Some Data on Mechanism of Leukopenia and Leukocytosis Following Irradiation

By JULIA GIDÁLI AND IMRE FEHÉR

With the technical assistance of Julia Osgyáni

THE LEUKOPENIA developing some days after a high dosage of ionizing irradiation is apparently due to direct injury of the bone marrow. On the other hand, the appearance of leukocytosis before leukopenia develops indicates that other factors may influence the level of circulating leukocytes in that phase. The short course of this initial leukocytosis suggests the possibility of an increased peripheral removal as shown by Cronkite et al.1 No direct effect of ionizing radiation on the granulocytes, in the commonly used dose range, has been shown thus far. The increase in granulocytes which appears within the first 24 hours following irradiation has generally been explained by irritation of the bone marrow, while the leukopenia preceding the development of the radiation injury to the bone marrow is often attributed to presumed toxins arising in the irradiated organism. Leukopenia has been demonstrated in normal animals following the injection of sera from irradiated humans or animals;2-7 to lesser extent, this has also been shown in vitro.8 However, there is no published uniform conception regarding the etiology of early leukopenia and a number of publications dispute the existence of the presumed toxins.9-11

The present paper is concerned with the demonstration, in the period shortly following irradiation, of the presence of humoral agents that might influence the circulating white blood cells and thrombocytes.

MATERIALS AND METHODS

Seventy-six chinchilla rabbits of both sexes, weighing 1800–3400 Gm., were used for this experiment. In order to study the effect of starch solution and saline injections, eight rabbits of different strains and sexes weighing 2000–3000 Gm. were also used. The rabbits were kept on a normal mixed diet, but feeding was discontinued 6 hours prior to the beginning experiment and the animals were maintained in a starved condition for the entire experimental period. Irradiation was delivered by a Medicor x-ray machine, type THX 250, 200 kv, 15 ma, 0.5 mm. Cu filter, target distance 100 cm, dose rate 16.8 r/min.

The rabbits were exsanguinated under sterile conditions by carotid puncture. A few minutes before exsanguination they were given intravenously, 1,000 I.U. of heparin. Each recipient was given 10 ml. of sterile plasma into the marginal ear vein. Blood samples were taken from the opposite ear.

Leukocytes were counted by a hemocytometer in the usual way. The count of thrombocytes was determined with a cell-counter (Celloscope, Lars Ljungberg, Sweden) after sedimentation for 2 hours. Smears were stained with azure-eosine methylene blue, 100 cells read per smear. Statistical calculations were executed according to Student’s formula.

From the Department of Pathophysiology, “Frederic Joliot-Curie” National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary.

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EXPERIMENTAL STUDIES

The authors assumed that if a toxin or some other substance affecting the peripheral blood picture really develops as a result of irradiation, the plasma should contain the largest amount immediately following irradiation. At that time the effect should be demonstrable in a change of the blood picture as well.

The first experiments, therefore, were aimed to study the changes in the level of the circulating granulocytes, lymphocytes and thrombocytes during the first 24 hours following irradiation (Fig. 1).

The reactions of the white blood cell counts of the animals irradiated with 600 or 150 r were almost identical: significant granulocytopenia developed within a few minutes \((p < 0.01)\) followed by granulocytosis after the fluctuation of the cell count. Granulocytopenia could be demonstrated in each case differing only in intensity and temporal course.

Only the respective temporal courses and intensities showed slight differences in the effect of the two doses. Granulocytosis began to develop as early as 60 minutes and increased about 200 per cent in the 2nd hour following irradiation with 150 r. At 600 r the granulocytotic phase began 2 hours after irradiation and did not reach the peak value before 24 hours. Fluctuation in the level of leukocytes preceding the leukocytotic phase was considerably greater after irradiation with 600 r than with 150 r.

The curve illustrating the changes of the thrombocyte level was similar...
and the curve of the lymphocyte level decreased in an indirect line as well. The decrease was very rapid in the first 5 minutes but showed fluctuations further on.

