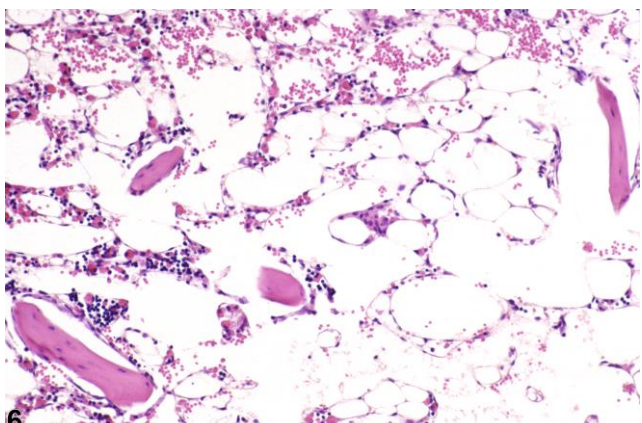
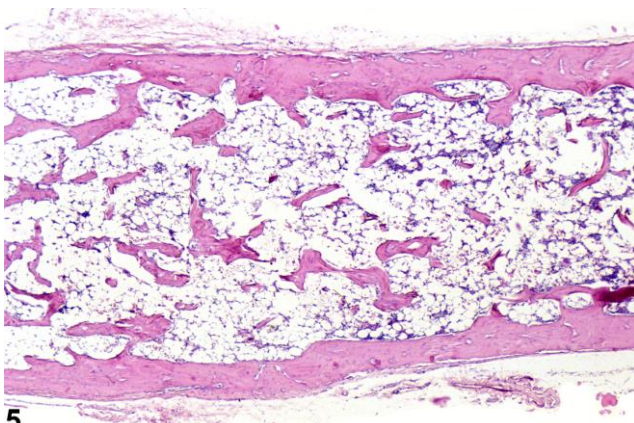
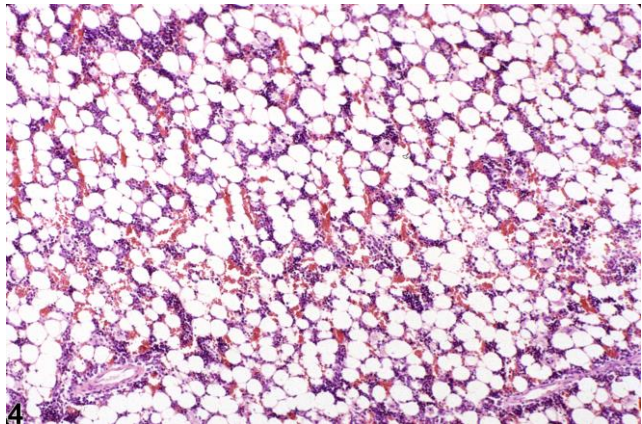
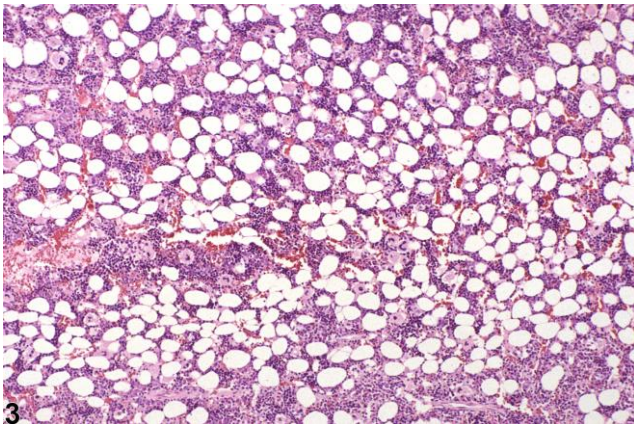
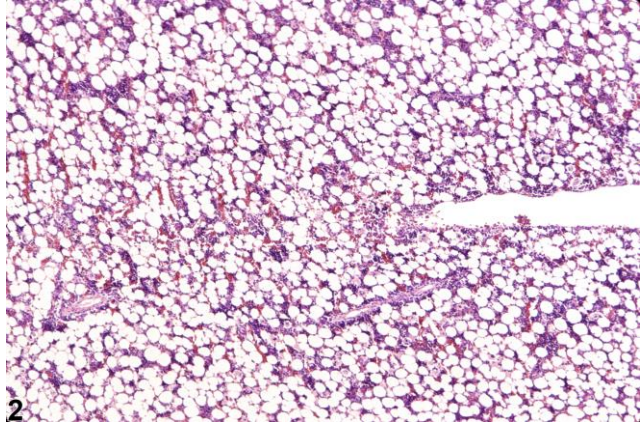
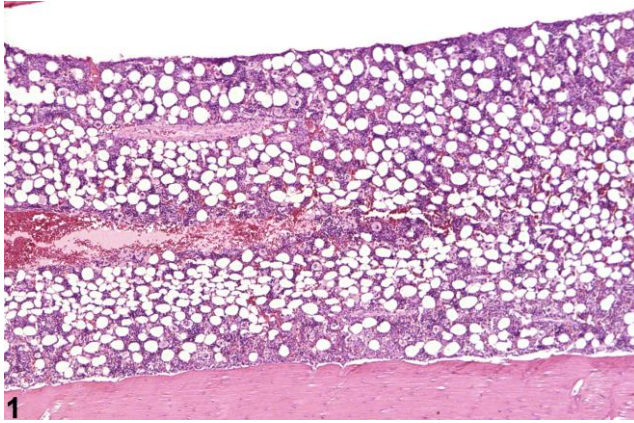


NTP Nonneoplastic Lesion Atlas

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





NTP Nonneoplastic Lesion Atlas

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Figure Legend: **Figure 1** Bone marrow in a control female F344/N rat from a subchronic study.

