Effects of Endotoxin and Nitrogen Mustard on Leukocyte Kinetics

By John C. Herion, Richard I. Walker, William B. Herring and Jeffress G. Palmer

BACTERIAL ENDOTOXINS have been shown to affect granulocytes in a variety of ways. When injected intravenously, these substances produce a decrease in circulating lymphocytes and granulocytes, followed by leukocytosis due exclusively to an increase in granulocytes. Large doses of endotoxin, however, may delay the onset of this leukocytosis. Granulocytopenia has been considered to result from increased margination of circulating cells to the endothelium of capillaries. The leukocytosis has been thought to be caused by movement of granulocytes from marrow into the circulation and may not occur when the marrow has been damaged by disease or by cytotoxic drugs. The use of endotoxin clinically to gauge marrow granulocyte reserves rests on this evidence.

Mitotic activity in marrow has been reported to be increased after endotoxin injection. It is not clear, however, whether this increase is real or only apparent due to loss of mature, nondividing cells into the circulation. There is no evidence yet that bacterial endotoxin, by a direct stimulation, increases mitosis of marrow cells.

Since endotoxin is potentially useful in studies of leukocyte kinetics, this investigation was carried out to define better its actions for that purpose. A model for this investigation was suggested from earlier studies in rabbits combining the labeling of leukocyte DNA with radiophosphorous (P32) and the administration of large doses of nitrogen mustard (HN2); the HN2 produced no significant effect on the postmitotic granulocytes. In this system the effects of endotoxin on marrow granulocyte stores can be studied during arrest of cell production by HN2. The results of these studies confirm prior estimates of the rabbit’s marrow granulocyte reserve and demonstrate that, within limits, endotoxin causes these cells to be released into the circulation independent of any effect on mitosis. Further, an increase in marrow cellularity accompanying induction of tolerance by multiple injections of endotoxin occurs in face of a decrease in the postmitotic granulocyte pool, indicating an increase in the mitotic pool.

MATERIALS AND METHODS

New Zealand white rabbits weighing 2–3 Kg. were used. All injections were into a marginal ear vein. E. coli lipopolysaccharide 027:B8, (Difco Laboratories, Detroit) was
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Fig. 1.—Changes in circulating granulocytes following the administration of HN₂ 2.5 mg./Kg. I.V. Each point represents the mean determined from 11–50 animals. The shaded area represents 2 S.D. about the mean granulocyte count of 70 normal rabbits.

dissolved in sterile, pyrogen-free, isotonic saline so as to give the desired dose per Kg. in a volume of 1.0 ml.; the dose varied from 2.5 µg. to 60 µg. per Kg. Tolerance was produced by giving 6 daily injections of 10 µg. endotoxin per Kg.

Nitrogen mustard, (Methyl-bis-(beta-chlorethyl)-amine hydrochloride, Mustargen®, Merck, Sharp & Dohme, Philadelphia) was dissolved in sterile, pyrogen-free, isotonic saline to a concentration of 1.0 mg. per ml. and promptly injected intravenously in a dose of 2.5 mg. per Kg. The methods for counting leukocytes, preparing smears for differential cell counts and for preparing both smears and sections of bone marrow have been described.3,25

RESULTS

Effects of HN₂ on Circulating Granulocytes

Figure 1 shows the changes in the level of circulating granulocytes in normal rabbits following a single injection of 2.5 mg. HN₂ per Kg. By 8 hours, granulocytosis was present and was maintained for about 24 hours. The granulocyte count then returned to about the control level and remained within the normal range until 52 hours after the injection of HN₂. At that time a rapid exponential fall in the concentration of granulocytes began, followed by maximum granulocytopenia at about 90 hours; thereafter recovery from granulocytopenia occurred. By 8 or 9 days the concentration of circulating
Endotoxin Studies in HN₂-Treated Animals

