0.502 Hct; estimated standard error, 5.91; $r = 0.757$) differs from the deficient (blood lead = 9.25 + 0.3518 RBC lead + 0.197 Hct; estimated standard error, 8.10; $r = 0.448$). On comparison of these two regression coefficients for any given blood lead and hematocrit, the enzyme-deficient group has a consistently higher red cell lead concentration than the nondeficient group (*11*).

The uncorrected mean blood lead, 28.4 μg/100 ml, of the 166 urban black students contrasts with the maximal mean value for urban women of 20.5 μg/100 ml reported by the Seven City Study of 1971 (*12*). Blood lead in the Omaha school children was not related to age, sex, or history of smoking, suggesting a masking effect by other phenomena. Lack of direct correlation between blood lead and air lead at the sampling sites does not invalidate the circumstantial evidence of proximity to a lead emission source since effective concentrations may relate more to particle size and localized climatic conditions than to prevailing winds (*13*).

The mean red cell lead of the 108 urban black school children (41.9 ± 16.2 μg/100 ml) was lower ($P < .001$) than that of 43 adult male garbagemen, ages 20 to 40, with variable exposure to exhaust fumes (53.5 ± 12.9 μg/100 ml) and of 100 lead workers (128.7 ± 41.5 μg/100 ml), but higher ($P < .001$) than that of 32 freshmen nursing and medical students predominantly from rural Nebraska (24.25 ± 7.61 μg/100 ml). In all of these groups, correlation of RBC lead with RBC δ-aminolevulinate dehydratase was comparable to that reported for whole blood lead (*14*).

A possible interaction of G-6-PD deficiency and lead toxicity is supported by (i) reports of acute hemolytic crises in enzyme-deficient subjects (specific type unknown) with only moderate increase in blood lead, by decrease in reduced glutathione in lead workers, and by in vitro studies of progressive decrease of G-6-PD in rats treated with low doses of lead (*15*). In our study, hemolytic effects of lead were found in neither the enzyme-deficient nor nondeficient children.

What was found is that G-6-PD deficient individuals have an apparent increase in blood lead associated with relatively higher concentrations of lead in the RBC and lower in the serum. All subjects were black, and the A⁻ variant of G-6-PD is the most likely; the effect of specific enzyme types including G-6-PD deficiency among white persons has yet to be studied. The significance of red cell binding is still speculative. It may be protective, as suggested by Goyer (*16*) and by clinical observations of the severe neurotoxicity of lead in anemic children, or it may be an index of biotoxicity, at least for the red cell, as supported by its correlation with δ-aminolevulinate dehydratase (*14*).

If validated, the apparent increase in blood lead in G-6-PD deficient blacks is of potential significance to the 12 percent of black males and 1.4 percent of black females with this genetic variant, most of whom live in inner city areas of high ambient lead (*16*).

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Protein Absorption by the Intestine of the Fetal Rat in Utero

Abstract. *Horseradish peroxidase (molecular weight, about 40,000) injected into the amniotic sacs in pregnant rats has been identified ultrastructurally, 6 to 18 hours later, within the fetal intestine in the absorptive cells and the underlying vascular endothelium. This indicates that macromolecular protein within amniotic fluid swallowed by the fetus can be absorbed and transported by fetal intestine, and may indicate that physiological compounds can be transported by this enteric route to contribute to fetal development.*

