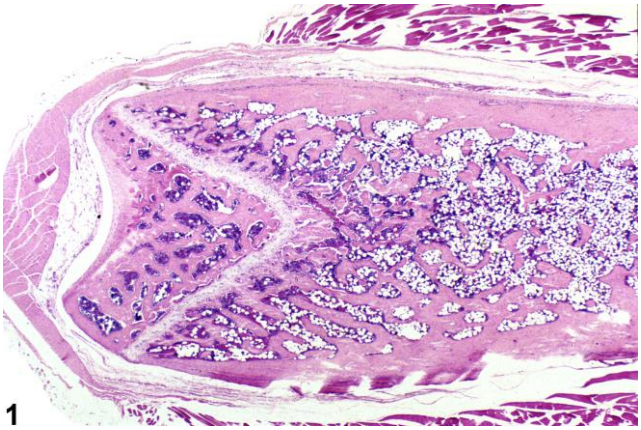
Bone Marrow – Hypercellularity, [Erythroid, Granulocytic, Megakaryocytic]



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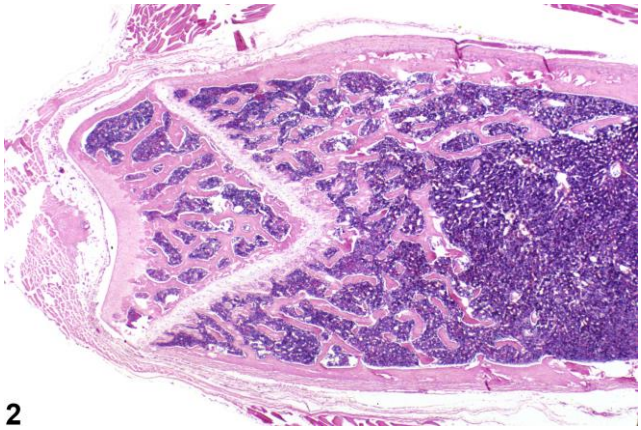

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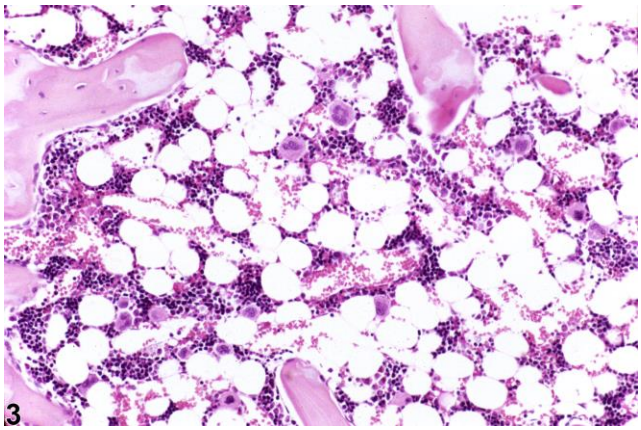

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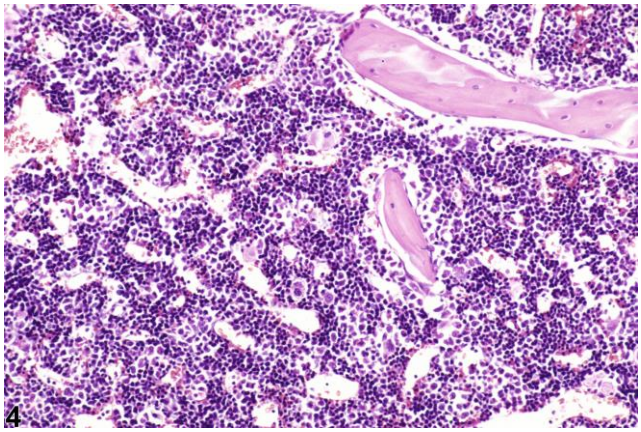

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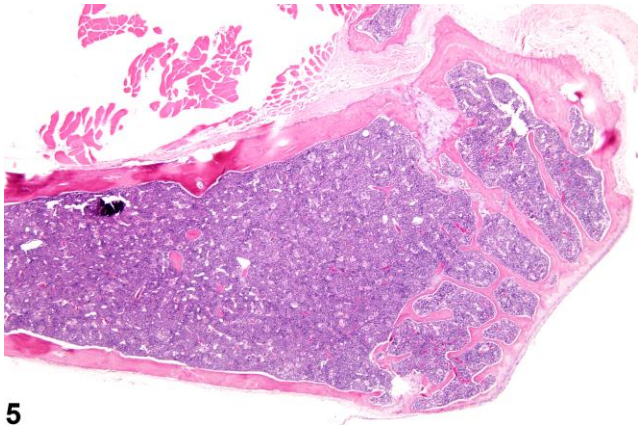

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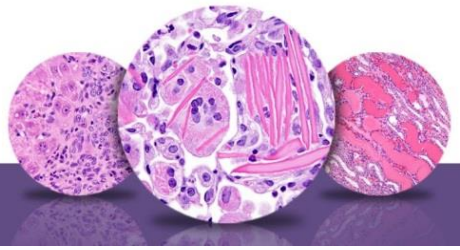

