biologischen Objekte übertragen werden können. Am bedeutungsvollsten wäre dabei neben der Feststellung einer nur innerhalb dünner Grenzschichten ablaufenden Kontrastierungsreaktion vor allem die Deutung der Bildentstehung. Schließlich wäre hieraus auch verständlich, weshalb zur erfolgreichen elektronen-
mikroskopischen Darstellung biologischer Objekte die Schnittdicke innerhalb gewisser Grenzen variiere-
ren kann.

Der Deutschen Forschungsgemeinschaft danke ich für Sachbeihilfen, Fräulein Christa Görtzen-
ger und Eva-Maria Finze für ihre Mitarbeit.

Sensitivity to 1-Methylnaphthalene of Whole-body Irradiated Rats

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Whole-body irradiation of the rat produces a decrease of the urinary excretion of glucuronides originating from the detoxication of 1-methylnaphthalene; in apparent contrast with the conclusion which could be drawn from this finding the rat exposed to X-irradiation has a higher resistance to the toxic action of the hydrocarbon. The results obtained show that the decreased sensitivity to 1-methylnaphthalene is due to the response of the gastrointestinal system of the rat to radiation: in the animals exposed to 400 r of X-rays before the administration of 1-methylnaphthalene, the absorption of the hydrocarbon is strongly delayed and takes place at a much slower rate. These changes may partially explain the so-called “paradoxical effect” of radiation on the sensitivity to certain toxic compounds administered to the rat by oral route.

In animals treated immediately after exposure to sublethal doses of X-rays with aromatic hydrocarbons, such as terphenyls¹ or 1-methylnaphthalene², the urinary excretion of conjugated metabolites has been found to be strongly reduced. These results, supported by “in vitro” experiments³ have led to the conclusion that X-irradiation had severely impaired the “detoxication mechanisms” and therefore a lower resistance to toxic compounds should be expected in rats previously exposed to radiations.

The work reported in this paper was undertaken to obtain more detailed information on the effect of X-irradiation on the toxicity of 1-methylnaphthalene in the rat, and to determine the possible causes to which this effect can be attributed.

It has been previously shown² that about 40% of a dose of 1-methylnaphthalene (2 grams/Kg body weight, by intragastric intubation) is excreted with the urine in the form of metabolites conjugated with glucuronic acid, while in the irradiated rat about 20% is eliminated in such a form. Since total glucuronide excretion has also been found to be reduced to 50% of the normal in the rat exposed to 1000 r of gamma-radiation⁴, the daily excretion of glucuronides was examined first to learn whether lower doses of X-rays (400 r) were able to produce a similar effect.

Total urinary glucuronide excretion was measured in male Sprague-Dawley rats (180—220 g); the animals were in metabolism cages and received synthetic diet (A.L.A.L, Milan-Italy) and water “ad libitum”; normal, fasted, and paired fed controls were used; paired fed controls received the same amount of food which had been ingested by the irradiated rats during the preceding 24 hours. All control groups were submitted to sham irradiation. The irradiation conditions were as follows: X-ray generator Seifert, mod. 300, operated at 250 kV, 10 mA, Cu filter 1 mm; the animals were placed in a rotating chamber made of plexiglas and containing 5 rats in separate compartments. The dose rate, measured with a Victoreen ionization chamber, mod. 575-A, was 25 r/min in air. Total exposure dose was 400 r. Faeces-free urine was collected every 24 hours, starting 4 days before the irradiation, and stored at –20°C until analyzed. Total glucuronides were determined by the method of Paul⁵, using the stabilized naphthoresorcinol reagent⁶.

1. K. Gerbaulet and P. Scoppa, unpublished results.
The results show that the excretion of total glucuronides is decreased only if the irradiated animals are compared with normal controls, but is not significantly modified with respect to paired fed controls (Table I). It would therefore seem that the reduced intake of food caused by irradiation is responsible for the observed decrease in the level of glucuronides excreted in the urine.

On the basis of these results (decreased glucuronic excretion as an effect, albeit indirect, of irradiation) it might be expected that the sensitivity to 1-methylnaphthalene would be higher in irradiated than in normal rats. To test this hypothesis, several experiments were conducted in which high doses of the hydrocarbon were given to rats by intragastric intubation.

After the rats had been irradiated with 400 r, 1-methylnaphthalene (4 grams/Kg body weight) was introduced into the stomach and the animal returned to its cage, having free access to food and water. The dose of 1-methylnaphthalene used was a LD75, causing the death of the unirradiated animal within 3 days. The sensitivity to 1-methylnaphthalene appeared reduced if the rats had been previously exposed to irradiation (Table II). The results obtained are apparently in contrast with previous findings concerning the effect of radiation on detoxication mechanisms. The present investigation was therefore extended to the effects of the exposure to X-rays on the gastrointestinal system of the rat, for example, possible modifications of the absorption rate of the toxic compound.

