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In China, the prevalence of Helicobacter pylori (H. pylori) infection and gastric cancer is high and the geographic variation is great.

1, Biology

In 1985, Zhang ZH[1]et al. first isolated H. pylori in China. Zhou DY et al. found that H. pylori might change from helical bacillary form to coccoid form (CF), thread-like, giant coccoid, glomerule and spheroplast after incubation in vitro. These variants were able to grow and reproduce under microaerobic conditions in vitro except CF, and they, especially CF, were associated with recurrent infection, transmission and resistance to drugs. Zhou LY[2] et al. observed that the subinhibitory concentration (SIC) of metromidazoie could induce gastric H. pylori CF transformation. Using PCR based random amplified polymorphic DNA (RAPD), Hua JS[3] et al. analyzed DNA finger printing of H. pylori, indicating that recrudescence was the main reason of relapse of H. pylori infection. Cui Yi et al. reported that the reinfection rate in adult was as low in developing countries as in western developed countries. Xiang ZY et al.[4] reported that the clinical isolates of H. pylori could be divided into two major types: type I (VacA+, CagA+) and type II (VacA-,CagA-), representing 56% and 16% respectively. CagA is not necessary for the expression of the vacuolating cytotoxin. Yan XJ et al [5] established a method of quantitative detecting H. pylori CagA gene. Zhang XY et al. found that VacA+cagA+ H. pylori strains were detected more frequently in peptic ulcer (PU) patients than in gastritis ones, and the detecting rates linked to the severity of disease. But in Shanghai, an investigation of H. pylori isolated from Chinese patients of gastritis and duodenal ulcer showed that the prevalence of CagA+ gene was almost 100%. Zheng PY et al.[6] found lipopolysaccharide (LPS) displayed the antigenic variants that might increase the heterogeneity of H. pylori. Ras, c-met, c-erb-2, P16 and P53 genes etc were reported to undertake mutations and anomalous expressions in H. pylori-related diseases[7-10]. Liang HJ et al.[11] found that H. pylori extract could induce human gastric mucosal cells acquiring some malignant phenotypes. Liu WZ and Chen SY et al found that H. pylori infection increased the gastric epithelial proliferation, apoptosis, metaplasia and dysplasia. The results supported that the sequence of phenotypes and genotypic changes ultimately leaded to intestinal type of gastric cancer, which was put forward by Goldstone and Dixon. The process includes the following steps: non-atrophic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and ultimately cancer[12, 13].

By sequencing 16sRNA gene of Helicobacter heilmannii (Hh), formerly named Gastrospirillum hominis (Gh), Chen Ye et al.[14] found out Hh was over 93.5% homologous to all other Helicobacter species and was most similar to H. pylori and H. felis. i.e. 97.1% and 96.5% similarities respectively.

2. Epidemiology

In 1996, Xiao SD reported that the prevalence of H. pylori infection was 21 - 93% in the common Chinese, 50% in the people in cities and 68.8% in the people in suburb. In 1987, Jiang SJ (Shanghai) first reported H. pylori detecting rates in endoscopic cases in China. Li YY[15] reported that H. pylori infectious rates in duodenal ulcer (DU), gastric ulcer (GU) and chronic gastritis were 74.1%, 71.9% and 63.6% in a meta-analysis of Chinese Journals form 1985 to 1989. Hu PJ[16] reported H. pylori infection was evident in 98.9% of patients with DU, 100% with GU, 83.3% with gastric cancer (GC) and 57.4% with functional dyspepsia (FD) in 1006 consecutive endoscopy cases. In this study, patients with antimicrobial medicine intake history were excluded from the analysis. Serological survey of population on large scale was carried out in Guangzhou, Lanzhou and Shanghai separately. The studies showed that the overall prevalence of H. pylori infection was 38.6 - 61.6%, which paralleled with age. But it is different from that seen in Western countries: the age-infection distribution curve showed infection rate markedly increased in the group of I - 5 years old, slowly increased in the group of 6 - 19 years old, and was up to or almost up to the peak over 19 years old and the difference of infection rates in different areas was generally reflected in the age range of I - 5 years. The studies clearly indicated that early period of childhood was much susceptible to H. pylori infection[17].