Since it was assumed that leukopenia observed in the blood shortly after irradiation was due to some substance appearing in the circulation as a result of irradiation, the irradiated animal was exsanguinated at the minimum of the initial granulocytopenia (about 10 minutes following irradiation), and 10 ml. of the plasma obtained was injected into a normal rabbit. Six chinchilla rabbits, used as controls, were given plasma of equal quantity from a non-irradiated chinchilla rabbit. The control plasma induced slight thrombocytosis, non-significant lymphocytopenia and a significant granulocytosis. Ten ml. of saline injected intravenously did not influence the blood picture. Smaller quantities (2–3 ml.) of the plasma obtained from irradiated rabbits (IP) were ineffective, 5–6 ml. gave less marked reactions, while 10 ml. induced a leukopenic effect in every case.

IP in every instance induced a reaction in the peripheral blood picture similar to that of irradiation (table 1). Granulo-, lympho- and thrombocytopenia developed within a few minutes after the administration of the plasma. Granulocytopenia was followed by prolonged granulocytosis with the level of granulocytes decreasing to the starting value in about 24 hours.

IP_{150} and IP_{600} had somewhat different effects upon the thrombocyte level. With IP_{150}, the thrombocyte level decreased evenly up to the 3rd hour, then slowly increased, approaching normal values after 24 hours (fig. 2). With IP_{600}, there was a quickly developing thrombocytopenia, significant by the 60th minute, followed by a slow, fluctuating increase in the thrombocyte level, which however, failed to reach the starting level even in 24 hours.

The lymphocyte level fell to a minimum between the 2nd and 3rd hour following the administration of the plasma (a depression of 40–60 per cent). Then it began to increase slightly and almost reached the initial level in 24 hours. Lymphocytopenia also developed when normal plasma was injected into normal rabbits; however, it was preceded by lymphocytosis, lasting for a few minutes. We are assuming that this type of lymphocytopenia was non-specific, perhaps as the result of stress. Stress, as a rule, presents a problem when studying the changes in the lymphoid system due to a specific stimulus. However, the fact that lymphocytopenia induced by the plasma obtained from irradiated animals was more marked than that induced by the normal plasma, suggested that the IP influenced the lymphocyte level through some other mechanism.

A further investigation as to whether the granulo-, thrombo-, and lymphopenic effect of the IP could be demonstrated as well, when taken at a later date after irradiation, was undertaken. Plasma was obtained from rabbits exsanguinated 7 days following irradiation (table 2). The effect of the plasma obtained from an animal irradiated with 150 r hardly differed from that exerted by the control plasma (table 1). Administration of IP obtained from an animal irradiated with 600 r first induced an initial slight granulocytopenia followed by an evenly increasing, prolonged granulocytosis. In contradiction to
Table 1.—Effect of 10 ml. of Plasma from Rabbits Irradiated with 150 or 600 r on the Number of Granulocytes, Mononuclear Elements and Thrombocytes in the Recipients