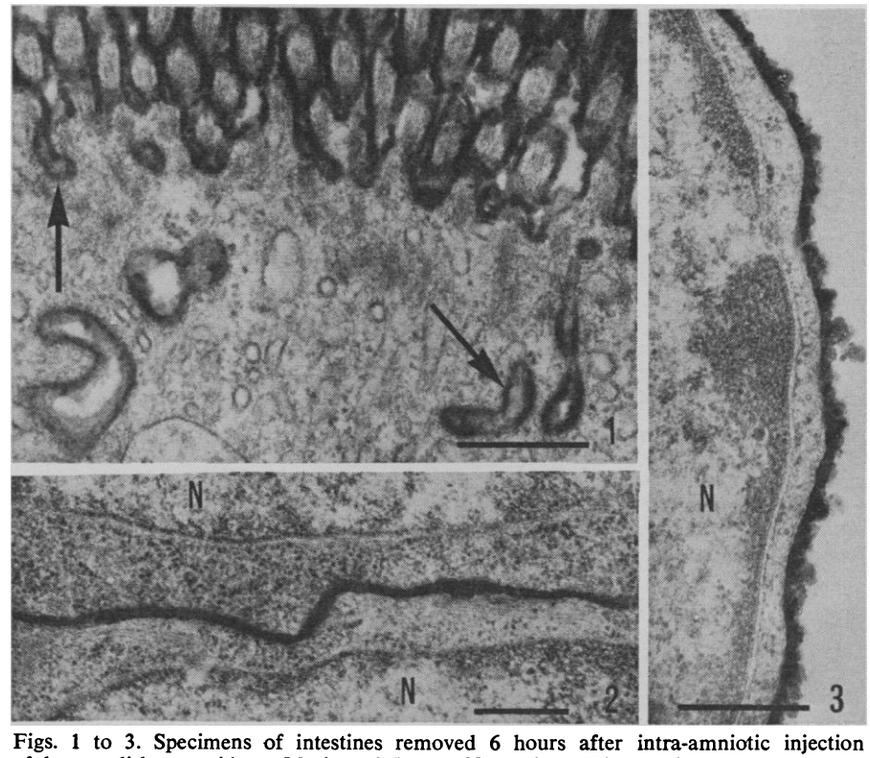
Although the mammalian gastrointestinal tract is not believed to function to any significant degree before birth (*1*), there is evidence that the intestine in the fetus in certain species possesses an absorptive capacity (*2–4*). The passage of macromolecules through the absorptive cells of the intestine has not been demonstrated in the fetus, however, in contrast to the many reports documenting this event in the newborn animal (*5, 6*). We present here ultrastructural evidence of intestinal uptake and transport, in the fetus of the rat, of horseradish peroxidase [a cytochemically demonstrable protein (molecular

weight, about 40,000)], injected into amniotic fluid that is subsequently swallowed by the fetus (*3*, *7*).

The surgically exposed amniotic sacs of rats in day 19 to 20 of pregnancy were injected with 2 mg of horseradish peroxidase (type VI, Sigma) in 0.1 ml of physiological saline. The abdominal incision in the pregnant animals was then sutured, and the animals were allowed to recover from anesthesia. After 1, 6, and 18 hours, segments of the jejunum and ileum of the fetus, totaling four to eight specimens at each time point, were obtained surgically, and were fixed in 3 percent glutaraldehyde for 2 hours. The specimens were bathed overnight in cacodylate buffer, and then 40-μm sections (*8*) were incubated in the diaminobenzidine–hydrogen peroxide medium described by Graham and Karnovsky (*9*) for 60 minutes at room temperature. After they were fixed in osmium tetroxide, and then dehydrated and embedded in Epon, thin sections were prepared from the specimens for study by electron microscopy, and 0.5-μm sections were prepared for study by light microscopy. The thin sections were either counterstained with uranyl acetate and lead citrate, or were examined without counterstaining. Counterstaining resulted in little or no increase in the density of peroxidase reaction product. For control specimens, we used fetuses whose amniotic sacs were injected with saline, and intestinal specimens from fetuses injected with peroxidase but incubated only in diaminobenzidine.

Specimens from the intestines of fetuses injected with saline and incubated in the complete medium, showed only endogenous peroxidase activity in red blood cells and in granulocytes. When incubated in diaminobenzidine alone, these specimens and those from fetuses injected with peroxidase failed to reveal any peroxidase reaction product.

