Asbestos

2. Gallagher JC, Jerpbak CM, Jee WSS, Johnson KA, DeLuca HF, Riggs BL. Administration of 1,25-dihydroxyvitamin D_3 to patients with postmenopausal osteoporosis: short- and long-term effects on bone and calcium metabolism. Proc Natl Acad Sci USA. (in press).
3. Jowsey J, Riggs BL, Kelly PJ, Hoffman DL. Effect of combined therapy with sodium fluoride, vitamin D, and calcium in osteoporosis. Am J Med. 1972; 53:43-9.
4. Riggs BL, Hodgson SF, Hoffman DL, Kelly PJ, Johnson KA, Taves D. Treatment of primary osteoporosis with fluoride and calcium: clinical tolerance and fracture occurrence. JAMA. 1980; 243:446-9.

TOLERANCE TO HYDRALAZINE IN CONGESTIVE HEART FAILURE

To the Editor: The article by Packer et al.[1] in the January 14 issue provided valuable information on the development of tolerance to long-term hydralazine therapy in some patients with congestive heart failure. I believe, however, that the potential role of fluctuations in the effects of digoxin was not adequately considered. Packer et al. did not indicate the serum digoxin concentrations of their patients, nor did they indicate that any digoxin dosage adjustments were made after the initiation of vasodilating agents. Although the authors acknowledged that hemodynamic alterations may produce changes in the absorption of orally administered drugs (including digoxin), they did not address the effect of vasodilators on the renal clearance of digoxin. Cogan et al.[2] recently found that the use of either hydralazine or nitroprusside in patients with congestive heart failure produced an increase of 30 per cent in the mean renal clearance of digoxin (from approximately 100 ml per minute to approximately 150 ml per minute). This increase in the renal clearance of digoxin, which was accompanied by an increase in renal blood flow without a change in the glomerular filtration rate, was apparently due to an increase in the renal tubular secretion of digoxin. Vasodilator therapy may therefore improve the patient's hemodynamics initially, but the increased renal clearance of digoxin may precipitate decompensated failure over the ensuing days by reducing the serum digoxin concentration. This information certainly does not challenge the findings of Packer et al., but it is presented as another important factor to consider when one is evaluating the recurrence of congestive heart failure in a patient who has recently responded to vasodilator therapy.

HENRY I. BUSSEY, PHARM.D.
University of Texas
San Antonio, TX 78284 Health Science Center

1. Packer M, Meller J, Medina N, Yushak M, Gorlin R. Hemodynamic characterization of tolerance to long-term hydralazine therapy in severe chronic heart failure. N Engl J Med. 1982; 306:57-62.
2. Cogan JJ, Humphreys MH, Carlson CJ, Benowitz NL, Rapaport E. Acute vasodilator therapy increases renal clearance of digoxin in patients with congestive heart failure. Circulation. 1981; 64:973-6.

The above letter was referred to the authors of the article in question, two of whom offer the following reply:

To the Editor: We thank Dr. Bussey for his interesting comments. The doses of digoxin in our patients were not altered during long-term therapy with hydralazine, but we did not measure serum digoxin concentrations in order to confirm that a constant digitalis effect was maintained. We should point out, however, that the hemodynamic variables after the development of tolerance to hydralazine did not differ from the values seen before the initiation of therapy; this finding suggests that the adequacy of digitalization was not changed. Although increased renal clearance of digoxin may result in subtherapeutic drug levels in some patients receiving hydralazine, it is likely that tolerance to this effect may also develop in the same patients who have tolerance to hydralazine's hemodynamic actions.

MILTON PACKER, M.D.
JOSE MELLER, M.D.
New York, NY 10029 Mt. Sinai School of Medicine

FAMILIAL LOWER ESOPHAGEAL RINGS

To the Editor: I would like to report the occurrence of a symptomatic lower esophageal ring in identical twins and two mother-son pairs.

A 68-year-old man had intermittent dysphagia without gastroesophageal-reflux symptoms for 12 years before a hiatal hernia and a lower esophageal ring were found on an esophagogram. Endoscopy revealed a thin ring, and bougienage relieved his dysphagia. His identical twin reported having had similar dysphagia for five years. Endoscopy revealed a hiatal hernia and a lower esophageal ring like his brother's, and bougienage was successful. No other relatives were known to have dysphagia.

A 52-year-old woman had intermittent dysphagia without reflux symptoms for 30 years before the radiographic demonstration of a hiatal hernia and a lower esophageal ring. Endoscopy was confirmatory, and bougienage eliminated her dysphagia. Her 20-year-old son had episodic dysphagia without reflux symptoms for seven years before presenting to the emergency room with a meat impaction in his lower esophagus. After the bolus was removed, endoscopy demonstrated a hiatal hernia and a lower esophageal ring, and bougienage stopped his dysphagia. One of his five siblings had dysphagia but had not sought medical attention.