<table>
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<tr>
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<th>BEFORE TREATMENT</th>
<th>5'</th>
<th>15'</th>
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<th>120'</th>
<th>180'</th>
<th>240'</th>
<th>24*</th>
</tr>
</thead>
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<td>CONTROL</td>
<td>1.97</td>
<td>2.96</td>
<td>3.30</td>
<td>3.25</td>
<td>4.20</td>
<td>4.20</td>
<td>5.42</td>
<td>2.50</td>
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<td></td>
<td>± 0.71</td>
<td>± 0.30</td>
<td>± 0.02</td>
<td>± 0.45</td>
<td>± 1.08</td>
<td>± 0.35</td>
<td>± 0.45</td>
<td>± 0.45</td>
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<tr>
<td>150**</td>
<td>2.50</td>
<td>2.96</td>
<td>3.50</td>
<td>4.20</td>
<td>5.42</td>
<td>5.42</td>
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<td>± 0.30</td>
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<td>± 0.45</td>
<td>± 1.08</td>
<td>± 0.35</td>
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<tr>
<td>600***</td>
<td>5.16</td>
<td>6.05</td>
<td>6.16</td>
<td>4.47</td>
<td>3.38</td>
<td>4.67</td>
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<td></td>
<td>± 1.85</td>
<td>± 1.84</td>
<td>± 1.44</td>
<td>± 2.32</td>
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<td>± 0.89</td>
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<tr>
<td>MONONUCLEAR</td>
<td>CONTROL</td>
<td>3.65</td>
<td>4.25</td>
<td>3.45</td>
<td>2.35</td>
<td>2.05</td>
<td>2.05</td>
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<tr>
<td></td>
<td>± 1.50</td>
<td>± 1.45</td>
<td>± 1.15</td>
<td>± 2.20</td>
<td>± 0.58</td>
<td>± 0.35</td>
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<tr>
<td>150**</td>
<td>3.50</td>
<td>3.95</td>
<td>3.06</td>
<td>2.35</td>
<td>2.05</td>
<td>2.05</td>
<td>2.05</td>
<td>2.05</td>
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<tr>
<td></td>
<td>± 0.76</td>
<td>± 0.87</td>
<td>± 0.67</td>
<td>± 1.20</td>
<td>± 0.55</td>
<td>± 0.35</td>
<td>± 0.35</td>
<td>± 0.35</td>
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<tr>
<td>600***</td>
<td>6.85</td>
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<td>8.15</td>
<td>7.05</td>
<td>6.75</td>
<td>6.75</td>
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<tr>
<td></td>
<td>± 1.04</td>
<td>± 1.46</td>
<td>± 1.15</td>
<td>± 2.70</td>
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<tr>
<td>THROMBOCYTE</td>
<td>CONTROL</td>
<td>286</td>
<td>260</td>
<td>260</td>
<td>297</td>
<td>341</td>
<td>324</td>
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<td>± 85</td>
<td>± 81</td>
<td>± 52</td>
<td>± 62</td>
<td>± 98</td>
<td>± 106</td>
<td>± 125</td>
<td>± 100</td>
<td>± 29</td>
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<tr>
<td>150**</td>
<td>498</td>
<td>539</td>
<td>575</td>
<td>539</td>
<td>504</td>
<td>504</td>
<td>575</td>
<td>485</td>
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<td></td>
<td>± 178</td>
<td>± 102</td>
<td>± 167</td>
<td>± 125</td>
<td>± 70</td>
<td>± 80</td>
<td>± 150</td>
<td>± 117</td>
<td></td>
</tr>
<tr>
<td>600***</td>
<td>503</td>
<td>585</td>
<td>475</td>
<td>365</td>
<td>350</td>
<td>525</td>
<td>412</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± 99</td>
<td>± 182</td>
<td>± 160</td>
<td>± 95</td>
<td>± 135</td>
<td>± 94</td>
<td>± 105</td>
<td>± 154</td>
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</tr>
</tbody>
</table>

+ mean of 6 animals, ++ mean of 9 animals, +++ mean of 12 animals

the thrombocytotic effect of the control plasma, this experimental plasma reduced the thrombocyte level in the 1st hour and the starting value was not reached in 24 hours. The lymphocytopenic effect of the experimental plasma taken at the minimum of lymphopenia was significant (p < 0.05), in contrast to that of the control plasma (p > 0.1).

Whenever plasma obtained from granulocytopenic animals (mean granulocytes: 1200/mm³) was administered, the injection always induced granulocytopenia in the recipient animal, lasting for a short time. This corresponded fully to the working hypothesis of the authors: that the agent that induced granulocytopenia in the irradiated animal had the same effect even when transferred to the recipient animal. Should this hypothesis prove to be correct, then the plasma obtained from a granulocytotic animal should not induce granulocytopenia. In order to prove this, two rabbits irradiated with 150 r
were exsanguinated 24 hours after irradiation with the above method (mean granulocytes: 5000/mm³), and 0.10–10 ml. of the pooled plasma of these animals were injected intravenously into six rabbits (table 3).

The characteristic significant initial granulocytopenia usually obtained when administering granulocytopenic plasma did not, in fact, develop in this case. The resulting curve resembled that obtained with the normal plasma; however, 2 hours after the injection, significant granulocytosis could be demonstrated (p < 0.02).