Chen JJ et al. found out different strains of H. pylori in different regions. Using SDS-PAGE protein profiles and immunoblot patterns. An early serum assay of H. pylori infection carried out in Kunming showed several epidemic factors: source of drinking water, diet habit, economic condition and drug abusing[18]. Family aggregation of H. pylori infection has been demonstrated in several studies. Faculties in the department of Gastroenterology have a higher risk o f H. pylori infection than the other groups in hospitals. All the studies above indicate a person-to-person transmission mode of H. pylori.

The fact of H. pylori positive in dental spots and salvia supports oral-oral transmission pattern. Wu LJ et al. had detected H. pylori in foul water by PCR. However, there were not significant differences between people drinking water from rivers or wells in one region of Guangzhou. Using the antibody to hepatitis A virus (HAV)

as a marker of fecal-oral exposure, seroprevalence data from 1501 subjects in rural and urban areas in Guangzhol, suggested that community wide fecal-oral spread of H. pylori might be of limited importance in the transmission of H. pylori in China[19]. Cat is found to be vertebrate host of H. pylori.

3. Animal model

Sun GH et al. established the "Chinese No.l Pig" model infected with H. pylori. Wang JD et al.[20] inoculated SPF Balb/c mice with Helicobacter felis (Hf). Chronic gastritis characterized by the infiltration of lymphoid cell and formation of lymphoid follicles (LF) could be found in 20 - 40 weeks after infection. Acute gastritis features could be seen lately. Xu KQ et al. set up a rat model where H. pylori could cause allergy. In wistar rat infected with H. pylori (CagA+/VacA+), the bacteria could colonize in gastric gland mucosa 3 months later, and the colony's densities increased as time went by. Chin MH et al.[21] immunized SPF Balb/c mice orally with H. felis sonicate plus cholera toxin, and succeeded in preventing infection of H. felis. First in the world, they proved intervention against H. pylori was a real possibility. Animal inoculated with Hh offered us a new clue to carry out comparative studies on H. pylori.

4. Mechanism

In vitro, H. pylori adhere to the gastric-type epithelial cells specially. Only in gastric mucosa that H.pylori receptor like materials exist. H. pylori infection decreased the gastroduodenal mucosal blood flow (GDMBF), increased the release of histamine and enhanced the mast cell degranulation[22]. Higher PGE2 and lower EGF can be seen in H. pylori positive group. Shi Li et al. recently confirmed the synergy of H. pylori's urease and ammonia[23]. The enhanced NO synthase activity in H. pylori infection suggested that NO, as a free radical, may be involved in gastric mucosal ROM damage[24]. Chen MH et al. found that H. pylori especially CagA+ strains, might induce gastric epithelial secretions of IL-8, IL-6, TNF-alpha[25].

Nie SH et al. found that as a consequence of H. pylori inflammation, delicate gastrin/somatostatin (SS) balance was broken, leading to hypergastrinemia and decreasing of SS. Chen JX et al. found that the levels of ascorbic acid and Copper Zinc superoxide dismutase (CuZnSOD) in gastric juice were significantly lower in H. pylori positive patients than H. pylori negative ones and normal controls ($P<0.05$). The degree of decrease in the two items was in the decreasing order of patients with superficial gastritis, atrophic gastritis and gastric cancer[26].

5, H. pylori associated diseases

5.1 gastritis and peptic ulcer

Many groups have confirmed the strong association between H.pylori and gastritis, and peptic ulcer.

