Brief Definitive Report

T Cells, but Not B cells, Are Required for Bowel Inflammation in Interleukin 2–deficient Mice

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Summary

Interleukin-2 (*IL-2*)–deficient ($IL\text{-}2^{-/-}$) mice develop anemia and colonic inflammatory bowel disease. To elucidate the mechanism of this disease, we have bred $IL\text{-}2^{-/-}$ mice to two strains of immunodeficient mice, *RAG-2*–deficient ($RAG\text{-}2^{-/-}$, lacking B and T cells) and *JH*-deficient mice ($JH^{-/-}$, lacking B cells). $IL\text{-}2^{-/-}$, $RAG\text{-}2^{-/-}$ double-mutant mice are disease free, while $IL\text{-}2^{-/-}$, $JH^{-/-}$ double-mutant mice succumb to bowel disease at the same rate as $IL\text{-}2^{-/-}$ littermates. $IL\text{-}2^{-/-}$, $JH^{-/-}$ mice do not, however, succumb to anemia. Thus, spontaneous intestinal inflammation in $IL\text{-}2^{-/-}$ mice requires mature T cells, not B cells, while anemia is dependent on B cells.

Transgenic mice bearing targeted deletions for *IL-2*, *IL-10*, *MHC class II*, or *TCR-β* genes develop intestinal inflammation (1–3). These findings have opened multiple avenues of investigation into the regulation of immune responses in the intestinal epithelium. The pathophysiological mechanisms of bowel inflammation in these diverse transgenic animals is unclear, although (*a*) a primary perturbation of the mucosal immune response seems to occur in all cases; and (*b*) the presence of luminal bacteria or their products influences the manifestation of disease. Disturbances in the balance between immunoregulatory lymphocyte subsets and/or cytokine imbalances have been postulated to be pathogenetic in these mice (4, 5).

The presence or expansion of particular lymphoid subsets provides some clues as to the effector cells responsible for these diseases. For example, $TCR\beta^{-/-}$ and $TCR\alpha^{-/-}$ mice develop bowel inflammation without α/βT cells, while $RAG\text{-}1^{-/-}$ animals, which lack both B and T cells, do not, suggesting that the loss of an immunoregulatory T cell subset combined with an intact B cell population may lead to B cell–mediated autoimmune disease (3, 5, 6). Bowel inflammation in *MHC class* $II^{-/-}$ mice, which selectively lack class II–restricted $CD4^+$ T cells, could also be caused by such a mechanism (3).

$IL\text{-}2^{-/-}$ mice initially contain normal numbers of B and T lymphocytes, and the lamina propria of inflamed colons in older mice contain elevated levels of $CD4^+$ and $CD8^+$ T cells, as well as $B220^+$ B cells, suggesting that both T and B cells are spontaneously activated in the colonic immune response (1, 6). In addition, anticolon antibodies are regularly detected in the serum, and these antibodies have been postulated to be involved in causing bowel disease (1, 5). Together, these observations suggest that T cells, B cells, and their autoantibody products may all be important for the development of bowel disease in $IL\text{-}2^{-/-}$ animals.

To determine the relative roles of T and B cells in $IL\text{-}2^{-/-}$ transgenic mice and to specifically evaluate their role in mediating bowel disease, we have bred $IL\text{-}2^{-/-}$ mice to two strains of immuodeficient mice: $JH^{-/-}$ mice, which bear a targeted deletion of Ig heavy chain J gene segments, and possess no mature B cells (7); and $RAG\text{-}2^{-/-}$ mice, which bear a targeted deletion of the *RAG-2* gene, cannot rearrange B or T cell antigen receptor genes, and thus possess no mature T or B cells (8). We report here the histological and clinical findings in these various single and double mutant transgenic mice.

Materials and Methods

Breeding and Housing of $IL\text{-}2^{-/-}$, $JH^{-/-}$, *and* $RAG\text{-}2^{-/-}$ *Mice.* All mice were housed and bred within one track in the specific pathogen–free barrier facility of the Animal Research Facility at Children's Hospital. Animals were monitored weekly for the development of loose bowel movements, wasting, or anemia. Clinically ill animals were monitored twice per week and killed when severely ill.

