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Publications of the Staff

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Titles and Selected Abstracts

Edited by G. B. Bluhm, M.D.

Familial medullary carcinoma of the thyroid. M. A. Block. *GP* 39:105-7, Mar 1969.

An uncommon histologic variety of thyroid carcinoma, the medullary type is of added significance because it is associated in some patients with other endocrine disorders, especially pheochromocytomas, and it occurs in some families with a dominant autosomal inheritance. It can be suspected in the patient with one or more thyroid nodules and a history of thyroid carcinoma in other members of the family, or a personal or family history of pheochromocytoma. Surgery is the only effective treatment. Bilateral involvement of the thyroid in approximately 80% of patients with the familial variety of medullary carcinoma should be considered in planning operation. Of interest is the evidence that medullary thyroid carcinoma produces hormones which can result in clinical manifestations in at least a few patients. Increased levels of calcitonin in the tumor and peripheral blood of patients appears to be a consistent finding and may prove to be of diagnostic importance. Production of serotonin and the carcinoid syndrome as well as increased levels of prostaglandin in the tumor and peripheral blood of patients have been recorded. The diarrhea, which is a prominent symptom in some patients with medullary thyroid carcinoma, may be related to production of humoral substances by the tumor.

Primary biliary cirrhosis. Immunoglobulins in surgical appraisal. M. A. Block, G. A. LoGrippe, and T. A. Fox, Jr. *Amer J Surg* 117:69-77, Jan 1969.

Persistently elevated levels of serum immunoglobulins, determined quantitatively, in four patients with primary biliary cirrhosis indicated that this examination can be of diagnostic aid—since serum immunoglobulins are usually within normal limits in patients with jaundice due to extrahepatic biliary tract obstruction. However, serum immunoglobulins are elevated in other forms of intrahepatic disease and are not entirely foolproof in separating jaundice due to intrahepatic disease from that due to extrahepatic biliary tract obstruction. In a review of 22 patients with primary biliary cirrhosis, it was noted that the association of cholelithiasis in 10 patients further confused the recognition and management of the intrahepatic disease. Eradication of the cholelithiasis did not alter the ultimate lethal outcome of the hepatic disease. Although cholecystectomy is justified for these patients with symptomatic or questionably symptomatic gallstones if the status of the liver function makes the operative risk low, high elevations on serial determinations of serum immunoglobulins indicate significant intrahepatic disease and an ultimate poor prognosis.

The immunofluorescent tumor imprint technic. III The diagnostic and prognostic significance of the "speckle"—inducing antinuclear antibody. T. K. Burnham, T. R. Neblett, and G. Fine. *Amer J Clin Path* 50(6):683-8, Dec 1968.

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Sera of 5723 patients with connective tissue diseases, dermatoses, and various miscellaneous diseases were tested for antinuclear factors by the immunofluorescent tumor imprint technic. Speckled nuclear immunofluorescence was almost exclusively confined to scleroderma and Raynaud's disease and its frequency was 24.1% in scleroderma and 27.3% in Raynaud's disease, whereas it was only 1.3% in SLE, 0% in discoid LE, and 0.5% in rheumatoid arthritis. Of 789 connective tissue disease patients, 80% demonstrating the speckled pattern had scleroderma. The correlation between the speckled fluorescent pattern and scleroderma in the connective tissue disease group was found to be statistically highly significant. Conversely, speckle-like thready fluorescence was seen almost as frequently in SLE (8.4%) as in scleroderma (9.6%), and slightly less frequently in discoid LE (4.4%), Raynaud's disease (2.3%), and rheumatoid arthritis (1.7%). These findings emphasize the importance of differentiating true speckles from speckle-like threads. Two important diagnostic and prognostic aids are suggested by these findings: Scleroderma is statistically the best diagnosis in a clinically atypical patient suspected of having a connective tissue disease if speckled fluorescence is seen; and patients with Raynaud's disease who demonstrate speckled nuclear fluorescence are probably the very patients who will develop scleroderma in this group.

Further observations on acoustic neurinoma. L. F. P. De Moura, R. C. Hayden, Jr., and G. H. Conner. *Trans Amer Acad Ophthalm Otolaryng* 73:60-70, Jan-Feb 1969.