Specimens from intestines obtained 1 hour after intra-amniotic injection of peroxidase exhibited endogenous peroxidase activity only. Jejunum and ileum obtained 6 hours after injection, however, showed definite evidence of peroxidase uptake. This reaction was most marked in the apical region of the villi. In the absorptive cells from some specimens, the reaction was confined to the microvillous border and to vesicular invaginations into the underlying apical cytoplasm (Fig. 1). In other 6-hour specimens abundant deposits were also found in the region above the nucleus of the absorptive cells. These deposits consisted of densely staining, membrane-limited granules (maximum diameter, 2 μm) generally occurring in aggregates. Smaller reactive vesicles with diameters of 800 to 1000 Å were frequently observed adjacent to the lateral cell membrane. These vesicles were, in some instances, fused with the plasmalemma; this may represent a mechanism by which peroxidase is discharged into the extracellular space between adjacent epithelial cells. Reaction product was frequently demonstrable in this space, mainly in the lower portion of the epithelial layer (Fig. 2), and between connective tissue cells in the underlying stroma. In several specimens the luminal surface of the endothelial lining of stromal vessels in the villi and beneath the crypts was coated with electron-opaque material (Fig. 3). The distribution of peroxidase staining in specimens obtained 18 hours after injection was similar to that found 6 hours after injection, except that reaction was observed less frequently in the microvillous border.



Figs. 1 to 3. Specimens of intestines removed 6 hours after intra-amniotic injection of horseradish peroxidase. Marker, 0.5 μm; *N*, nucleus. The sections were counterstained with uranyl acetate and lead citrate. Fig. 1. Reaction product is seen on the surface membranes of microvilli (above) and on vesicular invaginations and canalicular structures in the underlying apical cytoplasm (arrows). Fig. 2. Peroxidase is found in the intercellular space between adjacent epithelial cells. Fig. 3. Reaction product lines the luminal surface of an endothelial cell in a mucosal vessel.

There were no differences in absorption of peroxidase between the fetal jejunum and ileum; no large vacuoles were found above the nucleus of the absorptive cells in either site. Thus, the absorptive capacity of intestine in the fetal rat is independent of these vacuoles. Rodewald (*6*) has reached similar conclusions in his study of antibody transport in the jejunum of the neonatal animal. Previously, researchers [see (*6*)] had emphasized the prominent role of such large vacuoles in absorption by the ileum in neonatal animals.

In some species, antibody transfer from mother to fetus occurs by way of the fetal enteric, rather than the placental, route (*2*). Our data provide a morphological basis for the existence of this intestinal absorptive pathway. It is possible that this pathway may also be responsible for the uptake of macromolecules other than antibodies (for example, potential nutrients) contained within swallowed anmiotic fluid.

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Rapid Immunological Induction of Murine Lymphomas: Evidence for a Viral Etiology

Abstract. *A graft-versus-host reaction induced in (SJL/J × C57BL/1)F_1 hybrid mice by injection of SJL/J spleen cells resulted in 100 percent incidence of tumors at 40 days. Transplantation studies revealed that the tumors were antigenically C57BL/1. Since both SJL/J and C57BL/1 mice carry tumorigenic virus, the evidence suggests a viral etiology.*

Numerous experiments in different laboratories have established that the graft-versus-host reaction (GVHR) can eventuate in lymphomas (*1–3*). The etiologic mechanisms, however, were obscure. Although most tumors have been of host genotype, several experimenters have also observed the induction of tumors which, on the basis of transplantation characteristics, were presumed to be of donor type—that is, of the same genotype as the parental cells utilized for the induction of the GVHR (*2, 3*). This was considered evidence supporting the hypothesis of Tyler (*4*) that excessive immunological stimulation of the donor parental cells could result in unrestrained growth of these cells. Recently, however, by selecting mouse strains with known viral leukemogenic potentialities for such experiments, results have been obtained which provide strong evidence for a viral etiology of GVHR-induced tumors.