Colonic Histopathology. Colons from freshly killed animals were flushed with PBS to remove stool contents. Cross-sections were frozen directly in OCT compound (Miles Laboratories, Inc., Naperville, IL) using a cryostat (Bright Instruments, Huntingdon, UK). Frozen sections were cut on the cryostat and stained with hematoxylin and eosin.

Assessment of Anemia. Cardiac puncture was performed immedi-

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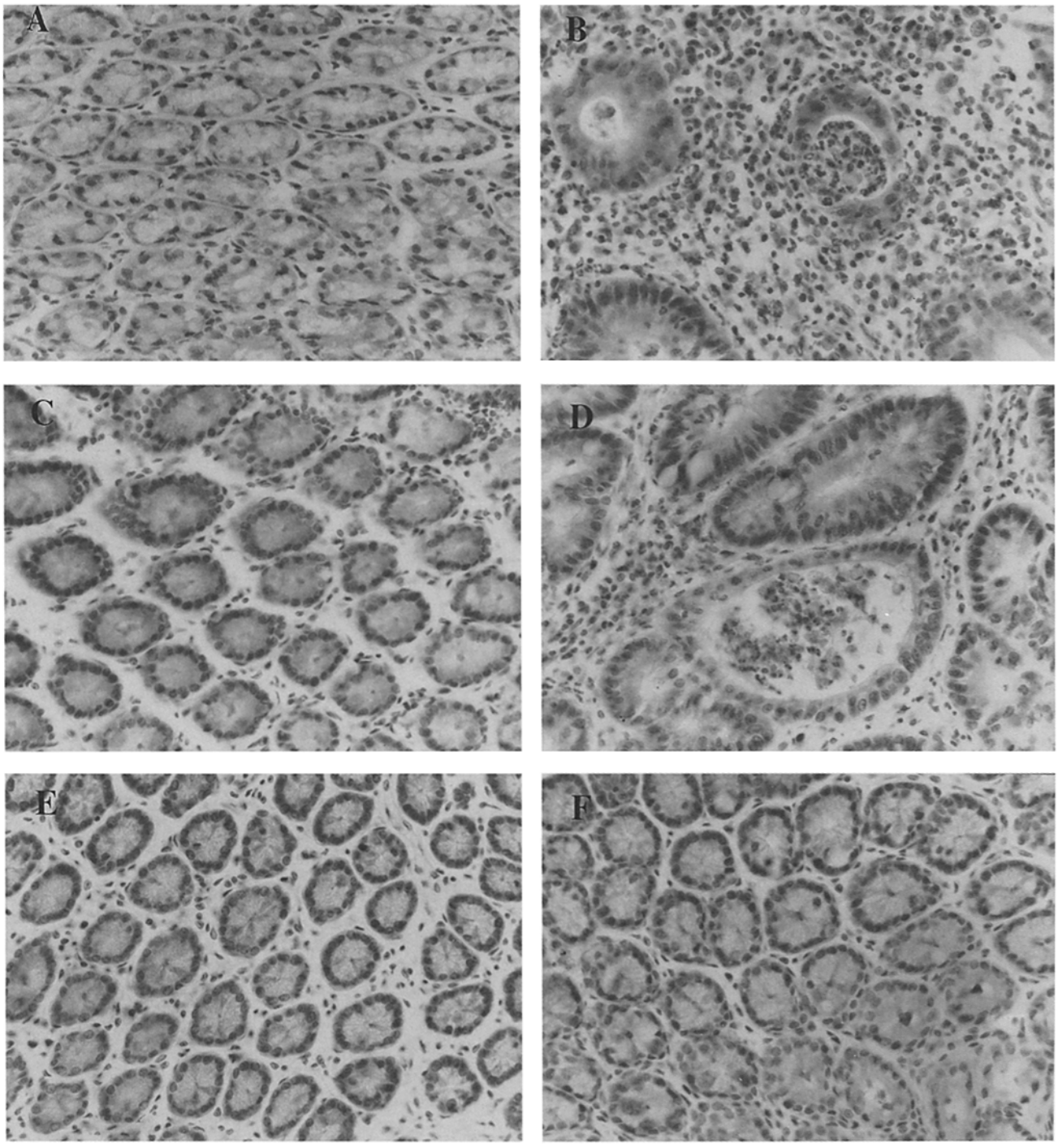
ately after cervical dislocation and blood was drawn into heparinized microhematocrit capillary tubes (Fisher Scientific, Pittsburgh, PA). Capillary tubes were then centrifuged for 5 min, and hematocrits were directly measured in the tubes.