The 1-methylnaphthalene content of the faeces, measured by a modification of the method of Chang7, was not much different in the irradiated rats, accounting in both groups for only a few percent of the administered dose.

Blood levels of 1-methylnaphthalene, determined by the method of Guertin and Gerarde8 for aromatic hydrocarbons, were found to be much lower in the irradiated rats at any time following the administration of the hydrocarbon.

Further experiments performed in the presence of phenol red as an unabsorbable marker, employing the technique described by Sögnen9, showed that

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### Table I. Urinary excretion of glucuronides (Average of 25 rats).

<table>
<thead>
<tr>
<th>Days</th>
<th>Normal</th>
<th>Fasted</th>
<th>Paired fed</th>
<th>Irrad. 400 r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Milligrams glucuronic acid/24 h/rat (95% fiducial limits)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24.8</td>
<td>24.3</td>
<td>24.6</td>
<td>25.2</td>
</tr>
<tr>
<td>1</td>
<td>25.4</td>
<td>26.6</td>
<td>25.4</td>
<td>25.6</td>
</tr>
<tr>
<td>2</td>
<td>25.8</td>
<td>25.5</td>
<td>25.2</td>
<td>25.8</td>
</tr>
<tr>
<td>3</td>
<td>26.1</td>
<td>25.5</td>
<td>25.2</td>
<td>26.1</td>
</tr>
<tr>
<td>4</td>
<td>26.4</td>
<td>26.6</td>
<td>26.4</td>
<td>26.6</td>
</tr>
</tbody>
</table>

### Table II. Mortality and mean survival time of rats treated with 1-Methylnaphthalene (4 grams/Kg). * Based on decedents only.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mortality</th>
<th>Mean survival time *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Methylnaphthalene</td>
<td>113/150 (75.3%)</td>
<td>34.4 hours</td>
</tr>
<tr>
<td>Irradiation (400 r) + 1-Methylnaphthalene</td>
<td>76/150 (50.7%)</td>
<td>43.6 hours</td>
</tr>
</tbody>
</table>
in the irradiated animals stomach emptying was much retarded and then proceeded at a slower rate than it had in the controls. We suggest that the reduced sensitivity to 1-methylnaphthalene in the irradiated rat could therefore be accounted for on the basis of the response of the gastrointestinal system to the radiation.

It has been known for several years that the early effect of an exposure to radiation on the gastrointestinal system of the rat consists mainly in a strong increase of gastric secretion and in a retardation of stomach emptying\textsuperscript{10,11,12}. When, a short time after the exposure to X-rays, the increase of gastric secretion takes place, the volume of the stomach content increases because the amount of gastric secretion is higher than the volume which passes from the stomach into the intestine: in some cases there is a regurgitation of the contents of the small gut into the stomach\textsuperscript{10}. If immediately after irradiation the rats are given a toxic compound, there is dilution by the gastric secretion and maybe by a part of the intestinal contents: this, and the delay of stomach emptying, results in smaller amounts of the given compound leaving the stomach per unit time. In our case, lower concentrations of 1-methylnaphthalene come in contact with the intestinal epithelium during the first hours after administration of the hydrocarbon. The time necessary for stomach emptying depends upon the radiation dose received\textsuperscript{12}; for the dose employed in the present experiments, even 24 hours after irradiation the stomachs were found enormously distended and contained the greater portion of the phenol red.

In conclusion: 1) the results concerning the excretion of urinary glucuronides favor the hypothesis of a decreased activity of the detoxication mechanisms in the irradiated rat; 2) experimental evidence showed that in this animal the sensitivity to high doses of 1-methylnaphthalene is reduced by irradiation; 3) the determination of hydrocarbon levels in the blood as well as in the stomach demonstrates that in the irradiated rat the absorption of 1-methylnaphthalene is delayed and takes place at a much slower rate. These changes give a possible explanation for the so-called “paradoxical effect”\textsuperscript{13} of radiation on the sensitivity to certain toxic compounds administered to the rat by oral route.

\textsuperscript{11} E. V. Hulse, Brit. J. exp. Pathol. 38, 498 [1957].
\textsuperscript{12} W. O. Caster and W. D. Armstrong, Radiat. Res. 5, 189 [1956].
\textsuperscript{13} W. Eger and C. Terruhn, Strahlentherapie 105, 296 [1958].