acetylisoleucine were examined for their *in vitro* effect on DNA and protein synthesis of erythrocytic forms of *P. knowlesi*. L-OMT inhibited markedly and L-alloisoleucine slightly the incorporation of orotic-6-^{14}C acid into DNA. The inhibitory effect of L-OMT was reversed by L-isoleucine. L-Alloisoleucine and *N*-acetyl-L-isoleucine did, while L-OMT probably did not compete with isoleucine for incorporation into plasmodial protein. The L-isoleucine antagonists are proposed as a possible new class of antimalarial drugs.

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Detection of Virus-Like Particles in Germinal Centers of Normal Guinea Pigs* (33613)

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In a previous electron microscopy (EM) study (1) we reported that C-type virus particles were localized throughout the preleukemic stage in the germinal centers of the spleen and lymph nodes of C58 mice. Similar studies of AKR mice (2), a strain which also has a high natural incidence of leukemia, revealed that C-type virus particles also appeared to be focally accumulated in the germinal centers of the spleen, mesenteric lymph nodes, and Peyer's patches of mice 1–6 months of age. Recently the occurrence of virus-like particles has been reported (3) in splenic germinal centers of BC3F mice, a strain with a low natural incidence of leukemia. There is substantial evidence (4) to support the concept that specialized reticular cells in germinal centers possessing elaborate dendritic processes (5–7) play an important role in the trapping of antigens. As an extension of our preliminary findings (1) we

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sought to determine whether virus particles could be detected by electron microscopy in germinal centers of other species. Because particles similar in ultrastructure to the mouse leukemia viruses have been found (8) in the lymphoid tissues of *leukemic* guinea pigs we attempted to detect similar particles in the germinal centers of *normal* adult guinea pigs. This communication reports the occurrence of C-type virus particles in the germinal centers of normal guinea pigs of the Hartley strain. Germinal centers also contained a second type of virus-like particle that was not similar to the C-type virus particles found in mouse leukemia.

Materials and Methods. Normal guinea pigs of the Hartley strain (Kuiper's Rabbit Ranch, Gary, Indiana) were used. Animals were either 2, 3, or 6 months old when killed. Pieces of the spleen, mesenteric lymph node, and Peyer's patches were fixed and prepared for EM as described previously (1).

Results. The germinal centers of the lymphoid tissues were conspicuous in the adult normal guinea pig. The C-type virus particles were observed only in germinal centers, *viz*, in mesenteric lymph nodes, Peyer's patches, and the spleen. All six animals studied contained virus-like particles. Although germinal centers contained several cell types the only cells (Fig. 1) which contained the doughnut-shaped C-type particles were the large tissue lymphocytes that had a large nucleus and a prominent nucleolus. Virus particles were found at what appeared to be various stages of development. Doughnut-shaped particles about 80–90 mμ were found in cisternae of the endoplasmic reticulum (Fig. 1A) or apparently budding into cisternae (Fig. 1B). No particles were found budding from the plasma membrane of cells. Particles resembling mature C-type viruses were found extracellularly (Fig. 1C and D) that ranged in size from 100 to 120 mμ in diameter. Their ultrastructural properties were very similar to the mouse leukemia viruses.

Virus-like particles, distinct in ultrastructure from C-type virus particles, also were found in these same germinal centers. The particles appeared to be associated (Fig. 2, arrows) with the labyrinthine network of cytoplasmic processes of germinal center cells. The particles were approximately 70 mμ in diameter, had a 30-mμ electron dense core, were uniform in ultrastructure, and were extracellular (Fig. 2A and B). No budding particles were detected. The outer coat of the particles sometimes appeared to be made up of concentric rings.

Discussion. Two comprehensive studies (9, 10) have provided evidence that leukemia is not uncommon in the usual laboratory strains of guinea pigs. The natural incidence in untreated animals 1 year or older appears to be (9) about 2–3%. However, experimental studies of leukemia in guinea pigs (*Cavia cobaya*) were confined principally to the inbred strain 2 line or its hybrids with the random-bred Hartley stock (8, 11). Opler (8) reported the cell-free transmission of leukemia in hybrids of strain 2 and Hartley stocks. Virus particles were found in leukemic animals (8) that were similar morphologically to the C-type virus particles described in the murine leukemias. Opler (8) did not find similar virus-like particles in normal control animals. Nadel *et al.* (12) reported the detection of virus-like particles in the L2C/NB subline of strain 2 guinea pigs that were not like C-type virus particles. Such virus-like particles were found in animals after they had received an intraperitoneal transplant of the L2C line of guinea pig transplantable leukemia. As a result of the success we had (1) in detecting C-type virus particles in the germinal center cells of *normal* C58 and AKR mice (both are high leukemic strains) we sought to detect similar particles in the lymphoid tissues of *normal* guinea pigs. The findings summarized in this report provide evidence that C-type virus particles, very similar morphologically to the murine leukemia viruses, could be found in normal adult guinea pigs of the Hartley strain and, like the findings for C58 and AKR mice (1, 2), appeared to be accumulated in the anatomically and functionally distinctive areas (4) that make up the germinal centers. Whether the virus particles are unique and indigenous to the guinea pig, or