Analysis of Lamina Propria Lymphocytes (LPLs). LPLs were harvested from individual colons of diseased mice, or from two to three nondiseased controls using an adapted version of a previously described protocol (9). Briefly, colons were rinsed with HBSS (GIBCO BRL, Gaithersburg, MD), incubated with serial washes of HBSS with 1 mM EDTA, washed, equilibrated with RPMI with 10% FCS and β-mercaptoethanol, and incubated with RPMI with collagenase and DNAse (0.1 mg/ml; Sigma Immunochemicals, St. Louis, MO) in a shaking incubator at 37°C. Liberated LPLs were purified via Percoll gradient (Sigma), washed, resuspended in PBS with 5% FCS, and stained with PE- or FITC-conjugated mAbs specific for CD3, CD4, CD8, CD69, B220, IgM, and M290 antigens (Pharmingen, San Diego, CA; 10) for 20 min at 4°C. After washing, lymphocytes were analyzed on a FACStar Plus® (Becton Dickinson & Co., Mountain View, CA).

Results

Bowel Inflammation in IL-2$^{-/-}$, but not in JH$^{-/-}$ or RAG-2$^{-/-}$ Mice. Because the manifestation of disease pheno-



types in transgenic animals can vary between animal facilities (1, 11), we initially established the course of disease of *IL-2*$^{-/-}$ mice in our facility by breeding and observing heterozygote and homozygote *IL-2*$^{-/-}$ mice. Mice were maintained together in one track (such that their cages would be changed together). *IL-2*$^{-/-}$ mice generated from breedings of *IL-2*$^{+/-}$ parents regularly developed anemia, splenomegaly, and bowel disease, and became moribund or died between 18 and 24 wk of age. Some mice (3 out of 10 *IL-2*$^{-/-}$ mice) developed profound anemia and died between 11 and 16 wk of age. These mice had normal colons at necropsy. *IL-2*$^{+/-}$ mice were maintained in the same cages as their *IL-2*$^{-/-}$ littermates, and all *IL-2*$^{+/-}$ mice lived >40 wk without visible or histopathological signs of illness. A total of 27 mice (10 *IL-2*$^{-/-}$ and 17 *IL-2*$^{+/-}$ mice) were studied before cross-breeding of these mice with *JH*$^{-/-}$ and *RAG-2*$^{-/-}$ mice. All *IL-2*$^{-/-}$ mice and no *IL-2*$^{+/-}$ mice became ill. Thus, *IL-2*$^{-/-}$ mice regularly develop bowel disease in our facility.

During the same period in which we observed the clinical course of *IL-2*$^{-/-}$ mice in our colony, we observed and killed multiple *JH*$^{-/-}$ and *RAG-2*$^{-/-}$ mice maintained in the same track as *IL-2*$^{-/-}$ mice. These mice have been described before, but colonic histopathology has not been performed (7, 8). Our studies revealed that *JH*$^{-/-}$ mice have grossly normal colons. Although immunohistochemical stains of colonic sections from *JH*$^{-/-}$ mice confirm the absence of κ-positive staining lymphocytes, consistent with the inability of *JH*$^{-/-}$ mice to rearrange Ig genes, the histological appearance of the colonic epithelium was otherwise normal and no epithelial damage, crypt hyperplasia, or signs of regeneration were noted (Fig. 1 *C*). Moreover, no wasting, weight loss, diarrhea, premature death, or other signs of clinical bowel disease were evident in *JH*$^{-/-}$ mice maintained for 40 wk. Thus, unlike cytokine- and T cell–deficient mice, B cell–deficient mice do not spontaneously develop bowel inflammation.