5.2 gastric carcinoma (GC)

GC is estimated to be the world's second most common cancer. In 1994, infection with H. pylori has been classified as the group 1 (definite carcinogen) carcinogenic exposure. In China, GC mortality ranks the first in the cancer death, accounting for 23.02% of all malignant tumors. The generous H. pylori infection of Chinese is 60-80%, higher than the 30% of American, whose GC mortality is only 20/l00,000. Both H. pylori infection and GC are prone to increase along with age. Studies to compare the seroprevalence of H. pylori in areas with high or low risks for GC (mortality 40/100,000 vs. 5/100,000) showed that in children under 5 years old; the prevalence of H. pylori infection in the area with high GC mortality (Lanzhou) was 45.1%, significantly higher than the 15.1% with low GC mortality (Guangzhou), however in children over 5 years old, the increase in prevalence of H. pylori infection was almost the same in the two areas. The peak age of infection in the former was in the group of 30 - 39 years old, i.e. 10 years younger than the latter, and moderate-severe intestinal metaplasia (IM) and atrophy emerged earlier in the former area (Fig. 1 - 3). The result strongly suggested the relationship between early H. pylori infection and GC. Chen MH et al.[17] stated that low mortality of GC could be found in the area with low H. pylori infection rate, while its uncertain high mortality of GC exists along with a high H. pylori incidence. The result suggested the pathologic consequence of H. pylori infection would depend on other factors other than H. pylori itself.

Hu PJ et al. reported the prevalence of H. pylori in tissue of the cancer, around the cancer, beneath the cancer were 16.1%, 71.4% and 93.6%. The cancer tissue itself does not fit for adhesion of H. pylori.

Several groups have confirmed the correlation of H. pylori with GC. In the above study, the detecting rate of serum anti-H. pylori antibody in advanced GC patients was 92.9%, significantly higher than the 69.6% of healthy individuals ($P<0.05$). But there is no difference between the intestinal-type and diffuse-type[27]. Xu SP et al.[28] detected H. pylori in antral tissue by PCR, and showed that H. pylori infection was closely related to GC (82.4 vs. 66.2), particularly in the intestinal-type and non-cardia GC. No remarkable difference was found between early and advanced GC. Correlation rate of natural population infection to GC death is 40% ($p=0.02$), which is not seen in other tumors.

But in a serological study on large-scale, Zhu YQ et al.[29] reported patients with GC or non-digestive ulcer had similar H. pylori prevalence. Prospective studies in Mainland and Taiwan showed that matching OR value of GC risk in H. pylori patients were only 1.1 (95%, CI: 0.6 - 2.1) and 1.6 (95%, CI: 0.7 - 2.6).

Zhong WR et al. found that H. pylori detecting rate in IM group was statistically higher than that in the group without IM ($P<0.05$). Yang RK et al.[30] reported no significant differences were seen among the four types of IM, H. pylori may be ineffective in the formation of IM. Dysplasia was found to be more common in H. pylori-related gastritis than in H. pylori negative cases.

Several international researches suggested that the worldwide variation in GC mortality might be associated more strongly with the H. pylori infection of CagA+ strains than of CagA- strains. But no evidence of correlation of CagA to GC was found so far in studies performed in China [31].