Twelve hours after the administration of HN₂, 3 successive injections of 10 μg of endotoxin per Kg. were given at 6-hour intervals to each of 6 animals; the changes produced in circulating granulocytes are shown in figure 2. Within 1 hour each of the 3 injections produced a fall in the concentration of granulocytes. No secondary fall in the granulocyte count was observed in these animals during recovery as reported by others to occur during recovery from granulocytopenia produced by radiation or benzene injection. Twenty-two days after the initial injection of HN₂, 11 animals were given a second injection, again 2.5 mg. per Kg. The changes in circulating granulocytes in these animals during the 4 days following this second injection of HN₂ were the same as observed following the first injection. Recovery from granulocytopenia after the second dose of HN₂ was not studied.

Endotoxin Studies in HN₂-Treated Animals

Fig. 2.—The changes in circulating granulocytes of 6 rabbits given 3 injections of endotoxin at intervals of 8 hours beginning 12 hours after the injection of 2.5 mg. HN₂/Kg. Nonendotoxin, HN₂-treated controls are depicted for comparison.
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Fig. 3.—Effect of 60 μg. endotoxin on the circulating granulocytes in 9 animals, given 12 hours after 2.5 mg. HN₂/Kg.

circulating granulocytes and was followed in 6 hours by granulocytosis. Although the degree of fall in concentration of circulating granulocytes following the administration of endotoxin was progressively less with succeeding injections, the concentration 1 hour after each injection was nearly one-fourth the preinjection level. Figure 3 shows the changes in circulating granulocytes produced by a single large dose of endotoxin, 60 μg. per Kg., when given 12 hours after HN₂. Granulocytopenia was marked by 1 hour and persisted for 6 hours; granulocytosis occurred by 8 hours, but it was not as striking as that seen following the second and third injections of the smaller dose of endotoxin (fig. 2). An exponential decrease in circulating granulocytes occurred eventually in both groups given endotoxin 12 hours after HN₂ (fig. 2, 3); the slope of the fall was the same as in control animals receiving only HN₂, but the onset of the fall, beginning at a higher concentration of circulating granulocytes, was earlier.

The onset of a rapid decrease in circulating granulocytes in HN₂-treated
Fig. 4.—Femoral bone marrow from rabbits. (A) Normal marrow.

Fig. 4.—(B) Marrow 52 hours after 2.5 mg. HN₂/Kg. I.V.
animals likely results from depletion of marrow granulocyte stores; serial histologic changes in the marrow (fig. 4) support this hypothesis. Maximum depletion of marrow cells was observed 52 hours after injecting HN2 at the time the concentration of circulating granulocytes began to fall sharply. At 90 hours, when granulocytopenia in the blood was maximal, substantial recovery of marrow cellularity was already evident.

The effect of endotoxin on the circulating granulocytes of HN2-treated animals at the time marrow stores are exhausted is shown in figure 5. Following a single dose of endotoxin at 51 hours, granulocytes disappeared more rapidly from the circulation than in controls resulting in maximal granulocytopenia about 24 hours earlier. No postendotoxin granulocytosis occurred. Recovery from granulocytopenia by these animals did not begin earlier than in the controls. The failure of these animals to recover from granulocytopenia within 6 hours or to develop granulocytosis after the injection of endotoxin is further evidence that body stores had been exhausted by 52 hours after the administration of HN2.

Exhaustion of Marrow Granulocytes by Endotoxin

Since in animals given endotoxin 12 hours after HN2 the onset of the rapid fall in concentration of circulating granulocytes appeared sooner than in controls, endotoxin was given to other animals promptly after HN2 to determine how quickly this rapid fall, correlating with depletion of marrow granulocytes, would begin.
Fig. 5.—Effect of endotoxin on the concentration of circulating granulocytes of 12 animals when given 51 hours after HN₂. The shaded area defines 2 S.D. of the mean granulocyte count in 70 normal rabbits.