RAG-2$^{-/-}$ mice were also placed in the same track with *IL-2*$^{-/-}$ and *JH*$^{-/-}$ mice, and they were were observed and histologically studied in the same fashion. Among 18 *RAG-2*$^{-/-}$ mice observed for 40 wk, only 1 mouse became ill. This mouse developed a wasting illness; autopsy revealed pulmonary lesions consistent with pneumonia caused by the protozoan *Pneumocystis carinii*, an opportunistic infection that infrequently affects *RAG-2*$^{-/-}$ mice. No significant bowel inflammation or epithelial damage was seen on histopathology. Furthermore, necropsy of six additional 40-wk-old mice failed to reveal evidence of bowel disease. Colonic sections from *RAG-2*$^{-/-}$ mice revealed no gross evidence of colonic inflammation mediated by polymorphonuclear cells, monocytes, or other nonlymphoid immune cells. In addition, epithelial cells were maintained in a normal architecture (Fig. 1 *E*). Thus, *RAG-2*$^{-/-}$ mice, like *JH*$^{-/-}$ mice, remained healthy during the 40-wk observation period. Colonic histology of *RAG-2*$^{+/-}$ and *JH*$^{+/-}$ mice, like *IL-2*$^{+/-}$ mice, was grossly normal (Fig. 1 *A*).

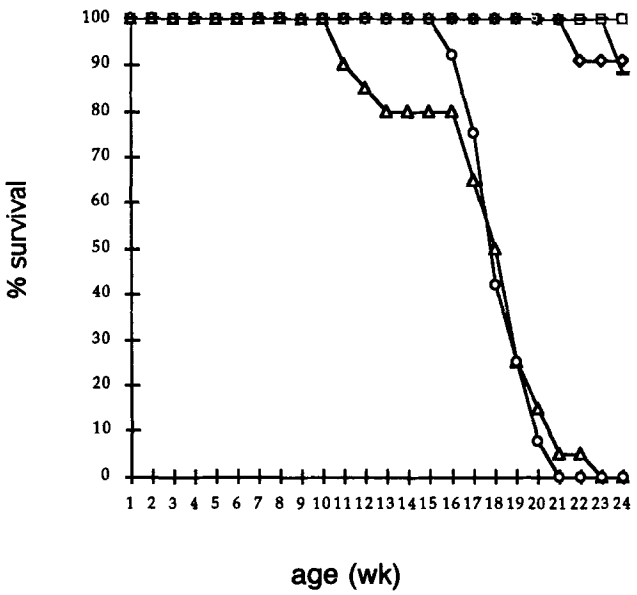


Figure 2. Survival of single- and double-mutant *IL-2*$^{-/-}$, *JH*$^{-/-}$, and *RAG-2*$^{-/-}$ mice. Surviving single- and double-mutant mice expressed as a percentage of the initial number of animals in each genotype group are plotted. All animals were observed until moribund or until 24 wk old, at which time necropsies were performed with colonic histopathology and hematocrit measurement. Wild type (combined survival of *IL-2*$^{+/-}$, *JH*$^{+/-}$ and *IL-2*$^{+/-}$, *RAG-2*$^{+/-}$ mice (- -□- -); *JH*$^{-/-}$ mice (- -□- -); *RAG-2*$^{-/-}$ mice (- - - -); *IL-2*$^{-/-}$ mice (- -△- -); *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice (- -○- -); and *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ (- -◇- -).