This report points out some of the possible problems in the early diagnosis of acoustic neurinomas. The presence of preexisting otologic pathology may easily mask the onset of signs and symptoms from the early tumor. In the three cases reported, the tumors developed in pathologic ears, presbycusis was present in one patient, stimulation deafness in another, and Meniere's disease in the third patient. To make the diagnosis of this condition even more challenging, the possibility of bilateral tumors is always present, as illustrated by two of the three patients. With the recent advances in surgical treatment of this disease, early diagnosis has become of paramount importance.

Regional migratory osteoporosis. H. Duncan, B. Frame, H. Frost and A. R. Arnstein. *Southern Med J* 62:41-4, Jan 1969.

The authors described a form of localized osteoporosis occurring at two or more different sites in seven subjects. This syndrome is characterized by the spontaneous onset of a subacute inflammatory reaction which may resemble gout or cellulitis but whose laboratory studies are normal and the severe weight bearing pain persists for 6-9 months. X-rays of the affected region show rapid demineralization of bone which returns to normal up to two years after the spontaneous resolution of the clinical symptoms. Some clinical response has been achieved with short courses of corticosteroids, but recurrence of the same clinical features in other parts of the lower limb distinguished this syndrome from Sudeck's atrophy.

Dose-response at each fraction in a radiotherapy series. L. A. Du Sault. *Front Radiation Ther Onc* 3:36-45, 1968.

Curves were obtained showing the cure rates of breast tumors in 1,500 mice treated by cure 50% of the tumors were read. These doses depended only on the number of fractions radiotherapy. The techniques used involved a range of total doses broken into different numbers of fractions, delivered in different overall times. From these curves the doses required to into which the total dose was broken, and not on the overall time, within the limits used in the experiment. Furthermore, the change in total dose required to keep the cure rate constant, when the number of fractions was changed, is in agreement with the change found by Fowler for constant reaction in pigs' skin. This suggests that it may be the same for many mammalian tissues. If the number of treatments is changed from five to three per week, the total dose should be reduced by 10 or 11%. If the change is from five to two treatments per week, the total should be reduced by 18 to 20%. Both cure rate and normal tissue reactions will then remain the same.

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Oxygen and L-Triiodothyronine in radiotherapy of mouse tumors. L. A. Du Sault. *Amer J Roentgen* 102:43-5, Jan 1968.

Radiotherapy was given to breast tumors in 815 mice. Those made hyperthyroid by T3 medication and those breathing 95% O₂ + 5% CO₂ during therapy showed a higher cure rate than those given conventional treatment. When both T3 and carbogen were used the death rate during treatment doubled and the cure rate was no further improved. In some situations T3 medication may be superior to hyperbaric oxygen (but not to carbogen) as a means of improving oxygenation of tumor cells during radiotherapy.

Cardiac myxoma. A morphologic and histogenetic appraisal. G. Fine, A. Morales, and R. C. Horn, Jr. *Cancer* 22(6):1156-62, Dec 1968.

A histologic study of 31 cardiac myxomas, using the hematoxylin eosin stain and a number of histochemical stains, showed a growth pattern and tumor cell type (lepidic cell) unlike that of thrombi and other cardiac neoplasms. Similarity of the tumor cells within the growth and on its surface with those cells lining the endocardium, coupled with the findings of tissue culture, electron microscopy and enzyme histochemistry lend credence to an endocardial cell origin for this long disputed growth. The epithelium-like and gland-like component infrequently reported in otherwise typical cardiac myxomas was noted in 8 of the 31 tumors studied. The morphologic findings suggest that proliferation of the myxoma cells and their polysaccharide production and not the growth of endodermal or mesothelial rests are the source of these uncommon histologic patterns.

Tetracycline bone labeling in anatomy. H. M. Frost. *Am J Phys Anthropol* 29:183-95, Sept 1968.