Figure 6 and table 1 depict the findings in animals given either 1, 2 or 3 injections of 10 μg. of endotoxin per Kg, at intervals of 8 hours beginning 1 hour after the administration of HN₂. After a single injection of endotoxin, the rapid exponential fall in concentration of circulating granulocytes began about 24 to 28 hours earlier than in the control animals. Two or 3 injections at intervals of 8 hours resulted in this fall beginning even sooner. The changes after the third injection, however, were not significantly different from those produced by only 2 injections of endotoxin since the third dose nearly coincided with the onset of fall in concentration of circulating granulocytes produced by the prior 2 injections. In these 3 groups of animals granulocytopenia was not as profound as in controls and recovery began earlier; by 5 days after the injection of HN₂ granulocyte counts were virtually back to control values.

These studies indicate that granulocytosis produced by endotoxin results
Fig. 6.—Effect of 1, 2, and 3 injections of endotoxin on the concentration of circulating granulocytes when given beginning immediately after 2.5 mg. HN2/Kg. The interval between endotoxin injections is 8 hours. Each group contains 4–6 animals.

from movement of cells into the blood from stores. In normal animals granulocytosis occurs sooner after small doses of endotoxin than after large doses. An attempt was made, therefore, to more rapidly deplete granulocyte stores in HN2-treated animals by injecting multiple small doses of endotoxin, each 2.5 μg. per Kg., at intervals of 4 hours. Figure 7 shows these results. Four hours after the initial injection of endotoxin, leukopenia was still present. Granulocytosis then appeared in spite of additional injections of endotoxin so that by 12 hours the granulocyte counts in these animals were in the range...
Circulating Granulocytes Per cu. mm. ± SE.

After

HN2

Hours

Controls (25-40)

I (5)

Endotoxin Treated Groups*

II (6)

III (4)

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*Endotoxin 10 μg./Kg. I.V. at 8-hour intervals after baseline count. Group I, a single injection; Group II, 2 injections; Group III, 3 injections.
†Mean of all animals in Groups I, II, III.
 Mean of all animals in Groups II, III.

seen in controls given no endotoxin. But they never attained significantly higher levels unless it happened during the 8 hours after the last endotoxin injection when no counts were made. As in animals given 2 or 3 injections of 10 μg. of endotoxin per Kg., the onset of the rapid decrease in circulating granulocytes in these animals began about 26-28 hours earlier than in controls, and the slope of the curve representing this is similar to that of the controls. In these animals, as in those given 1-3 doses of 10 μg. of endotoxin per Kg., recovery from granulocytopenia after day 4 occurred more rapidly with normal granulocyte levels being reached 24 hours earlier than in the controls.

Even with multiple injections of endotoxin and with different doses it was impossible to produce the onset of the exponential fall in circulating granulocytes, reflecting depletion of marrow stores, before about 24 hours after injecting HN2. Since after multiple injections animals become refractory or tolerant to certain other effects of endotoxin, the role of tolerance in this phenomenon was examined by studies in tolerant animals. Twenty-four hours after the sixth daily injection of endotoxin, given to produce febrile tolerance, 2.5 mg. of HN2 per Kg. was given intravenously to each of the tolerant controls. In a similar group of tolerant animals 2 additional injections of endotoxin were given after the administration of HN2, the first immediately and the second 8 hours later. The dose of endotoxin was twice as large as that used to
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Fig. 7.—Effect of multiple injections of endotoxin, each 2.5 μg./Kg., on 12 animals when given at intervals of 4 hours beginning immediately after 2.5 mg. HN2/Kg. The shaded areas define 1 S.E. of the mean granulocyte count for both the control and the endotoxin-treated groups. The solid lines describe 2 S.D. about the mean granulocyte count of 70 normal rabbits.