Absence of Bowel Inflammation in IL-2$^{-/-}$, *RAG-2*$^{-/-}$ *Mice.* We then bred *IL-2*$^{+/-}$ mice into both *JH*$^{-/-}$ and *RAG-2*$^{-/-}$ backgrounds. All parental strains were from a mixed C57Bl/6/SV129 background. All offspring were genotyped by PCR and/or Southern analysis of genomic DNA isolated from tail tips at 3 wk of age. Genotypes were confirmed by repeat anaylsis of genomic DNA at necropsy. Double-heterozygote mice from F1 breedings, i.e., *IL-2*$^{+/-}$, *JH*$^{+/-}$, and *IL-2*$^{+/-}$, *RAG-2*$^{+/-}$ mice, remained healthy and were interbred for two generations. Fourth, fifth, and sixth generation *IL-2*$^{-/-}$, *JH*$^{-/-}$ and *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ mice were observed along with their littermate controls until they developed gross disease, became moribund, or until 24 wk of age if they remained healthy.

IL-2$^{-/-}$, *JH*$^{+/-}$ and *IL-2*$^{-/-}$, *RAG-2*$^{+/-}$ animals exhibited a similar wasting disease to *IL-2*$^{-/-}$ mice by 24 wk, including weight loss, anemia, a hunched stance, abdominal

Figure 1. Histology of single- and double-mutant *IL-2*$^{-/-}$, *JH*$^{-/-}$, and *RAG-2*$^{-/-}$ mice. Colonic sections from various mice were stained with hematoxylin and eosin. Paired littermates are shown (*A* and *B*, *C* and *D*, and *E* and *F*). All sections are ×1,300: (*A*) *IL-2*$^{+/-}$, *JH*$^{+/-}$ (wild type); (*B*) *IL-2*$^{-/-}$, *JH*$^{+/-}$ (*IL-2*$^{-/-}$); (*C*) *IL-2*$^{+/-}$, *JH*$^{-/-}$ (*JH*$^{-/-}$); (*D*) *IL-2*$^{-/-}$, *JH*$^{-/-}$ (*IL-2*$^{-/-}$, *JH*$^{-/-}$); (*E*) *IL-2*$^{+/-}$, *RAG-2*$^{-/-}$ (*RAG-2*$^{-/-}$); (*F*) *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ (*IL-2*$^{-/-}$, *RAG-2*$^{-/-}$).