Tetracyclines are deposited *in vivo* at centers of active bone formation, and can be seen by fluorescence microscopic examination of undecalcified bone sections. With this marker, the rate of bone formation at the level of the osteon can be measured, and is taken to indicate the speed of bone formation at the level of the osteoblast. When the number of bone-forming centers is then counted, it becomes possible to compute: (1) the number of new centers initiated per unit time, which number is taken to indicate the number of new osteoblasts created from the osteoprogenitor cell (mesenchymal cell) pool; (2) the rate of bone formation averaged over the whole sample, which is the form of protein anabolism characteristic of bone. Therefore the tetracycline-labeling technique permits the quantitative analysis of skeletal growth, as well as the maintenance of the mature skeleton, in terms of tissue dynamics and cell population dynamics. Of major importance in the design of future studies is the frequent finding that abnormalities in the rate of bone formation over the whole tissue may be the opposite of abnormalities in the rate of bone formation at the level of the osteoblast. This situation can exist because osteoprogenitor cell behavior can—and frequently does—produce major changes in the total number of functional osteoblasts, changes which do not correlate with changes in the behavior of individual osteoblasts.

The effect of autogenous urine on leukocytic defenses in man. B. F. Knoll, A. J. Johnson, C. W. Pearce and J. W. Rebeck. *Invest Urol* 6:406-11, Jan 1969.

The skin window technique of Rebeck permits the study of leukocytic behavior in inflamed abraded skin. In this investigation, the technique was used to study leukocytic responses when the inflammatory environment initiated by diphtheria toxoid was modified by the addition of autogenous urine to the window sites of human volunteers. The results show that urine inhibits the inflammatory cellular outpouring and compromises the structural integrity of the inflammatory cells, and that hypertonic urine, at least, reduces the phagocytic ability of the responding cells. There is an osmotic gradient in the renal medulla. It seems possible that leukocytic inhibition in a hypertonic environment may be a factor in the pathogenesis and localization of pyelonephritis.

Abstracts

The mechanism of tetracycline fluorescence in experimental squamous cell carcinoma of the rat. G. R. Mikhail, A. R. Kelly, and H. Pinkus. *J Invest Derm* 52:37-44, 1969.

The mechanism of fluorescence produced by tetracycline HCL in dimethylbenzanthracene induced squamous cell carcinoma was studied concurrently by fluorescence microscopy and spectrophotofluorometric analysis. Rats with tumors received 60 mg/kg of tetracycline intraperitoneally. Controls were other tumor and normal rats. Animals were sacrificed at 5, 24, 48 and 72 hours post-injection for blood and tissue studies. Tetracycline levels of blood, liver, kidney and tumor were assayed. The data obtained indicate that tumors accumulate tetracycline, retain it for long periods as a stable complex in keratinizing cells, and slowly release it into the circulation. Gross fluorescence was not reliable in detecting malignant tissue, and microscopic fluorescence did not correlate well with fluorometric assay. The latter was more sensitive and accurate.

Ovarian lipid cell tumor: urinary steroid response to adrenocorticotropin and chorionic gonadotropin. L. B. Morrow, R. J. Thompson and R. C. Mellinger. *J Clin Endocr* 28(12): 1756-62, Dec 1968.

The excretion of 17-hydroxycorticosteroids, total and fractional 17-ketosteroids, pregnanetriol, pregnanediol and testosterone were determined in the urine of a 34-year-old Negro woman with virilization caused by an ovarian lipid cell tumor. Urinary levels of 17-ketosteroids (17-KS), androsterone (A) and etiocholanolone (E) were significantly elevated, were not suppressed by dexamethasone, but were augmented by metyrapone, presumably through increased ACTH secretion. Human chorionic gonadotropin (HCG) administration also resulted in a marked increase in 17-KS. Basal levels of pregnanetriol and testosterone glucuronide, significantly above normal, were further elevated by HCG and metyrapone. These findings are interpreted to indicate that the tumor secreted 17-hydroxyprogesterone and an androgen which may have been androstenedione, testosterone or both. 11-Hydroxylase function characteristic of adrenal steroid synthesis was not proved for the tumor, but the increased excretion of pregnanetriol and testosterone which followed both metyrapone and HCG stimulation suggests cellular functional responses characteristic of both ovarian and adrenal tissue.

The diagnostic value of marrow hemosiderin patterns. R. K. Nixon and J. P. Olson. *Ann Intern Med* 69:1249-54, Dec 1968.