A 64-year-old woman had episodic dysphagia without reflux symptoms for five years before her hiatal hernia and lower esophageal ring were found by esophagography. Endoscopy confirmed the diagnosis, and bougienage was curative. Her 41-year-old son had intermittent dysphagia without reflux symptoms for five years before an esophagogram showed a hiatal hernia and a lower esophageal ring. Endoscopy was confirmatory, and bougienage was successful. A family history revealed no more dysphagia.

I am not aware of any other reports of the concordance in twins or the familial occurrence of a symptomatic lower esophageal ring. Although an asymptomatic lower esophageal ring may be found in 6 to 14 per cent of the population,[1-3] a lower esophageal ring productive of dysphagia is much less common. Although its pathogenesis is problematic, anatomic data suggest a developmental origin.[4] These cases suggest a hereditary factor in the genesis of the symptomatic lower esophageal ring.

GEORGE F. LONGSTRETH, M.D.
Southern California
San Diego, CA 92120 Permanente Medical Group

1. Kramer P. Frequency of the asymptomatic lower esophageal contractile ring. N Engl J Med. 1956; 254:692-4.
2. Keyung WS, Baker GM, McCarver RR, et al. The lower esophagus. Am J Roentgenol. 1960; 84:1070-5.
3. Goyal RK, Bauer JL, Spiro HM. The nature and location of lower esophageal ring. N Engl J Med. 1971; 284:1175-80.
4. Goyal RK, Glancy JJ, Spiro HM. Lower esophageal ring. N Engl J Med. 1970; 282:1298-305.

HLA-B27 AND COLORECTAL CANCER

To the Editor: The high familial incidence of colorectal cancer[1] suggests the possibility of a linkage or an association of this disease with histocompatibility antigens. Sivak et al. have reported a family study compatible with the linkage of adenocarcinoma of the colon with the major histocompatibility complex.[2] On the other hand, previous studies have failed to show such an association, particularly with HLA-A and B antigens.[3]

We studied 81 patients (43 men and 38 women, 19 to 83 years old) with histologically proved colorectal lieberkühnian epithelioma. Sixteen of them (20 per cent) had a close relative affected by the same disease. HLA-A and B antigens were compared with those of 319 controls. B27 antigen was found in 16 patients (19.9 per cent) and in 27 controls (8.5 per cent). The relative risk was 2.67 ($P<0.01$). No other antigen was found with a significant difference in frequency between the two groups. The frequency of the B27 antigen was comparable among the patients with affected relatives (three of 16) and in the whole sample (16 of 81). Abdominal films in all patients showed definite sacroiliitis in three, all of whom were B27-positive and none of whom had clinical evidence of ankylosing spondylitis.

Thus, provided that o[redacted] patients,

colorectal cancer may join the group of diseases associated with HLA-B27. The increase in the frequency of this histocompatibility antigen was not higher in familial forms of colorectal cancer; the frequency of radiologic signs of ankylosing spondylitis among B27-positive patients with colonic cancer (three of 16) was comparable to that found by some of us among B27-positive healthy blood donors (16 of 40),[4] suggesting that the existence of colorectal cancer in B27-positive people has no influence on the incidence of radiologic signs of sacroiliitis.

These results raise the question of a possible causal role of B27 antigen in colonic carcinoma and ankylosing spondylitis. Since some microbial species (e.g., klebsiella) are thought to have a responsibility in the genesis of ankylosing spondylitis,[5] and since some others (*Streptococcus faecalis* and clostridia) are thought to be colonic carcinogens,[6,7] it is conceivable that B27 antigen favors some intestinal dysmicrobisms that would lead to different specific diseases. Finally, it is noteworthy that another potential colonic carcinogen, asbestos,[8] can give rise to another B27-associated disease, asbestosis.[9]

M. Alcalay; D. Bontoux; Ph. Maire; Cl. Matuchansky; D. Alcalay; and J. Tanzer
Hôpital Jean Bernard
86021 Poitiers, France

1. Dunsmore GH, Knaggs TWL. Familial cancer of the colon and rectum. J Med Genet. 1972; 9:451-4.
2. Sivak MV, Schlesinger Sivak D, Braun WA, Sullivan BH. A linkage study of HLA and inherited adenocarcinoma of the colon. Cancer. 1981; 48:76-81.
3. Terasaki PI, Perdue ST, Mickey MR. HLA frequencies in cancer: a second study. In: Mulvihill JJ, Miller RW, Fraumeni JF Jr. eds. Genetics of human cancer. New York: Raven Press, 1977:321-8.
4. Alcalay M, Amor B, Hauser F, et al. Ankylosing spondylitis and chlamydial infection in apparently healthy HLA B27 blood donors. J Rheumatol. 1979; 6:439-56.
5. Ebringer RW, Caldwell DR, Cowling P, Ebringer A. Sequential studies in ankylosing spondylitis: association of Klebsiella pneumoniae with active disease. Ann Rheum Dis. 1978; 37:146-51.
6. Hill MJ. The role of colon anaerobes in the metabolism of bile acids and steroids, and its relation to colon cancer. Cancer. 1975; 36:2387-400.
7. Report from the International Agency for Research on Cancer Intestinal Microecology Group. Dietary fibre, transit-time, faecal bacteria steroids and colon cancer in two Scandinavian populations. Lancet. 1977; 2:207-11.
8. Lambert R. Epidemiology of colorectal carcinogenesis. Symposium on colonic carcinogenesis — May 27-28, Tirnau, Germany, 1981.
9. Matej H, Lange A, Smolik R. HLA antigens in asbestosis. Arch Immunol Ther Exp. 1977; 25:489-91.

