesis first, on the conviction that the native granular substance is heparin, and secondly, on the close perivascular localization of the tissue mast cells (29, p. 63). However that may be, no direct evidence supports this theory. No one has observed the hypothetical delivery of granular substance to the intercellular fluid or to the blood under physiological conditions. The perivascular cell distribution may be due to a variety of other factors, e.g. a need for high oxygen tension or other matter supplied through the blood.

The physiological function of the mast cell granular substance is still open for discussion. When considering this topic it seems of primary importance to relinquish one-sided, unproved theories (29) prejudicial to further work, and instead keep an open mind toward different lines of approach. The native granular substance probably contains several other biologically active substances (38) and consequently the granular system may have some bearing on several types of biological reactions. A number of observations indicate a close relationship between the granular substance and different growth processes (44-50), but the underlying mechanism is as yet not fully understood (50). Secondly, according to the present investigation, the granular substance seems to take part in local detoxication reactions.

**SUMMARY**

1. Following single applications of benzene, phenol, and naphthalene to mouse skin the early depletion of granular substance on the part of dermal mast cells was reported. This effect was not obtained by using phenanthrene or 20-methylcholanthrene.

2. The agents cause reversible damage to the intracellular structures of mast cells.

3. In an attempt to interpret these findings the concomitant secondary changes could with some certainty be ruled out as operative factors. The interpretation is advanced that some constituents of the granular substance, viz. ethereal sulfate and hexuronic acid, take part in detoxication reactions aiming at the elimination of the agents under question. Continued investigations are needed for the elucidation of the operating factors.

4. It is concluded that the native granular substance of tissue mast cells has some bearing on local detoxication reactions as well as on other types of biological reactions.

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DESCRIPTION OF FIGURES 6 TO 11

FIG. 6.—Unpainted left control skin area showing the normal distribution of mast cells. Toluidine blue. Mag. X 325.

FIG. 7.—Three days after one single application of phenol 2.7 per cent in ether almost all granule-bearing mast cells have disappeared. Epidermal necrosis, marked dermal inflammatory cell infiltration. Same animal as in Fig. 6. Toluidine blue. Mag. X 325.

FIG. 8.—Same as Fig. 7. V. Gieson. Mag. X 325.

FIG. 9.—Unpainted left control skin area from a naphtalene treated mouse. Normal number of mast cells. Toluidine blue. Mag. X 325.

FIG. 10.—Two days after one single application of naphtalene 2.7 per cent in ether. Almost all superficial dermal mast cells have disappeared, and the number of hypodermal mast cells has decreased considerably. Toluidine blue. Mag. X 325.

FIG. 11.—Same as Fig. 10. No conspicuous cell changes are seen; only slight inflammatory symptoms. V. Gieson. Mag. X 325.
DESCRIPTION OF FIGURES 12 TO 15

Fig. 12.—Three days after a single painting with methylcholanthrene 0.6 per cent in benzene. A marked depletion of superficial mast cells; some are left in the deeper part of dermis and in the hypodermis. Toluidine blue. Mag. X 325.

Fig. 13.—Same as Fig. 12. The changes in epidermal texture and cytology are seen, as well as edema and cell infiltration in dermal connective tissue. V. Gieson. Mag. X 325.

Fig. 14.—Ten days after one single application of methylcholanthrene 0.6 per cent in benzene, a normal number of mast cells is reattained. Toluidine blue. Mag. X 325.

Fig. 15.—Same as Fig. 14. Marked changes are still seen in both epidermal and dermal layers. V. Gieson. Mag. X 325.
Figs. 12-15
DESCRIPTION OF FIGURES 16 TO 18

Fig. 16.—Unpainted left control skin area from the same methylcholanthrene treated mouse as in Fig. 17. Normal number and distribution of mast cells. Toluidine blue. Mag. × 325.

Fig. 17.—Four days after a single application of methylcholanthrene 0.6 per cent in acetone. A slight decrease in the number of superficial dermal mast cells is seen. Toluidine blue. Mag. × 325.

Fig. 18.—Same as Fig. 17. Marked epidermal nuclear changes, and dermal edema and inflammatory cell infiltration. V. Gieson. Mag. × 325.
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*Cancer Res* 1948;8:449.