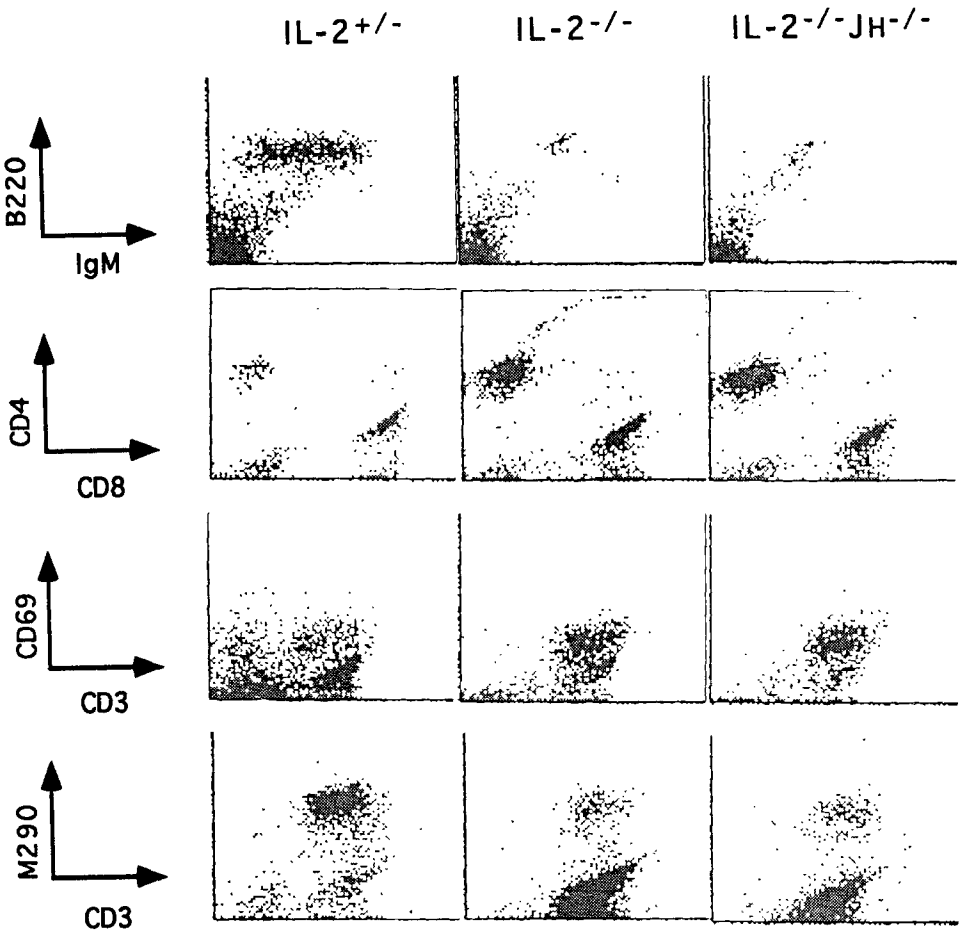


Figure 3. FACS® analysis of LPLs from *IL-2*$^{-/-}$ and *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice. LPLs from freshly killed normal (*left panels*), *IL-2*$^{-/-}$ (*middle panels*) and *IL-2*$^{-/-}$, *JH*$^{-/-}$ (*right panels*) mouse colons were stained with mAbs directed against the following antigens: PE-B220/FITC-IgM; PE-CD4, FITC-CD8; PE-CD69/FITC-CD3; and PE-M290/FITC-CD3.

retraction, loose stools (but rarely rectal bleeding), and occasional rectal prolapse. At autopsy, distal segments (1–5 cm) of *IL-2*$^{-/-}$ descending colons were uniformly thickened and enlarged. Mesenteric lymph nodes were increased 3–10-fold in size as compared to control littermates. Colonic histopathology revealed gross infiltration of colonic lamina propria with lymphocytes, lesser numbers of polymorphonuclear cells, crypt abscesses, and crypt hyperplasia and branching, when compared to normal colons (Fig. 1, *A* and *B*). Loss of mucin from crypt goblet cells and polymorphonuclear cell infiltration of crypts was documented by scanning electron microscopy (data not shown).

While *IL-2*$^{-/-}$, *RAG-2*$^{+/-}$ mice reproducibly developed anemia and colonic inflammation within 24 wk of age, most *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ double-mutant littermates remained disease free while sharing cages with *IL-2*$^{-/-}$, *RAG-2*$^{+/-}$ littermates (Fig. 2). One *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ mouse became ill during the 24-wk observation period; necropsy of this mouse had hepatic and pulmonary lesions and no colonic inflammation. To determine whether *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ mice developed disease in a delayed fashion, several *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ mice were maintained for 12 mo, after which they were killed, and again no colonic lesions were noted. Thus, the elimination of mature lymphocytes prevented bowel inflammation and anemia in *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ mice, and demonstrated that either mature B or T cells are required for these manifestations of disease.

Bowel Disease in IL-2$^{-/-}$, *JH*$^{-/-}$ *Mice.* To determine whether B cells or autoantibodies are necessary for the development of inflammatory bowel disease or anemia in *IL-2*$^{-/-}$ mice, we monitored *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice along with *IL-2*$^{+/-}$, *JH*$^{-/-}$ and *IL-2*$^{-/-}$, *JH*$^{+/-}$ littermates. Except for the absence of early (<16 wk old) deaths in *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice (see below), *IL-2*$^{-/-}$ mice developed a wasting disease of comparable severity at a similar onset regardless of the genotype at the J_H locus (Fig. 2). Histopathological analyses revealed the same lymphocyte predominant infiltrates in *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice as were seen in *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice (Fig. 1, *C* and *D*). Flow cytometric analyses of purified colonic lamina propria lymphocytes confirmed that inflammatory infiltrates from both *IL-2*$^{-/-}$, *JH*$^{-/-}$ and *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice are comprised predominantly of activated CD3$^+$, CD4$^+$, CD69$^+$, and M290$^-$ T cells, and virtually no B cells (Fig. 3). Since most murine intraepithelial lymphocytes bear the $\alpha M_{290}\beta_7$ integrin, this data suggests that intraepithelial lymphocytes are not a major population infiltrating the colons of *IL-2*$^{-/-}$ mice (10). Crypt branching, loss of mucin, and crypt abscesses in both these mice indicate that bowel inflammation leading to epithelial dam-