Routine study of some 500 marrows in a variety of diseases has enabled the formulation of quantitative and qualitative hemosiderin patterns which provide a morphologic expression of ferrokinetics. Utilizing these patterns, one can gain a diagnostic orientation which is provided otherwise only by more complicated and cumbersome radioactive iron tracer techniques. By direct examination of the unstained marrow particle, hemosiderin is evaluated both with respect to quantity and predominant particle size. A designation of normal, decreased, absent or increased amounts with normal, predominantly small particle or predominantly large particle size can be made. Based on the foregoing, patterns of true iron deficiency, refractory, hemorrhagic and hemolytic states are characterized. Folic acid and B₁₂ deficiencies reveal a variable pattern primarily dependent upon the degree of ineffective erythropoiesis and peripheral hemolysis. It is felt that direct visualization of marrow hemosiderin patterns provides an accurate, rapid and simple means of evaluating iron dynamics. Quantity and particle size of hemosiderin allow an interpretation of iron adequacy, turnover rate and red blood cell utilization, information basic to the proper study of anemia, polycythemia and hemochromatosis. The facility of the technique lends itself to routine application in contrast to the employment of radioactive iron tracer studies.

Abstracts

Preliminary trials with combination therapy of cyclophosphamide (NCS-26271), vincristine (NCS-67574), and 5-fluorouracil (NCS-19893). W. G. Tucker, R. W. Talley, R. W. Brownlee, J. H. Burrows, P. B. Stott, E. L. Moorhead II, and E. L. San Diego. *Cancer Chemother Rep* 52(5):593-6, Sept 1968.

Eighty-nine patients, selected from the Division of Oncology of the Henry Ford Hospital, Detroit, were treated with the triple drug combination of cyclophosphamide, vincristine, and 5-fluorouracil with courses repeated every three weeks. Toxic manifestations of the combination chemotherapy were limited chiefly to alopecia, mild-to-moderate gastrointestinal cramping, and moderate leukopenia. Satisfactory regressions were noted in carcinomas of the breast, colon, liver, pancreas, and prostate, and Ewing's sarcoma. The combination of these three agents, at dosage levels according to a predetermined protocol, is considered safe, moderately effective in these tumor categories, and warrants further evaluation.

Radiation nephritis. E. J. Van Slyck and G. A. Bermudez. *Yale J Biol Med* 41: 243-56, Dec 1968.