produce febrile tolerance. The results, presented in figure 8, show that the rapid fall in concentration of circulating granulocytes began sooner in both groups of tolerant animals than in nontolerant ones, but that large doses of endotoxin given to tolerant animals after HN2 did not result in an even earlier fall. Subsequent studies, however, have shown that this dose of endotoxin (20 μg./Kg.) is insufficient to abolish febrile tolerance produced by 10 μg. endotoxin per Kg.28 Therefore, in a further effort to abolish tolerance, other groups of tolerant animals were given 2 ml. Thorotrast* per Kg. intravenously 6 hours after the last dose of endotoxin. Eighteen hours later 2.5 mg. HN2 per Kg. was given intravenously. After the administration of HN2, one group of Thorotrast-treated animals received 2 additional injections of endotoxin; the other group none. Febrile tolerance was demonstrated to have been abolished in the group given additional endotoxin. The fall in circulating granulocytes in both groups of Thorotrast-treated, tolerant animals did not begin significantly earlier than in tolerant animals given no Thorotrast. In all groups of tolerant animals the concentration of circulating granulocytes fell

*Testagar & Co., Inc., Detroit, Michigan.
sooner than in the nontolerant controls; tolerant animals also recovered more rapidly from HN₂-induced granulocytopenia.

In the tolerant animals, including those given Thorotrast and endotoxin after HN₂, the sharp fall in concentration of circulating granulocytes began about 42 hours after the administration of HN₂. The marrow of these animals was maximally hypocellular then (fig. 9), but it still contained more cells than the marrow of nontolerant controls when it was maximally hypocellular, 52 hours after HN₂.

**DISCUSSION**

Eight hours after receiving a large dose of HN₂, normal rabbits exhibit granulocytosis and lymphopenia. By 24 hours the granulocyte count returns
Fig. 9.—Femoral bone marrow from tolerant animals. (A) Marrow obtained 12 hours after the last of 6 daily injections of 10 μg. endotoxin/Kg. Note increased cellularity and diminished size of fat cells compared with normal marrow.

Fig. 9.—(B) Marrow of tolerant rabbits 42 hours after 2.5 mg. HN2/Kg. I.V. when concentration of circulating granulocytes begins to fall.
to the normal range where it remains on a plateau until about 50-52 hours. A rapid exponential fall in the concentration of circulating granulocytes then begins, resulting in severe granulocytopenia maximal at about 86-90 hours; recovery begins thereafter.

The granulocytosis, evident by 8 hours after injecting HN2 and persisting for about 24 hours, could result from accelerated release of cells from the marrow by HN2, longer intravascular survival of the circulating granulocytes, recirculation of granulocytes from extramedullary tissues, or redistribution of those already in the blood from marginal sites to active circulation. Previous studies in rabbits combining DNA-P32 labeling with HN2 injection indicate that HN2 does not bring about premature release of marrow cells or otherwise significantly decrease the number in the postmitotic reservoir. Although there is no definite evidence excluding longer intravascular survival of granulocytes after HN2 administration, this is believed to be an unlikely explanation for the granulocytosis, and studies with labeled leukocytes offer evidence against significant recirculation of granulocytes. It is more likely that the granulocytosis following the injection of HN2, like that following irradiation, results principally from redistribution of intravascular marginated leukocytes, perhaps as a consequence of epinephrine release; such a redistribution of blood granulocytes does occur in humans given epinephrine.

Since the normal rabbit has about a 48-hour supply of postmitotic granulocytes in the marrow, not altered significantly by the injection of HN2, the onset of the exponential decrease in circulating granulocytes at 50-52 hours must represent depletion of granulocyte stores; this is supported by the presence of a markedly hypocellular marrow at this time (fig. 4). The maintenance of normal levels of circulating granulocytes for at least 2 days following administration of HN2 further supports the conclusion from in vitro studies and in vivo studies that HN2 does not kill nonproliferating granulocytes. A second dose of HN2, given 3 weeks after the initial injection, produced alterations in circulating granulocytes similar to those following the first injection and indicates that granulocyte stores have by this time been repleted.