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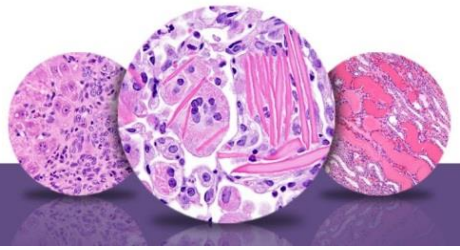
Figure Legend: **Figure 1** Bone marrow in a control female F344 rat from a subchronic study. **Figure 2** Bone marrow in a treated female F344/N rat from a subchronic study. Compared with the concurrent control (Figure 1), there is erythroid hypercellularity in response to a treatment-related anemia. **Figure 3** Bone marrow in a control female F344/N rat from a subchronic study (higher magnification of Figure 1). **Figure 4** Bone marrow in a treated female F344/N rat from a subchronic study (higher magnification of Figure 2). Compared with the concurrent control (Figure 3), there is erythroid hypercellularity in response to a treatment-related anemia. **Figure 5** Hypercellular bone marrow in a male B6C3F1 mouse from a chronic study.

Comment: Bone marrow cellularity refers to the amount or percentage of hematopoietic cells relative to marrow fat. It has been shown that normal bone marrow (sternum and femur) of rats 2 months of age contains 80% or more hematopoietic cells, with the majority of the remaining cells composed of adipocytes; normal bone marrow of rats 4–16 months of age contains approximately 60–75% hematopoietic cells. It is known that as rodents and other species age, normal bone marrow cellularity decreases and is accompanied by a relative increase in adipocytes. In addition, rats 2 years of age show greater interanimal variability than do 4- to 16-month-old rats. In general, mice have higher overall bone marrow cellularity than do rats of the same age.

Changes in bone marrow cellularity may involve all or individual cell lines. Changes in the erythroid or myeloid cell lines may shift the M:E ratio relative to controls. Normal M:E ratios of rats and mice are reported between 0.80 and 2.79, with an average of 1.5, and are dependent on strain and age, stressing the importance of comparing treated animals with concurrent controls. Histologic sections allow for a rough estimate of the M:E ratio to aid in the evaluation of cellularity, while cytologic preparations are needed for a more precise determination of the M:E ratio and evaluation of subtle changes in synchrony of maturation.

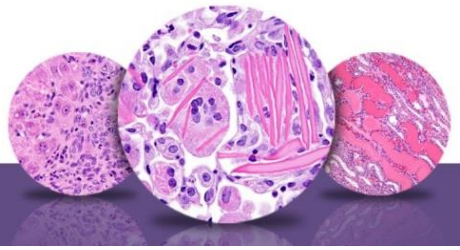
Hypercellularity of the bone marrow is recorded in treated animals when there is an increase in hematopoietic cells relative to adipocytes compared with concurrent controls (Figures 2, 4, and 5). Hypercellularity may occur as a nonspecific or direct (e.g., with cytokine administration)



response to compound administration but more commonly is due to a regenerative response as a consequence of decreases in peripheral blood cells, recovery from a xenobiotic-induced bone marrow injury, or inflammation. For example, hypercellularity may be secondary to sepsis or a result of blood loss, hemolytic anemia or platelet consumption/destruction. Stimulation to produce more of one cell line can cause increased production of other cell lines, causing an overall increase in bone marrow cellularity. With marked hypercellularity, hematopoietic cells may fill the entire marrow space, even extending through the nutrient foramina.

Recommendation: To evaluate bone marrow cellularity, that is, the percentage of hematopoietic cells relative to marrow fat, bone marrow from treated animals must be compared with same-site concurrent control bone marrow. Changes in cellularity should be recorded and graded, and the grading scheme should be described in the narrative. Grading is based on the degree of change compared with concurrent controls as defined by the study pathologist. While changes in cellularity may be due to a change in a specific cell line, it can be difficult to appreciate this with histologic evaluation alone. If changes in specific cell lines are not explicitly clear, it is more appropriate to record the changes as just hypercellularity. It is not appropriate to diagnose the concurrent decrease in adipocytes because it is considered secondary to the increase in hematopoietic cells.

Clinical, interpretative, or diagnostic terms (e.g., “hyperplasia”) should not be used when recording changes in bone marrow cellularity but rather the descriptive term “hypercellularity” as discussed herein. When changes in cellularity warrant further explanation or are treatment related, they should be described and interpreted in the pathology narrative, where interpretive terms or diagnoses, such as erythroid hyperplasia, can be used in context with other histologic findings, available hematologic data, in-life findings, and bone marrow cytologic (e.g., M:E ratio) or flow cytometric findings.



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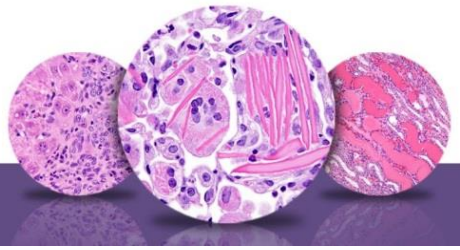

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