The GVHR was induced in 16 (8 male and 8 female) 44-day-old (SJL/J × C57BL/1)F_1 [abbreviated (SB)F_1] hybrid mice by five weekly intraperitoneal injections of 6×10^6 to 8×10^6 spleen cells from 4- to 5-month-old male SJL/J mice. Total cell dosage was 37×10^6 cells in 4 weeks. A control group of 15 (SB)F_1 hybrids was given a similar dosage of spleen cells from 4- to 5-month-old male (SB)F_1 donors. Cell suspensions were prepared by a standard technique (*3*). On day 33 (after the initial cell injection), two mice in the experimental group died of acute allogeneic disease. There was no evidence of tumor at autopsy. On day 40, the remaining 14 mice were found to have large spleens; autopsy and transplantation studies were carried out.

The tumors in the experimental group of mice involved the spleen, lymph nodes, liver, and lungs. Spleen weight varied from 0.8 to 2.5 g. The mesenteric, retroperitoneal, mediastinal, and cervical lymph nodes were most frequently involved. Histologically, the tumors were reticulum cell sarcomas, with numerous mitoses. The thymus was not involved. No tumors were present in the control group.

Tumors from eight mice were transplanted initially into syngeneic (SB)F_1 mice. All were accepted. The tumors were then transplanted into syngeneic (SB)F_1 mice; parental strain mice, SJL/J and C57BL/1; mice containing a parental component, (NZB × SJL/J)F_1; and into an unrelated strain, NZB. A tumor cell suspension, prepared by a standard technique (*3*), was injected intraperitoneally into six to eight weanling mice in each group. During a 5-month observation period, tumor growth was observed only in (SB)F_1 and C57BL/1 mice, but in none of the other groups; this was uniformly true for all of the eight original tumors. In those groups in which tumor acceptance occurred, this was clearly evident by the fourth week after transplantation. The clinically observable rate of tumor growth was also uniform. Tumor growth was confirmed by autopsy and further transplantation.

Various theories, not mutually exclusive, have been proposed to explain the induction of lymphomas by the GVHR (*1*). The experiments reported here provide evidence for a viral etiology because of (i) the characteristics of the strains of mice utilized for the GVHR, (ii) the short latent period required for tumor induction, and (iii) the induction of tumors which differ antigenically from either donor or host.

Studies of the mouse strains used in these experiments, SJL/J and C57BL/1, have shown conclusively that both strains carry tumorigenic virus; tumor inducibility, however, is quite different. The SJL/J strain exhibits an increasing incidence of spontaneous reticulum cell sarcoma with age, reaching 90 percent by 13 months (*5*). Histologically, the tumors resemble Hodgkin's disease of humans. Dmochowski and co-workers have proved the viral origin of such tumors (*6, 7*). Vertical transmission of the virus from mother to embryo was also demonstrated. In contrast, the C57BL strain exhibits a very low incidence of spontaneous lymphoma (*8*). Kaplan and his associates have established that the C57BL strain is a carrier of a latent leukemogenic virus that is readily activated by x-irradiation (*9*). [A viral etiology of spontaneous murine lymphomas was first demonstrated by Gross (*10*). He subsequently confirmed the principle of radiation activation of latent leukemogenic virus in another low-leukemia strain, C3H (*11*)]. Recent experiments in my laboratory have provided evidence that subline 1 of the C57BL strain is also a carrier of a latent leukemogenic virus.

First, parabiosis of (C57BL/1 × A)F_1 hybrid mice with syngeneic partners, followed by supralethal irradiation of one partner, has resulted in a significantly increased incidence of lymphomas, compared to that in normal control mice, in the shielded nonirradiated partner (unpublished observations). Second, it has been noted that neonatally thymectomized (C57BL/1 × A)F_1 hybrid mice develop a significantly higher incidence of spontaneously occurring lymphomas (as well as autoimmune changes) than do normal controls (*12*). Third, when (SB)F_1 mice were injected with massive doses of C57BL/1 spleen cells, all of the F_1 recipients developed reticulum cell sarcomas by 120 days. On transplantation, these tumors were accepted by both the F_1 and donor strain parent, but not by the SJL/J parent, and were presumed to be of donor genotype (*3*). All these findings can be best explained if it is assumed that the C57BL/1