TABLE I. Influence of Alpha Tocopherol on Insulin Requirements of Alloxanized Dogs.

Dog No.	Wt, kg	Fasting blood sugar, mg %	Alloxan dosage, mg/kg	Blood sugar after alloxan, mg %	Prot. zinc insulin daily units before α-tocoph.	α-tocoph. oral daily I.U.	α-tocoph. intramusc. 2 day intervals, mg	No. of days	Prot. zinc insulin concluding daily units
1	11.4	55	75	252	10	300	0	40	10
6	15.5	64	100	319	25	300-600	0	40	25
9	13.6	68	65	92	8	300-600	0	40	8
12	6.4	64	75	210	5	300-600	0	35	5
24	20.5	55	65	216	10	300	0	27	10
15	21.0	68	75	207	25	0	50-200	28	25
18	15.9	53	65	136	10	0	50-200	26	10
16	17.7	57	65	104	5	0	0	36	8
Control									
17	11.8	49	65	118	6	0	0	35	8
Control									
23	14.5	55	65	74	5	0	0	33	5
Control									

dogs were treated with diet and insulin. In all instances protamine zinc insulin was used to control the diabetes. Blood sugar determinations were done before alloxan and approximately 48 hours after alloxan. Thereafter, blood sugars were determined at various intervals in order to follow the hyperglycemic state. Insulin dosage was established by daily morning urinalysis. After control of the glycosuria was definitely established, alpha tocopherol was administered to the experimental dogs an average of 4½ weeks. Five of the experimental dogs received oral alpha tocopherol daily, 2 of the experimental dogs received injectable alpha tocopherol every other day.

Results. Table I presents data on each dog. In all cases regulation of the diabetes was readily attained. The general nutritional status of all dogs was well maintained throughout the experiment. In no instance was the insulin requirement reduced in the experimental animals.

Summary and conclusions. 1. Alpha tocopherol does not alter the insulin requirements of alloxan diabetes in the dog.

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Hyperpigmentation in Acute Leukemia Treated with Folic Acid Antagonists.* (18189)

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The treatment of acute leukemia with folic acid antagonists has resulted in encouraging clinical responses. While it is recognized that such antagonists as Aminopterin and A-methopterin (Lederle) do not cure acute leukemia they nevertheless depress abnormal bone marrow response by correcting the dysplastic process and thereby prolong life in many instances. Folic acid antagonists can therefore be useful tools in studies designed to elucidate the abnormal cellular metabolism of the leukemic marrow. During our observations on 10 children who received the antagonists over long periods we were impressed by the development of

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hyperpigmentation in 7 patients. While the examination of tissues from all the patients is in progress, complete histologic data in one case is so striking that we wish to present this case history documented by microscopic evidence of marked epidermal pigmentation. Tissues from 4 other patients have provided preliminary evidence of similar findings. While it is true that Aminopterin prolongs life, this degree of pigmentation has not been noticed previously in cases of acute leukemia not treated with folic acid antagonists.

A 10-year-old boy, admitted for treatment of acute leukemia received either 0.5 mg Aminopterin or 5.0 mg A-methopterin (Lederle) for six months. The patient gradually developed hyperpigmentation; first, at the ankles and wrists. This was followed by darkening of the skin at the nail folds of the fingers. The skin of the abdomen and back likewise became darker during the last 3 months of life. At the time of autopsy, approximately 9 months after the onset of the disease, the entire skin appeared appreciably darker than normal. Skin specimens from the ankle, wrist, abdomen and back were secured in order to ascertain the histological nature of the hyperpigmentation. Fresh autopsy specimens were studied by means of the dopa-incubation method of Becker(1). Other specimens of the same skin areas were fixed in 10% formalin and stained according to Mason's ammoniated silver nitrate technic(2) for the detection of dendritic melanoblasts and of any epidermal cells containing either premelanin or melanin granules. In view of the possibility that the darkening of the skin might have been due to abnormal deposits of iron-salts (hemosiderin) following transitory periods of icterus, ferrocyanide reactions according to the method of Perls(3) were made on some sections of the various skin specimens. These Prussian-Blue stains were negative, thus eliminating iron as a factor in the hyperpigmentation.