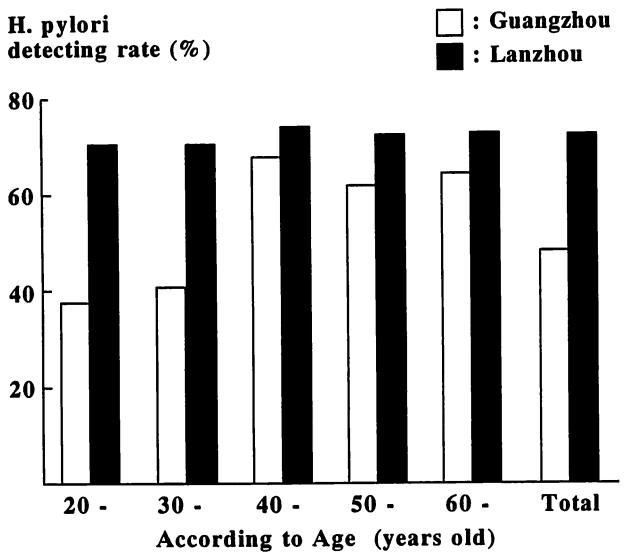


Figure 1. H. pylori detecting rate according to Age in high and low GC mortality

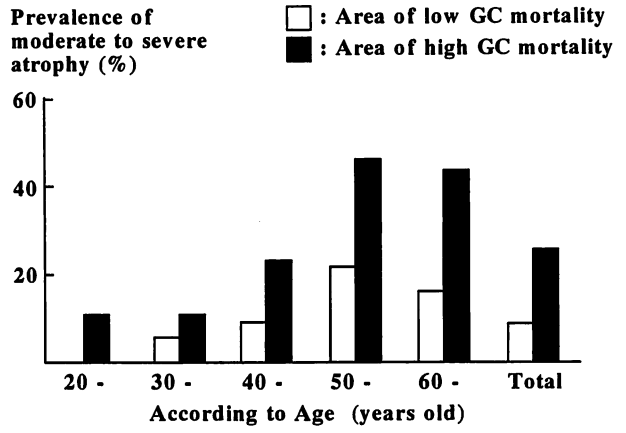


Figure 2. Prevalence of moderate-severe atrophy according to Age in high and low GC mortality areas

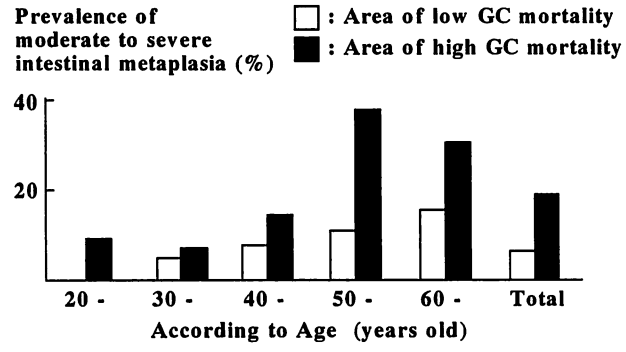


Figure 3. Prevalence of moderate-severe intestinal metaplasia accprding to Age in high and low GC mortality areas

5.3 Primary gastric malignant lymphoma (PGML)

PGML is an uncommon cancer, accounting for only 0.93 -2.4% of gastric neoplasm in China[32]. It remains, however, the most frequent extranodal form of lymphomas. The majority of the tumors derive from mucosa-associated lymphoid tissue (MALT), making for 5% of lymphomas and 51% of all these MALT lymphomas. The incidence is lower than that in western countries, but in recent years, the number is reported to be rising in China[33].

Yi ZH et al.[34] found that H. pylori detecting rate of 39 cases with PGML was significantly higher than that of control groups with lymphocytic gastritis and H. pylori unrelated diseases, respectively (87.18 vs. 63.64, 53.13) ($P<0.005$). MALT type was accounted for 92,31% of PGML and the H. pylori positive rate was 86.11%. The data indicated the association of H. pylori with PGML, which was also supported by another group who detected H. pylori infection in all 15 PGML patients. However, Shao JY et al.[35] reported that the H. pylori detecting rate was only 17,65% in Guangdong, obviously lower than the 79.06% in the control with gastritis ($P<0.01$). The result supported the speculation (Fagiol in 1994, Luppi in 1996, Xu et al. in 1997) that other infectious agents and environmental factors might have a pathogenic role in lymphomagenesis of MALT PGML.

The onset of MALT lymphoma in stomach is preceded by the acquisition of MALT as a result of H. pylori infection. ZhaugWei[36] reported that lymphoid follicle (LF) rate in patients with H. pylori infection was 60.01%, remarkably higher than that in patients without H. pylori infection (17.1%), LF rate could decrease after eradication of H. pylori, indicating the presence of LF might directly associated with H. pylori infection.