The lymphocytopenic effect of this IP was greater than that of the control plasma but was smaller than the effect of the plasma taken immediately following irradiation. The thrombocytotic effect of this plasma was characteristic (fig. 2). Three hours after the injection of IP, the thrombocytes had increased to double the starting values and were still at that level after 24 hours.

In evaluating the results of the experiments carried out, it was apparent that the reaction or irradiation and the administration of IP was a two-phase one—that is, initial granulocytopenia followed by granulocytosis. According to the literature, similar reactions might be produced by the intravenous administration of colloids. Thus a qualitatively fully resembling, just quantitatively differing reaction was observed after administration of a 2 per cent starch solution. However, when a more dilute solution was administered, the reaction approached also quantitatively that following irradiation or the injection of IP (fig. 3).
Table 2.—Effect of Plasma from Rabbits Irradiated with 150 or 600 r, Exsanguinated 7 Days after Irradiation, on the Number of Granulocytes, Mononuclear Elements and Thrombocytes in the Recipient

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5'</th>
<th>15'</th>
<th>60'</th>
<th>120'</th>
<th>180'</th>
<th>240'</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRANULOCYTE</td>
<td>150+</td>
<td>1.71 ± 0.28</td>
<td>1.64 ± 0.21</td>
<td>2.00 ± 0.60</td>
<td>4.75 ± 1.26</td>
<td>5.44 ± 1.16</td>
<td>5.42 ± 1.16</td>
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<td></td>
<td>600+</td>
<td>2.21 ± 1.04</td>
<td>1.92 ± 0.95</td>
<td>1.92 ± 1.35</td>
<td>2.83 ± 1.68</td>
<td>5.32 ± 3.42</td>
<td>5.56 ± 3.73</td>
</tr>
<tr>
<td>MONONUCLEAR ELEMENT</td>
<td>150+</td>
<td>5.18 ± 2.27</td>
<td>5.75 ± 2.00</td>
<td>6.01 ± 3.14</td>
<td>5.96 ± 2.56</td>
<td>5.01 ± 1.37</td>
<td>5.01 ± 1.72</td>
</tr>
<tr>
<td></td>
<td>600+</td>
<td>7.05 ± 2.94</td>
<td>6.04 ± 2.16</td>
<td>5.56 ± 2.04</td>
<td>4.87 ± 2.24</td>
<td>3.70 ± 1.75</td>
<td>3.46 ± 1.85</td>
</tr>
<tr>
<td>THROMBOCYTE</td>
<td>150+</td>
<td>413 ± 3.31</td>
<td>403 ± 7.97</td>
<td>326 ± 109</td>
<td>341 ± 107</td>
<td>318 ± 56</td>
<td>364 ± 58</td>
</tr>
<tr>
<td></td>
<td>600+</td>
<td>458 ± 7.94</td>
<td>457 ± 7.86</td>
<td>348 ± 87</td>
<td>310 ± 87</td>
<td>326 ± 85</td>
<td>407 ± 165</td>
</tr>
</tbody>
</table>

+ Mean of 5 Animals
++ Mean of 8 Animals

This striking resemblance could be demonstrated by the change in value of both granulocytes and lymphocytes when studied in the first 2 hours after the administration of a 0.1 per cent starch solution or of IP obtained from animals irradiated with 600 r (fig. 4).

DISCUSSION

The existence of radiotoxins has been the subject of controversy since the beginning of the century. The so-called leukotoxin has been debated fully. Several authors have attributed the leukopenic effect of the IP (plasma obtained from irradiated animals) to this toxin, while others noted no effect when administering IP to normal animals or in transfused animals when one of the partners had been irradiated.11

During the course of the experiments discussed above, IP obtained in the granulocytopenic phase always gave a characteristic reaction: prompt granulocytopenia persisting for a short time followed by prolonged granulocytosis. This reaction is similar to that following irradiation and can be easily reproduced, both quantitatively and qualitatively, by the intravenous administration of dilute starch solution (fig. 3). The authors are of the opinion that their hypothesis is sufficiently supported by the similarity of these reactions:
the granulocytopenic effect of the IP is not due to some toxin but to a substance produced even under physiologic conditions, with different stimuli and regulating the level of leukocytes.