The rate of decrease in concentration of granulocytes after 52 hours is believed to reflect the intravascular survival time of granulocytes; the circulating granulocyte half-time (T½) calculated from the slope of this curve is approximately the same as that found in normal rabbits with DFP labeling, suggesting that the single dose of HN2 has not altered the T½ of these cells.

The absence of granulocytosis when endotoxin is given 51 hours after HN2, whereas it occurs regularly if endotoxin is injected up to 12 hours after HN2, indicates that granulocytosis following endotoxin is produced by movement of cells from the marrow into the circulation. The persistence of granulocytopenia without granulocytosis when endotoxin is given 51 hours after HN2 suggests not only that the marrow reservoir is depleted but that in these animals significant recirculation of granulocytes from extramedullary sites does not occur.

The granulocytopenia produced immediately by the intravenous injection of endotoxin is maximal within 1 hour. At the time marrow granulocyte reserves are exhausted in animals given HN2, the more rapid fall in the con-
centration of circulating granulocytes after an injection of endotoxin (fig. 5) suggests that the granulocytopenia produced by endotoxin results from accelerated removal of cells from the circulation either to intravascular marginal sites or into tissues as recently described by Mulholland and Cluff. This prompt effect of endotoxin on circulating granulocytes does not persist, however, for in those animals whose marrow stores are exhausted after lapse of 8 hours or more from the time of endotoxin injection (fig. 6, 7), the rate of disappearance of circulating granulocytes is the same as in controls given no endotoxin.

Animals given multiple injections of endotoxin after HN₂ did not develop granulocytosis more striking than controls (fig. 7), but depletion of their marrow granulocyte stores occurred sooner. Also more rapid depletion of granulocyte stores in the face of a sustained granulocytopenia was noted in the animals given 60 µg of endotoxin per Kg. (fig. 4). A considerable number of cells, therefore, must leave the marrow without entering the circulation or, if they enter the circulation, are removed from the blood at a rate much faster than normal. Yoffey's findings in guinea pigs given endotoxin lead to similar conclusions; he could not quantitatively account for all granulocytes lost from the marrow by the calculated total number in the circulation. Thus endotoxin may result in increased destruction of granulocytes both in the marrow and in the circulation.

It is not known how endotoxin increases the movement of granulocytes out of marrow. Our studies have shown that radioactive chromium-labeled endotoxin is not present in circulating granulocytes and that it has been removed from the blood before changes in the concentration of these circulating cells occur. Labeled endotoxin, however, is removed from the circulation by normal rabbit bone marrow but this function of marrow is not diminished after depletion of granulocytes with HN₂.

In studies using perfused, isolated rat femurs, Dornfest et al. have demonstrated that normal numbers of leukocytes in the perfusate suppressed the release of marrow granulocytes. It is therefore possible that the stimulus for the release of marrow cells is the leukopenia present within an hour after endotoxin injection. Gordon and Handler have recently described a factor, present in the plasma of rats 3–4 hours after injecting typhoid vaccine, that accelerates the release of granulocytes both in the isolated femur preparation and in the intact animal. King has demonstrated that material with the properties of endogenous pyrogen, extracted from rabbit leukocytes or obtained from serum 2 hours after injecting endotoxin, produces a prompt granulocytosis when given intravenously to rabbits. These findings suggest that a substance liberated from the circulating granulocytes themselves as a consequence of endotoxin injection may be in part responsible for the movement of cells out of the marrow.