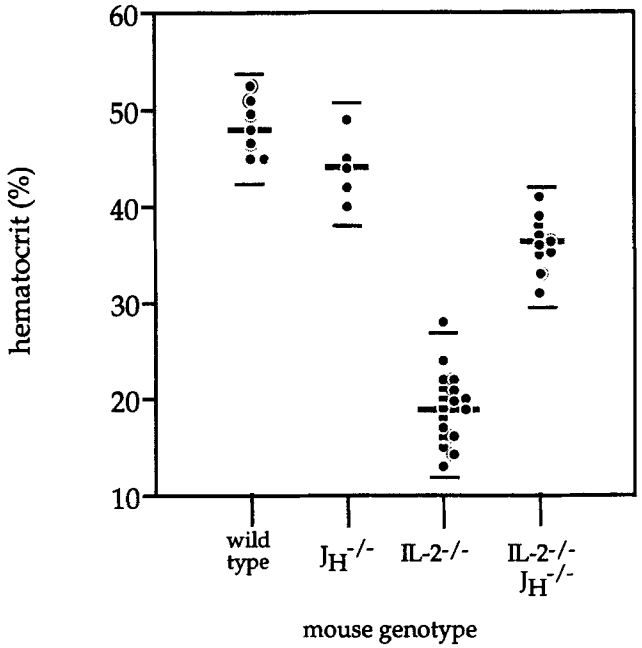


Figure 4. Terminal hematocrit measurements in *IL-2*$^{-/-}$ and *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice. Blood samples from terminally ill *IL-2*$^{-/-}$ and *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice, as well as control (*JH*$^{+/-}$ and *JH*$^{-/-}$) mice, were taken at necropsy, and hematocrits were measured in centrifuged heparinized capillary tubes. Means (μ) and SDs were calculated for each group. *JH*$^{+/-}$ mice: μ = 48%, SD = 3.0%; *JH*$^{-/-}$ mice: μ = 44%, SD = 3.4%; *IL-2*$^{-/-}$ mice: μ = 19%, SD = 3.6%; *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice: μ = 36%, SD = 2.9%.

age, rather than simple lymphocyte infiltration, has occurred (Fig. 1, *C* and *D*). The similarity of disease onset and severity in *IL-2*$^{-/-}$, *JH*$^{-/-}$ and *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice indicates that mature B cells and anticolon autoantibodies are not necessary for the bowel inflammation that occurs in *IL-2*$^{-/-}$ mice.

Amelioration of Anemia in IL-2$^{-/-}$, *JH*$^{-/-}$ *Mice.* Some *IL-2*$^{-/-}$ mice developed severe anemia leading to death within 17 wk of age, before the development of bowel disease, while older mice developed severe anemia concomitantly with the development of severe bowel disease. No deaths occurred in *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice before the age of 17 wk. The mean hematocrit from *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice (19 ± 3.6%) was markedly lower than from terminally ill *IL-2*$^{-/-}$, *JH*$^{-/-}$ littermates (36 ± 2.9%) ($P < 0.001$, Fig. 4). Heterozygote *JH*$^{+/-}$ mutant mice possessed a mean of 48 ± 3.0%, which was not significantly different from the mean from *JH*$^{-/-}$ mutant mice, 44 ± 3.4% ($P > 0.05$, Fig. 4). The amelioration of anemia in *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice, as compared to *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice, indicates that B cells contribute significantly to the development of anemia seen in *IL-2*$^{-/-}$ mice. This anemia is associated with splenic hemosiderin deposits and an abundance of early erythroid forms in peripheral blood smears and splenic sections (data not shown). The moderate anemia seen in *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice, as compared to normal mice, may result from malnutrition associated with bowel disease.