The dopa-reactions and ammoniated silver nitrate impregnations as well as unstained sections of the various skin areas revealed a true process of melanogenesis within the epidermis. Typical pigmentary dendritic cells (melanoblasts) were easily recognized. These cells gave a slightly positive dopa-reaction which is characteristic for the true melanin-producing cells and reveals the presence of an active oxidizing enzyme. Both the dopa and silver preparations brought into evidence the dendritic processes of these cells which pervade the intercellular spaces of the deeper layers of the epidermis. They contained premelanin and melanin and the process of a secondary transfer of melanin from the dendritic cells to ordinary epithelial cells was clearly under way. Additional melanin-containing cells were conspicuous, in fairly large numbers, in the upper dermis (papillary layer). These cells were identified as large phagocytic leucocytes which had merely ingested melanin granules produced elsewhere. Their melanin content consisted of coarse, irregularly sized granules, in contradistinction to the finely granular melanin within the melanoblasts. These phagocytes of the dermis were merely carriers (melanophores) and it can be presumed that they obtained melanin granules from the sites of abnormal melanin production within the epidermis, by way of the slowly seeping intercellular fluid from that layer of the skin. They are not concerned with the true process of melanogenesis which occurred within the epidermis. Such phagocytic melanin-carriers remain dopa-negative and when accumulated in large numbers may indirectly affect the color of the skin which would then have a slate-bluish tinge. The skin specimens of our cases were various shades of brown. It is well established that the elaboration of melanin is dependent on the enzymatic oxidation of tyrosine. The presence of dihydroxyphenylalanine (dopa) catalyzes the reaction and evidence is accumulating that the human melanoblasts contain tyrosinases capable of oxidizing tyrosine and related substances. Since tyrosinase is a copper-protein complex,

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several interesting relationships exist, especially those concerned with inhibition of the enzyme. It has been suggested by Lerner and Fitzpatrick(4) that sulfhydryl groups of glutathione and cysteine inhibit tyrosinase by binding the copper. It has also been postulated that in addition to the sulfhydryl compounds, the high oxidation potential of other substances also influences the copper containing enzymes so that they are unable to function optimally.

This paper does not provide data nor is any information available on the effect of folic acid antagonists on tyrosinase or on tyrosine metabolism, but several authors have pointed out the relationship of both folic acid and ascorbic acid to increased excretion of "tyrosyl" compounds. Woodruff and Darby (5) have shown that the increased excretion of "tyrosyl" compounds in scorbutic guinea pigs could be corrected either with ascorbic acid or folic acid. Evidence already exists that folic acid is concerned with tyrosine metabolism since Govan and Gordon(6) showed earlier that the premature infant's inability to cope with a high protein diet resulted in increased excretion of "tyrosyl" compounds which could be corrected by folic acid therapy or by ascorbic acid administration(7) and Johnson and Dana(8) have shown that ascorbic acid given to folic acid deficient rats can modify the loss of weight after the deficiency is induced by a diet containing sulfasuxidine. The chemical relationship of tyrosine to adrenochrome compounds also permits speculation regarding the role of the adrenal glands in the pigmentation of our patient. Since tests for adrenocortical function were all within normal limits, the possibility of an Addisonian type of pigmentation is unlikely in our patient.

Summary. Hyperpigmentation of the skin has been observed in several cases of acute leukemia receiving folic acid antagonists and histological studies in one patient confirmed the impression that true melanogenesis had occurred. The role of antagonists in influencing the tyrosinases concerned in melanin formation is unknown.

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Role of Detergent Complexes in Experimental Gastric and Duodenal Ulcers.* (18190)

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Dogs injected with histamine by the method of Code and Wangensteen(1) develop a gastric hypersecretion, "peptic" ulcers, and usually expire within two weeks. Shoch(2) produced ulcers in 70% of all animals when he subjected them to daily intramuscular injections of 30 mg of histamine base in beeswax and mineral oil. The average survival time was 17 days. He later produced perforated ulcers in 100% of the animals within 9 days using the same regime. Shoch pre-

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