5.4 Functional dyspepsia (FD)

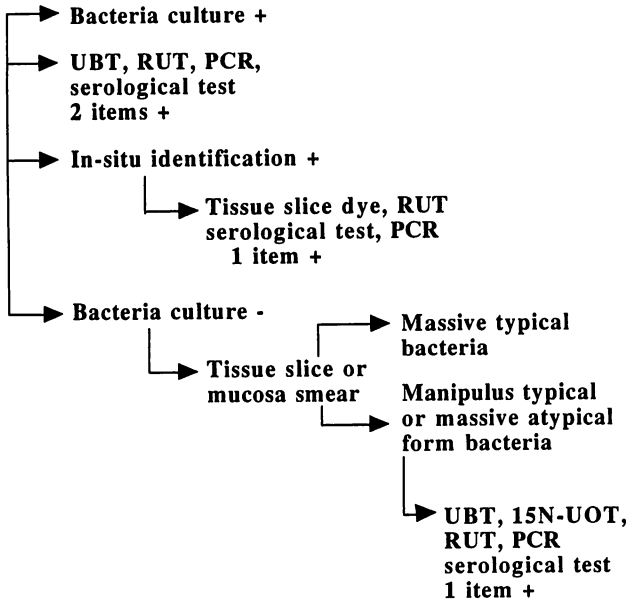
It is still not sure whether or not H. pylori infection and FD are related to each other. Several studies in China have shown that H. pylori infection and H. pylori associated active chronic gastritis have no effect on dyspeptic symptoms and gastric emptying in FD patients, though some patients' symptom can be unreleased or disappear after H. pylori's eradication. The positive rate of H. pylori in patients with FD was 48.2%, significantly lower than the 89.5% in patients with peptic ulcer ($P<0.01$). H. pylori may play an unimportant role in the pathophysiology of FD[37].

6. Diagnosis method[38]

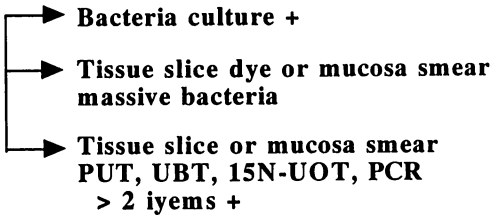
(I) Urease breath test (UBT)
(2) Rapid urease test (RUT)
(3) Serological test: ELASA, purified urease, ultrasound pulverization antigen
(4) Gastric mucosa biopsy
(5) Bacteria isolate and culture
(6) In-situ identification technique
(7) PCR
(8) Histological examination

7. Diagnosis criteria

7.1 Research diagnosis standard



7.2 Clinical diagnosis standard



Patients using anti-H. pylori drugs in 2 weeks should be excluded from all the tests.

References

l, Zhang ZH, Li XB, Yuan MY. Study on curved bacilli detected from gastric mucosa biopsy Chin J Dig 5(4):231, 1985

2, Zhou LY, Liang Ping Yu FF. Experimental study on Helicobacter pylori colloid form transformation under subinhibitory concentration metromidazoie. Chin J Dig 17(1):55-6, 1997

3, Hua JS, Xiao HX, Zheng PY. Analyses of recrudescence and reinfection of Helicobacter pylori infection after antimircobial treatment by DNA fingerprinting. Chin J of Gastro and Hepato 7(3):209, 1998

4, Xiang ZY, Censini S. Bayeli PF. Analysis of expression of CagA and VacA virulence factors in 43 strains of Helicobacter pylori reveals that the clinicals isolates can be divided into two major types and the CagA is not necessary for expression of the vacuolating toxin. Infect Immuno 63:94-8, 1995

5. Zhang XY, Zhang HJ, Zhao ZQ. Association of Helicobacter pylori with CagA gene infection and gastroduodenal mucosa damage. Chin J Dig l8(4):243-4, 1998

6, Zheng PY, Tang FA, BJ Appelmelk. Antigen variation in Helicobacter pylori lipopolysaccharide. Chin J of Gastro and Hepato 7(3):204-8, 1998