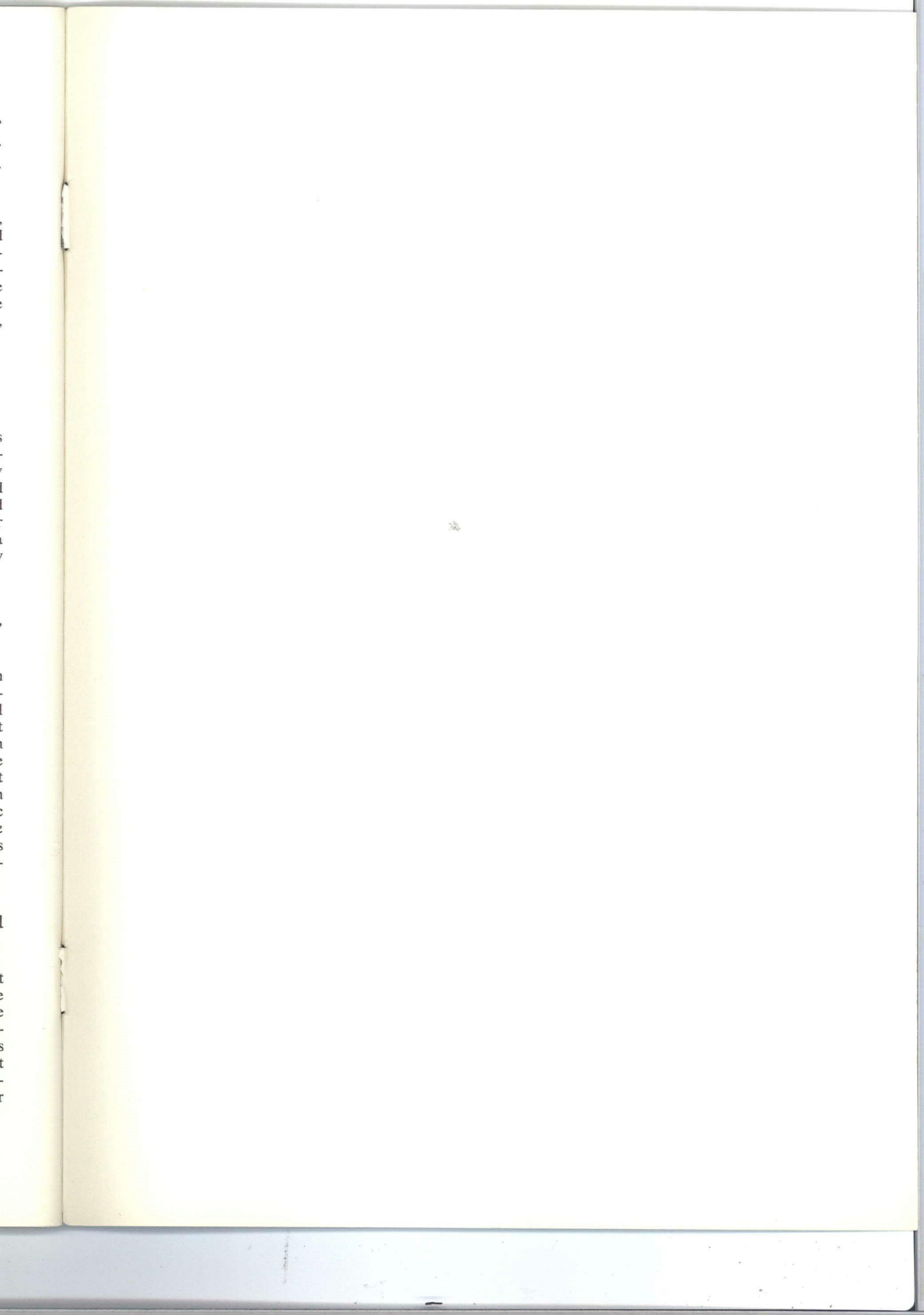
Renal damage as a result of incidental irradiation of the kidney in the treatment of various malignancies, particularly metastatic seminoma of the testis, needs wider recognition. Manifestations range from subclinical nephritis and late development of hypertension to rapidly occurring renal failure and death from severe sclerosis of the kidneys. The two cases described in detail represent the late occurrence of chronic radiation nephritis, one of which terminated fatally. The attendant anemia, seemingly more severe in radiation nephritis than in other forms of chronic nephritis, was investigated with ferro-kinetic studies in both patients and a plasma erythropoietin assay in one. The associated radiation of vertebral and pelvic marrow contributes an effect on hematopoiesis not seen in other types of renal failure.

Electron microscopy in medical diagnosis. J. H. L. Watson. *Microscope* 17:63-9, Jan 1969.

The emerging use of the electron microscope as an instrument useful to the clinician in medical diagnosis is reported. Applications are described briefly for Whipple's disease, differentiation of tumors, amyloidosis, muscle disease, diabetes, viral lesions, lung and bronchial diseases, and particularly, for kidney diseases. It is emphasized that electron microscopy is not yet truly routine in any of its diagnostic application. Reasons for the increasing use of electron microscopy in diagnosis are the excellent and informative light microscopy which can be done on serial tissue sections prepared by the techniques of electron microscopy; the present high quality of both reproducibility and reliability which can be expected from the electron microscopic techniques; the present acceptable rapidity with which electron microscopic results may be expected; and the improved instrumentation available. The advantages of the use of electron microscopy as an aid in diagnosis are expected to outweigh the present costs and time factors, so that use of this instrument will become increasingly routine in an increasing number of disease areas.

Acrodermatitis enteropathica persisting into adulthood. R. R. Tompkins and C. S. Livingood. *Arch Derm* 99:190-5, Feb 1969.

The authors report a 47½-year-old, white female with the disease that persisted into adult life. To their knowledge, it is the oldest, and only the fourth, reported case recorded in the medical literature persisting to adulthood. Prompt exacerbation of the disease, following the administration of cow's milk, was demonstrated; also an equally prompt and dramatic improvement occurred after the administration of diiodohydroxyquin. Mechanisms of pathogenesis are discussed and the action by which diiodohydroxyquin brings about its therapeutic effect proposed. Diarrhea did not occur, and its absence should not exclude the diagnosis of acrodermatitis enteropathica. The disease is probably more common than indicated by the number of patients thus far reported.



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