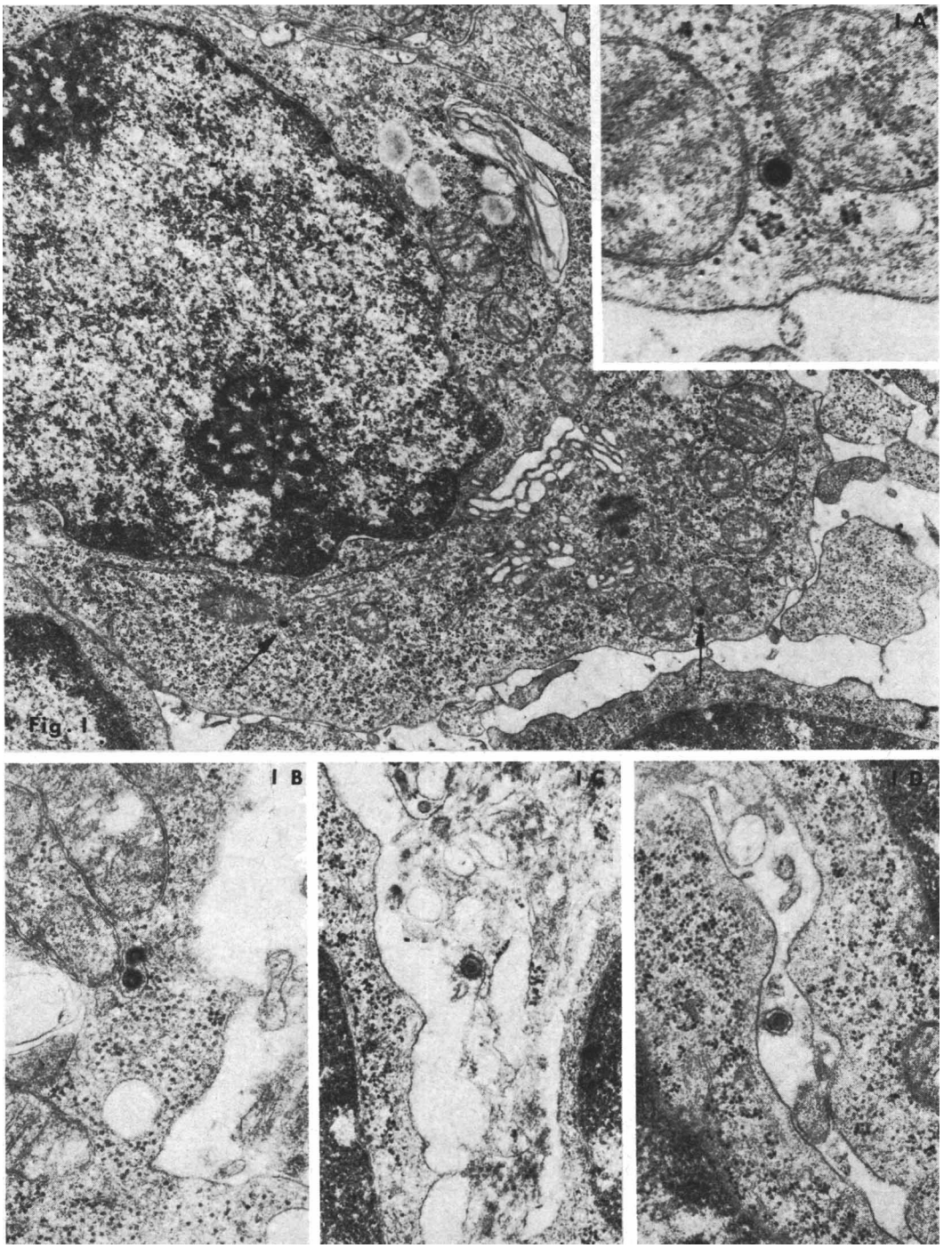

FIG. 1. The sections shown are representative. They were made from germinal centers of Peyer's patches excised from a 6-month-old guinea pig. Three doughnut-shaped virus-like particles (arrows) are located in the cisternae of a large lymphoblastic cell (13,700×). (A) A typical double-shelled doughnut-shaped particle (60,200×); (B) a particle budding into the cisternae (40,000×); (C) and (D) show typical extracytoplasmic mature C-type virus particles (30,400×).