Regardless of the mechanism, the failure to decrease the granulocyte reservoir by more than about 50 per cent of its original size, even with multiple injections and different doses of endotoxin, suggests either that the animals have become refractory to this effect of endotoxin or that release of...
normal cells from marrow may be strongly conditioned by some property of
the cell itself, such as the degree of maturity. In those tolerant animals given
large doses of endotoxin after HN₂, even when febrile tolerance had been
abolished by Thorotrast, depletion of the marrow granulocyte reservoir did
not occur significantly earlier than in the tolerant controls and suggests that
the factor limiting movement of cells from the marrow by endotoxin is not
that responsible for febrile tolerance. Furthermore, Harris et al.²² and Yoffey
and his co-workers²³ have demonstrated in guinea pigs that endotoxin injection
depletes the marrow principally of the more mature granulocytes. These ob-
servations and our results in the tolerant animals suggest that cells are released
from the marrow by endotoxin only after they have reached a certain degree
of maturity.

Recovery from the granulocytopenia induced by HN₂ seems related to the
time granulocyte stores are depleted rather than to the time of maximum
leukopenia in the blood, as suggested by Patt²⁹ from studies in irradiated
animals. In those animals given endotoxin 51 hours after HN₂, even though
maximum granulocytopenia occurred about 24 hours earlier than in the
controls, recovery began at the same time. Further, marrow recovery was
already well under way by the time granulocytopenia in the blood was
maximal.

There is no good evidence that endotoxin stimulates mitosis directly. Yoffey
and his co-workers²³ found that myeloblasts were not increased in the guinea
pig marrow until about 48 hours after the administration of typhoid vaccine,
long after the segmented and band forms had disappeared. Thus the earlier
onset of recovery from leukopenia by those animals given endotoxin after HN₂
likely results from the more rapid depletion of granulocyte stores by endotoxin;
the granulocyte reservoir was depleted about a day earlier than controls and
recovery began about a day sooner.

The fall in concentration of circulating granulocytes earlier in tolerant than
in nontolerant animals indicates that despite an increased marrow cellularity,
tolerant animals may have a smaller than normal marrow pool of postmitotic
granulocytes. Furthermore, the increased marrow cellularity in tolerant animals
plus the probability that the more mature marrow cells were removed each
day by the endotoxin²³ given to produce tolerance suggests that tolerant
animals have an increased pool of cells still capable of mitosis. This is further
supported by the finding that myeloblasts in the marrow are doubled by about
48 hours after a single injection of endotoxin and do not return to normal
levels before at least 72 hours.²³

After repeated injections of endotoxin a similar increased cellularity in the
marrow has been found in mice by Smith et al.³⁸ and in rats by Zweifach and
co-workers.³⁹ Both groups reported such animals to be more resistant to the
lethal effects of x-ray and to recover sooner than controls from the irradiation-
induced granulocytopenia. Our observation that tolerant rabbits recover from
granulocytopenia more rapidly than nontolertant controls after receiving large
doses of HN₂ indicates the exposure to endotoxin may afford some measure of
resistance to antimitotic drugs as well.
Summary and Conclusions

In rabbits given a single large dose of HN₂ circulating granulocytes are maintained at a normal concentration until 50-52 hours; thereafter the onset of a rapid fall in concentration coincides with maximum marrow hypocellularity. Recovery from granulocytopenia, however, does not begin until after 90 hours when considerable recovery of marrow cellularity is evident.

Bacterial endotoxin in differing doses given at various times up to 24 hours after HN₂ produces the same changes in circulating granulocytes as in normal animals. The rapid decline in circulating granulocytes, heralding exhaustion of the pool of postmitotic granulocytes, occurs earlier in HN₂-treated animals; they also recover sooner than controls from HN₂-induced granulocytopenia. Endotoxin given at 51 hours after HN₂ when the postmitotic pool is exhausted, increases the rate of fall in the concentration of circulating granulocytes producing an earlier appearance of maximum granulocytopenia, but recovery by these animals from HN₂-induced granulocytopenia does not occur sooner than in controls. Thus the time of recovery from HN₂-induced granulocytopenia appears to be related to the time of depletion of marrow stores of postmitotic cells.