Discussion

Bowel inflammation has been noted in several strains of transgenic mice bearing immune deficiencies resulting from gene-targeted mutations. This condition could directly result from one or several types of infections caused by the abundant microbiological flora of the colon, or it could represent an autoimmune response to intestinal antigens. By establishing that both *JH*$^{-/-}$ and *RAG-2*$^{-/-}$ mice grow and live normally without developing bowel inflammation in our colony, we have established that (*a*) immune deficiency per se does not lead to bowel inflammation from putative intestinal pathogens in our colony; and (*b*) neither of these immune-deficient conditions leads to spontaneous autoimmune bowel inflammation. Furthermore, the absence of gross bowel disease in both strains of animals makes them appropriate for directly testing the roles of B and T lymphocytes in murine models of inflammatory bowel disease.

Previous work demonstrated that intestinal luminal contents influence the onset and severity of bowel inflammation in *IL-2*$^{-/-}$ mice (3). The absence of bowel inflammation and general health of *IL-2*$^{-/-}$, *RAG-2*$^{-/-}$ mice formally demonstrates that infectious agents alone do not cause bowel disease in *IL-2*$^{-/-}$ mice. Rather, antigen-specific immune cells are required for this process. This process can be distinguished from conditions such as the bowel inflammation induced by oral administration of dextran sulfate sodium, since dextran sulfate sodium induces colitis in both *SCID* (12) and *RAG-2*$^{-/-}$ mice (Ma, A., unpublished data). It should also be distinguished from the cecal bowel inflammation seen in IL-2 γ chain–deficient mice, where lymphopenia is associated with the presence of *Helicobacter helicus* organisms (13).

The presence of bowel inflammation in several strains of transgenic mice with compromised T cell compartments suggested that the loss of a particular subset(s) of T cells might lead to dysregulated B cell activity and autoimmune bowel disease (6). Our finding that *IL-2*$^{-/-}$, *JH*$^{-/-}$ double-mutant mice develop disease with comparable severity and onset as *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice demonstrates that neither B cells nor autoantibodies are necessary for this disease. While this does not completely rule out a role for B cells in the colonic immune response, the similarity of *IL-2*$^{-/-}$, *JH*$^{-/-}$ and *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice suggests B cells play at most a minor role. Formal testing of the role of particular T cell subsets in mediating *IL-2*$^{-/-}$ bowel disease by breeding of *IL-2*$^{-/-}$ mice with *TCR*$\alpha^{-/-}$, *TCR*$\beta^{-/-}$, or *MHC II*$^{-/-}$ mice may be complicated by the spontaneous appearance of bowel inflammation in the latter strains of mice (3). Direct comparisons of these mouse models of bowel inflammation await simultaneous studies of the various strains in the same inbred background, in the same facility, and ideally as interbred littermates.

The amelioration of anemic symptoms in *IL-2*$^{-/-}$, *JH*$^{-/-}$ vs *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice suggests that B cells are important for mediating an autoimmune hemolytic anemia in *IL-2*$^{-/-}$ mice. The absence of MHC class I molecules on mature

erythrocytes makes them unlikely targets for T cell–mediated destruction. The finding that *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice die at approximately the same age as *IL-2*$^{-/-}$, *JH*$^{+/-}$ mice despite retaining significantly higher hematocrits indicates that bowel inflammation (vs anemia) is likely to be the major cause of death in mice of this age. The separation of bowel inflammation from anemia in *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice demonstrates the use of B cell–deficient mice in distinguishing the immune mechanisms involved in autoimmune processes. *JH*$^{-/-}$ mice have previously been used to demonstrate the critical role of B cells in mediating nephritis and vasculitis in *lpr/lpr* mice (14). Bowel inflammation in *IL-2*$^{-/-}$ mice is thus pathogenetically distinct from the autoimmune processes seen in *lpr/lpr* mice. Finally, *IL-2*$^{-/-}$, *JH*$^{-/-}$ mice are now a useful reagent for studying the specific mechanism(s) by which *IL-2*$^{-/-}$ T cells cause bowel inflammation.

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