Several authors did not succeed in inducing leukopenia when injecting IP. In all probability the plasma used was obtained either from animals in the leukocytotic phase or, if leukopenic, the quantity must have been insufficient. Some workers, as Lawrence et al., must have obtained their negative results because of the low dosage applied (20-40 r). Capps and Smith succeeded in demonstrating that IP in vitro inhibits phagocytosis and the motility of leukocytes. However, even this result does not prove the existence of the leukotoxin, since, as demonstrated by Kertai et al., the leukopenic serum induced by the administration of starch solution has the same effect.

Since the production of the leukopenic substance is induced by the intravenous administration of colloids (such as starch, India ink, PVC), it might be possible that it is not the effective agent itself which is directly released as a result of irradiation. Alternatively, other delicately dispersed particles may become aggregated and as colloid induce the formation of the effective agent. It is well-known that irradiation is frequently followed by lipemia. The possibility arises, therefore, that the colloid inducing the early post-irradiation leukopenic effect discussed in the foregoing might be some kind of lipid.

The working hypothesis on which these experiments are based accounts sufficiently for the granulocytopenia developing after irradiation as well as the granulocytosis that follows: the very same stimulus provoking the initial granulocytopenia induces granulocytosis in the second phase of the reaction. An analogous two-phase reaction is observed after the intravenous administration of colloids: granulocytopenia followed by prolonged granulocytosis. Through the effect of hormones, granulocytes are removed from the circulation by their adhesion to the lung capillaries. The output of granulocytes from the bone marrow is increased equally on hormonal effect, provided

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Table 3.—Effect of Plasma from Granulocytotic Rabbits Irradiated with 150 r on the Number of Granulocytes, Mononuclear Elements and Thrombocytes in the Recipients

<table>
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<th>BEFORE</th>
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<th>15'</th>
<th>30'</th>
<th>60'</th>
<th>120'</th>
<th>180'</th>
<th>240'</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GRANULOCYTE</strong> (10^9)</td>
<td>2.82 ± 0.86</td>
<td>3.0 ± 1.08</td>
<td>2.75 ± 1.08</td>
<td>5.32 ± 1.08</td>
<td>5.83 ± 1.08</td>
<td>3.85 ± 1.08</td>
<td>3.7 ± 1.08</td>
<td>(P &lt; 0.02)</td>
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<tr>
<td><strong>MONONUCLEAR ELEMENT</strong> (10^9)</td>
<td>5.18 ± 1.05</td>
<td>5.0 ± 1.05</td>
<td>5.07 ± 1.05</td>
<td>3.6 ± 1.05</td>
<td>3.3 ± 1.05</td>
<td>3.6 ± 1.05</td>
<td>3.3 ± 1.05</td>
<td>(P &lt; 0.01)</td>
<td></td>
</tr>
<tr>
<td><strong>THROMBOCYTE</strong> (10^9)</td>
<td>450 ± 194</td>
<td>410 ± 213</td>
<td>406 ± 213</td>
<td>648 ± 213</td>
<td>712 ± 213</td>
<td>930 ± 213</td>
<td>826 ± 213</td>
<td>(P &lt; 0.01)</td>
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</tbody>
</table>

Data refer to the mean of six animals; exsanguination 24 hours after irradiation.
Fig. 3.—Effect of irradiation with 600 r (○—○), starch solution of 0.05 per cent (●—●), and of plasma from rabbits irradiated with 600 r (○—○), on the absolute number of granulocytes in the recipients (mean of 16 animals).

Fig. 4.—Effect of 10 ml. 0.1 per cent starch solution (○—○), of control plasma (○—○), and of plasma from rabbits exsanguinated immediately after irradiation with 600 r (X—X), on the number of thrombocytes in the recipients.