Figure 2 Bone marrow in a treated female F344/N rat from a subchronic study. Compared with concurrent control (Figure 1), there is mild hypocellularity. **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 concurrent control (Figure 3), there is mild bone marrow hypocellularity.

Figure 5 Severely hypocellular bone marrow from a B6C3F1 male mouse in a subchronic study. The marrow space is largely devoid of hematopoietic cells and consists primarily of adipose tissue and vascular sinuses due to treatment-induced aplastic anemia. **Figure 6** Severely hypocellular bone marrow from a B6C3F1 male mouse in a subchronic study (higher magnification of Figure 5). The marrow space is largely devoid of hematopoietic cells and consists primarily of adipose tissue and vascular sinuses due to treatment-induced aplastic anemia.

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



NTP Nonneoplastic Lesion Atlas

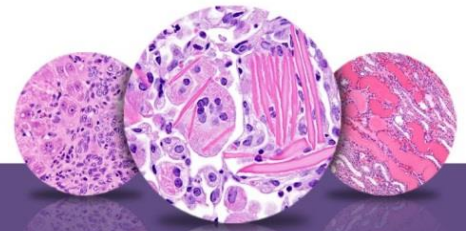
Bone Marrow – Hypocellularity, [Erythroid, Granulocytic, Megakaryocytic]

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.

Hypocellularity of the bone marrow is recorded in treated animals when there is a decrease in hematopoietic cells relative to adipocytes compared with concurrent controls (Figures 2 and 4–6). Hypocellularity may occur as a direct or indirect treatment-related effect, of which numerous examples exist but in general include xenobiotics that affect hemoglobin production, alter rates of hematopoiesis, disrupt porphyrin metabolism (e.g., lead), alter cytokine networks, or induce direct cellular injury (e.g., chemotherapeutics, certain antimicrobials), as well as such conditions as chronic inflammation or chronic renal failure (i.e., reduced renal erythropoietin production). In severe cases (e.g., aplasia), the marrow will appear devoid of hematopoietic cell lines and consist primarily of adipose tissue and vascular sinuses. Low numbers of scattered lymphocytes, macrophages, and plasma cells may also be observed, depending on the pathogenesis or mechanism of action of the xenobiotic or treatment (e.g., radiation).

Occasionally, relatively well-delineated focal areas of hypocellularity (previously known as “focal atrophy”) have been seen. These areas may contain variable numbers of adipocytes and/or a relative increase in reticular stromata. This finding has been described in young adult rats, with an apparent higher rate among females. These areas alone seemingly have no clinical significance. Focal areas of hypocellularity may be part of, or result in (if numerous areas exist), an overall decrease in bone marrow cellularity. Such observations should be included with, or diagnosed as, hypocellularity rather than recorded as a separate distinct finding of “focal” hypocellularity.

Diet restriction and severe inappetence are known to cause decreases in all hematopoietic cells with an apparent increase in marrow fat cells; the M:E ratio seems unaffected. Specifically, in one study, diet restriction sufficient to stop weight gain in young rats caused 50%, 40%, and 20% decreases in erythroid, myeloid, and megakaryocytic precursors, respectively.

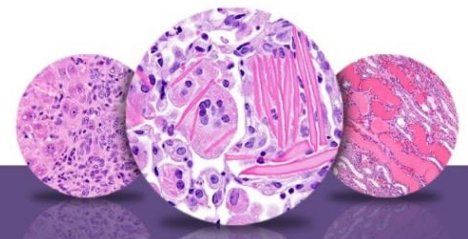


NTP Nonneoplastic Lesion Atlas

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

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 hypocellularity. It is not appropriate to diagnose the concurrent increase in adipocytes because it is considered secondary to the decrease in hematopoietic cells.

Clinical, interpretative, or diagnostic terms (e.g., “atrophy,” “hypoplasia”) should not be used when recording changes in bone marrow cellularity but rather the descriptive term “hypocellularity” 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 aplastic anemia, 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.



NTP Nonneoplastic Lesion Atlas

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

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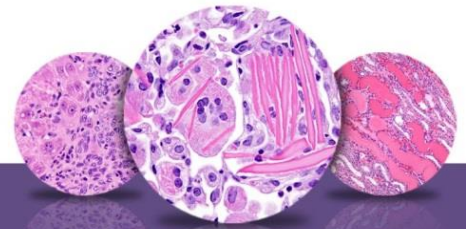
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