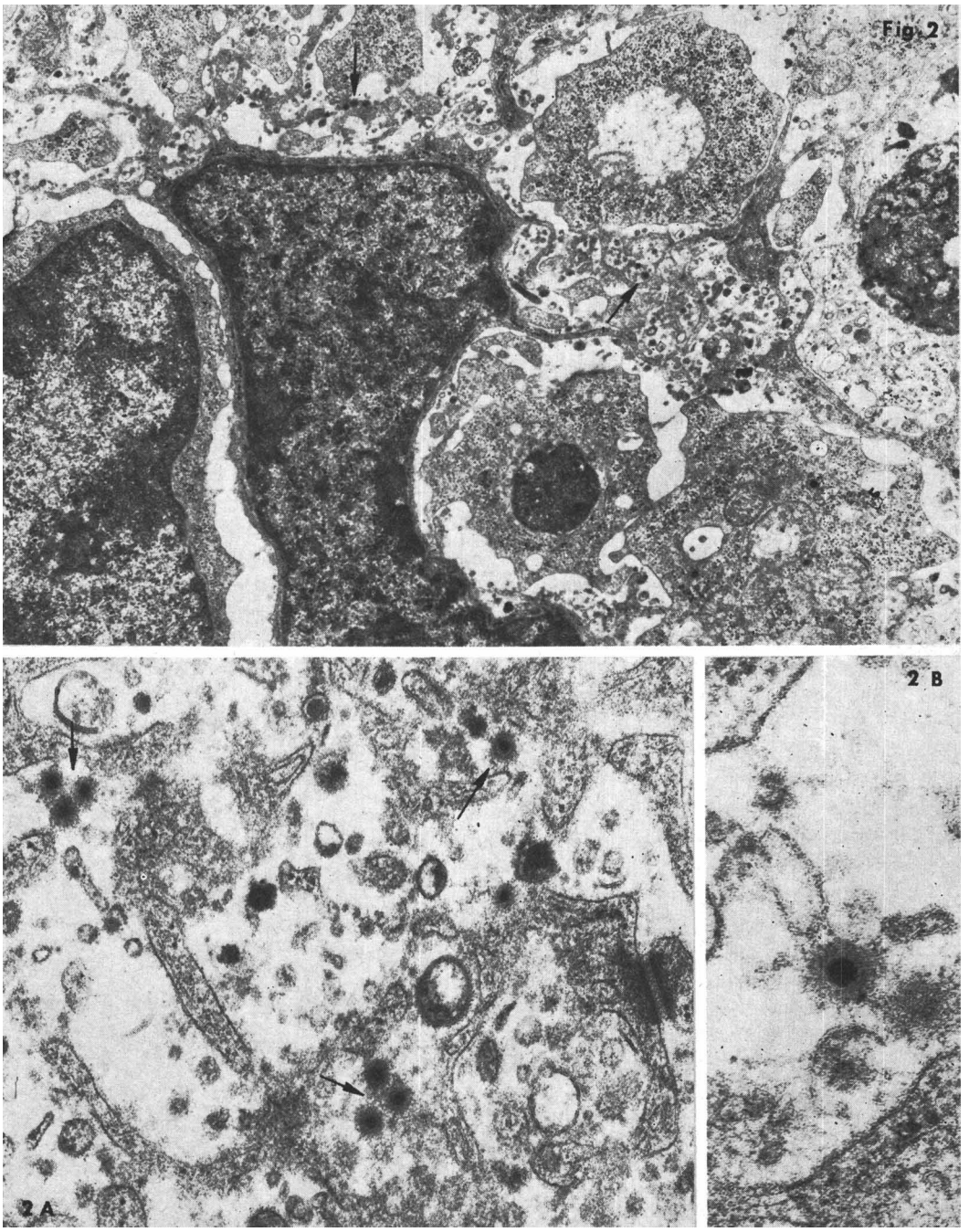

FIG. 2. A section from the germinal center of a Peyer's patch illustrating a typical reticular dendritic cell with elaborate cytoplasmic process where virus-like particles appeared to be trapped (arrows—13,700×). Fig. 2a shows typical virus-like particles at a magnification of 60,200× and Fig. 2b at a magnification of 121,000×.

were transmitted to them from mice at some point in the long husbandry of these two common laboratory animals, is unknown. The leukemogenic potential of such particles likewise has not been evaluated. Whether relatively virulent or avirulent cavian leukemogenic viruses can be delineated requires substantial future experimentation.

Virus-like particles dissimilar to those described by Nadel *et al.* (12), and Opler (8), also were detected in guinea pig germinal centers. The simultaneous occurrence of two different types of virus-like particles in the lymphoid tissues of normal adult guinea pigs can complicate an evaluation of their leukemogenic potential. For example, three recent publications illustrated the difficulty in evaluating the leukemogenic activity of either A-type or C-type virus particles in mouse leukemia (13, 14), or virus mixtures in avian myeloblastosis stock preparations (15). Apart from these considerations, it appears from this and our previous report that virus particles, like other antigens (4), can be selectively localized in germinal centers. Whether their occurrence in germinal centers represents both entrapment and local proliferation, or whether it has an immunologic specificity, or whether it represents a filtrative process made possible by the elaborate cytoplasmic processes of germinal center dendritic cells, remains to be established. As both Opler (8) and Nadel *et al.* (12) pointed out, studies of the pathogenesis of leukemia in the guinea pig provide another model system which may provide important clues in etiologic studies of human leukemia.

Summary. Virus-like particles similar in ultrastructure to the C-type virus particles found in the mouse leukemias were found selectively localized in the lymphoid germinal centers of 2–6-month-old normal guinea pigs of the Hartley stock. A second type of virus-like particle with a diameter of about 70 mμ and dense central core of 30 mμ was also found in germinal centers.

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