Rabbits made tolerant to endotoxin and given HN₂ show an earlier onset of the rapid fall in circulating granulocytes and an earlier recovery from granulocytopenia. Maximum marrow hypocellularity appears sooner after HN₂ in tolerant animals, but marrow cellularity is always greater than in nontolerant rabbits. The increased cellularity of the marrow of tolerant animals may represent an increase in the size of the mitotic compartment of cells since the postmitotic compartment seems smaller than in normal animals.

The granulocytopenia produced by endotoxin results from an increased removal of granulocytes from the circulation and significant numbers of these cells do not appear to recirculate. Granulocytosis following the injection of endotoxin results from movement of cells out of the marrow and occurs only if there is a store of postmitotic granulocytes. Release of cells from the marrow following this stimulus, however, appears to be related to cell maturity; only the more mature ones enter the circulation.

Movement of mature cells out of the marrow, depleting the reservoir of these elements, may provide the stimulus for the increased cell production that appears in normal animals given endotoxin.

Summario in Interlingua

In conilios tractate con un sol massive dose de HN₂, le granulocytes del circulation se mantene in un concentration normal durante 50 a 52 horas. Postea, le declaration de un rapide declino del concentration coincide con un maximal hypocellularitate del medulla. Le restablimento ab le granulocytopenia non comencia in minus que 90 horas, i.e., a un tempore quando un considerabile restablimento del cellularitate medullari es evident.

Endotoxina bacterial, administrate in varie doses a varie intervalllos de usque a 24 horas post HN₂ produce le mesme alterationes in le circulante granulocytos como in normal animales (non pre-tractate con HN₂). Le rapide declino
in le granulocytos circulante, annunciante le exhaustion del reservas de granulocytos postmitotic, occurre plus tosto in animales del gruppo tractate con HN2 si illos ha etiam recipite un endotoxina bacterial. Illos etiam se restabl plus tosto que le animales de controlo ab le granulocytopenia inducite per HN2. Endotoxina administrate 51 horas post HN2 (a un tempore quando le reservas de granulocytos postmitotic es exaurite) acceleria le declino in le concentration de circulante granulocytos. Isto causa un plus precoce apparition del maximo granulocytopenic, sed le restablimento de iste animales ab le granulocytopenia inducite per HN2 non occurre plus tosto que in le animales de controlo. Assi le tempore del restablimento ab granulocytopenia inducite per HN2 pare esser relationate al tempore del depletion de cellulas postmitotic in le reservas medullari.

Conilios rendite tolerante pro endotoxina e tractate con HN2 monstra un plus rapide declino in le granulocytos circulante e un plus prompte restablimento ab le granulocytopenia. Le maximo del hypocellularitate medullari se manifesta plus promptemente post HN2 in animales tolerante, sed le cellularitate medullari es semper plus grande que in non-tolerante conilios. Le augmentate cellularitate del medulla de tolerante animales representa forsan un augmento del magnitude del compartimento de cellulas mitotic, proque le compartimento postmitotic postmitotic pare esser plus micre que in animales normal.

Le granulocytopenia producite per endotoxina resulta ab un accelerate elimination de granulocytos ab le circulation, e il pare que significative numeros de iste cellulas non es reponite in circulation. Granulocytosis post le injection de endotoxina resulta ab le emigration de cellula ex le medulla e occurre solmente si il existe un reserva de granulocytos postmitotic. Tamen, le liberation de cellulas ab le medulla post iste stimulo pare esser relationate con le maturitate del cellulas. Solmente le cellulas plus matur entra in le circulation.

Emigration de cellulas matur ex le medulla, con le resultante depletion del reservas de iste elementos, provide possibilmente le stimulo pro le augmentate production de cellulas que se manifesta in animales normal post le administration de endotoxina.

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John C. Herion, M.D., Assistant Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, N. C.

Richard I. Walker, M.D., Assistant Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, N. C.

William B. Herring, M.D., Assistant Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, N. C.

Jeffress G. Palmer, M.D., Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, N. C.