There are mature cells ready. In rabbits, after high doses of radiation and the development of radiation injury to the bone marrow, the first phase of the reaction takes place—that is, the temporary increase of granulocytopenia on the injection of starch solution. However, the second phase of the reaction, granulocytosis, does not develop (unpublished data).

The agents inducing granulocytopenia and, afterward, granulocytosis are
produced either with the same stimulus but at different rates (the granulocytopenic agent at first) or it is the granulocytopenic agent itself that induces the release of the agent evoking granulocytosis.

When taking frequent blood samples from irradiated animals during the first 24 hours, a significant periodic fluctuation might be explained by assuming a mutual inductive ability existing between the respective agents. However, it is possible that the increase or decrease of the granulocyte level itself represents the stimulus inducing the formation of the granulocytopenic or granulocytotic substance. The experiments carried out by Gordon et al. seem to support this latter hypothesis: the serum of leukocytapheresed rats induces leukocytosis in normal animals.

It might be possible that the substance inducing granulocytosis exerts a direct effect on the function of the bone marrow sinuses. This hypothesis is confirmed by the findings of Stodtmeister et al. They demonstrated that irradiation intensifies the physiologic, periodic dilatation of bone marrow sinuses, each dilatation being followed by a peripheral granulocytosis.

The IP affected not only the level of circulating granulocytes but also lymphocytes and platelets. The hormones contained in the IP (should different ones exist) seem to have the common feature of being induced by the administration of macromolecules or by irradiation.

Several authors have reported the existence of agents controlling the platelet level. The changes occurring in the thrombocyte count of experimental animals, either after the intravenous administration of India ink and starch solution or following UV-irradiation, are generally known and the agent regulating the platelet level is demonstrable in the plasma. The effectiveness of the IP in the dose range commonly used is dose-independent. IP obtained immediately after irradiation with 150 or 600 r was equally effective. On the other hand, the effect of IP obtained after a dose of 50 r was uncertain. Occasionally, the response shown by the recipient proved to be identical with that evoked by the control plasma; in other cases, an effect characteristic of IP, though less marked, could be observed (unpublished data).

**SUMMARY**

1. In rabbits irradiated with 150 to 600 r, granulocytosis is preceded by a prompt significant granulocytopenia developing 5–15 minutes after irradiation but persisting for a short time.

2. The plasma taken at the minimum of the initial granulocytopenia produced a similar two-phase reaction when injected into normal animals: a promptly developing significant granulocytopenia persisting for a short period followed by prolonged granulocytosis. Prolonged thrombocytopenia might be induced by the very same plasma.

3. The above-mentioned reactions may be reproduced satisfactorily with the administration of dilute starch solutions.

4. On the basis of the results obtained, it seems likely that the agent demonstrable in the plasma after irradiation, and influencing the level of circulating granulocytes and thrombocytes, is not a toxin (leukotoxin) but a substance that may be formed following physiologic stimuli as well.
SUMMARIO IN INTERLINGUA

1. In conilios irradiate con 150 a 600 r, granulocytosis es precedite per un prompte granulocytopenia de grado significative que se disveloppa 5 a 15 minutas post le irradiation, sed que persiste solmente durante un curte intervallo de tempore.

2. Specimens de plasma obtenite al nadir del granulocytopenia initial produceva un simile reaction biphasic quando illo esseva injicite in animales normal, i.e., il se disveloppava promptemente un grado significative de granulocytosis. Un prolongate thrombocytopenia poterea esser inducite per le mesmisse plasma.

3. Le supra-mentionate reactiones pote esser reproducite satisfacentemente per le administration de diluite solutiones de amylo.

4. A base del resultatos obtenite, il para probabile que le agente demonstrabile in le plasma pcst irradiation como e capace a influentiar le nivello de granulocytes e thrombocytes in le circulation non es un toxina (leucotoxina) sed un substantia que etiam pote esser formate post stimulation physiologic.

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Julia Gidáli, M.D., Research Fellow, Department of Pathophysiology, "Frederic Joliot-Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary.

Imre Fehér, M.D., Head, Department of Pathophysiology, "Frederic Joliot-Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary.
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