PYRIDOXINE (B6) SUPPRESSES THE RISE IN PROLACTIN AND INCREASES THE RISE IN GROWTH HORMONE INDUCED BY EXERCISE

To the Ed.: The role of monoamines in control of the secretion of anterior pituitary hormones has been widely studied in the past few years.[1] The hypothalamic dopaminergic pathways have been shown to be involved in the regulation of prolactin, growth hormone, ACTH, and gonadotropins.[2]

Pyridoxine (vitamin B_6) is one of the natural precursors of pyridoxal-5'-phosphate coenzyme in the decarboxylation and transamination of amino acids. As a coenzyme of dopa decarboxylase, this vitamin can induce the transformation of dopa to dopamine, thus sharing the endocrine effects of this amine. In fact, this drug has been reported to reduce prolactin levels and raise growth hormone levels,[3] although this action has not been confirmed.[4]

We conducted a study to evaluate the effect of pyridoxine on prolactin and growth hormone levels during exercise, since exercise provides a good model for the physiologic release of the adenohypophyseal hormones.[5,6] Six healthy subjects 25±3 years old volunteered to enter the study. Informed consent was obtained from all subjects. Each volunteer was tested at two different times separated by a seven-day interval (once with drug and once with placebo).

Physical exercise, performed on a bicycle ergometer, was monitored by an open-circuit gas analyzer. A spirometer included in the system was used to evaluate the static and dynamic lung volumes.[5]

The bicycle workload was adjusted so that the heart rate, monitored from a V_5 lead, was constant at a value corresponding to 80 per cent of the maximum heart rate of each subject (about 170 beats per minute), during the eight minutes of maximum workload. The exercise phase was preceded by a 20-minute rest period and followed by a 45-minute recovery phase. Saline or 600 mg of pyridoxine in 250 ml of saline was given by infusion for the duration of the test (rest, exercise, and recovery phases).

The subjects were not told which infusion was given. A catheter was introduced into a forearm vein to collect blood at the beginning of the 20-minute rest period, immediately before the start of exercise, and then five, 15, 30, 45, and 60 minutes after the end of the exercise period. After blood collection the test tubes were placed on ice; the plasma was immediately separated and frozen at −70°C. Levels of growth hormone and prolactin were measured by means of sensitive and specific radioimmunoassays.[7]

The results, analyzed with Student's t-test, are shown in Table 1. A significant increase in growth hormone and prolactin occurred in response to maximal effort during the test performed after the saline infusion. The hormonal response to physical exercise performed after the pyridoxine infusion showed that prolactin response was suppressed ($P<0.001$) whereas the growth hormone response was enhanced ($P<0.001$).

The present data indicate the efficacy of vitamin B_6 in stimulating growth hormone and suppressing the rise in prolactin induced by exercise. This phenomenon is probably due to the increase of dopaminergic activity by pyridoxine.[3]

Costanzo Moretti, M.D.; A. Fabbri; L. Gnessi; V. Bonifacio; and F. Fraioli
00100 Rome, Italy
University of Rome

A. Isidori
02100 Sassari, Italy
University of Sassari

Table 1. Plasma Levels of Growth Hormone and Prolactin before and after Exercise, Performed in Subjects Given a Saline or Pyridoxine Infusion.

Time	Growth Hormone *	
	with saline	with pyridoxine
	ng/ml	
Before exercise		
20 min before	2.2±0.9	4.8±0.8
At start (basal)	1.9±0.8	4.5±1.4
After exercise		
5 min	1.8±4.6	2.2±5.1
15 min	25.5±7.4	81.6±20.4 †
30 min	20.1±6.8	41.9±6.2 †
45 min	12.4±4.2	27.4±5.3 †
60 min	6.11±1.8	17.0±4.2 †
	Prolactin *	
	with saline	with pyridoxine
	ng/ml	
Before exercise		
20 min before	7.2±1.6	3.8±0.9
At start (basal)	5.4±1.4	4.5±0.8
After exercise		
5 min	16.9±2.1	4.8±0.9 †
15 min	23.0±4.1	3.2±0.6 †
30 min	12.1±1.6	3.8±0.6 †
45 min	6.4±0.4	4.8±0.9
60 min	6.1±1.4	4.0±1.2

*Mean ±S.D. in six subjects.
†Significantly different from value with saline infusion ($P<0.001$, Student's t-test).