7, Zhang JK, Yu Jun. Study on the association between Helicobacter pylori infection and the pathogenesis of gastric cancer by using molecular biological techniques. Chin Clin J of Dig 5(3):97, l993

8, Wang JY, Jin FL, Li JY. Analysis of relation between Helicobacter pylori infection and c-met gene expression in gastric mucosa lesion. Chin J Dig 16(6):360-1, 1996

9, LuWer, Chen LY, Gong HS. PCNA and c-erb-2 expression in gastric mucosal intestinal metaplasia with Helicobacter pylori infection. World Chin J of Dig 7(2):111-3, 1999

10, Gao Hua, Yuan Yual, Wang Lan. Study of tumor suppressor gene P16 expression in Helicobacter pylori related gastric diseases. Chin J of Dig 17(4):242, 1997

11, liang HJ, Liu WW, Liu Wei. Transform of Helicobacter pylori extractive upon human gastric mucosa cells. Chin J Dig 17(1):57, 1997

12, Liu WZ, Zheng Xong, Dong QJ. Effect of Helicobacter pylori infection on gastric epithelial cell proliferation and apoptosis. Chin J Dig 18(4):204-6, 1998

13, Chen SY, Liu TS, Wang JY. Helicobacter pylori infection, gastric mucosal intestinal metaplasia and dysplasia. Chin J New Gastroentero 5(9):570, 1997

14, Chen Ye, Wang JD, Ren XR. Phylogenetic analyses of Helicobacter heilmannii by sequencing of 16s ribosomal RNA gene. Chin J of Gastro and Hepato 6(2): 129, 1997

15, Li YY, Hu PJ, Du GG. The prevalence of Helicobacter pylori infection in the People's Republic of China. Am J Gastroenterol 86(4):446-9, 1991

16, Hu PJ, Chen MH, Tang DF. The Sydney system-a new classification of gastritis patients. Chin Acad J SUMS 13(3):56-60,1992

17, Chen MH, Li YY, Hu PJ. A comparison of the prevalence of Helicobacter pylori infection in areas of high and low mortality of gastric cancer. Chin Acad J SUMS 18(2):124-6,1997

18, Chen JJ, Zhang JZ, Jiang XG. Typing of Helicobacter pylori strains isolated from patients with gastric diseases. Chin J Epidemiology 18(6):338, 1997

19, Hazell SL, Michell HM, Shi X. Hepatitis A and evidence against the community dissemination of Helicobacter pylori via faces. J Inf Dis 74(11):679, 1994

20, Wang JD, Zhou DY, Zhang YL. Animal experimental study on the pathogenicity of Helicobacter. Chin J of Dig 17(6):315, 1997

21, Chen MH, Hu PJ, Lee A. Animal experimental study of immunization against Helicobacter pylori infection. Chin J of Dig 15(Supple):19-20, 1995

22, Xu KQ, Zhang WD, Zhou DY. Study on the pathogenicity of histamine in gastric mucosa with Helicobacter pylori infection. Chin New J of Dig 5(7):447, 1997

23, Shi Li, Han XH, Yi CQ. Vacuolation induced by Helicobacter pylori. Chin J of Dig 19(1):22-4, 1999

24, Zhao Kui, Shang QH. Ma SY. Gastric mucosal nitric oxide synthase activity and lipid peroxidation in Helicobacter pylori infection. Chin J Med 37(7):455-7, 1998

25, Chen MH, Pan XZ, Peng XW. Cag A gene and cellular factors in Helicobacter pylori pathogenicity. Chin J Med 37(8):547-8, 1998

26, Chen XS, Chen Qing, Xu YR. Changes of ascorbic acid, CuZnSOD and LPO in gastric juice and blood of patients with Helicobacter pylori infection. Chin J of Dig 15:339, 1995

27, Hu PJ, Mitchell HM, Li YY. Association of Helicobacter pylori with gastric cancer and observation on the detection of this bacterium in gastric cancer sites. Am J Gastroenterol 89(10):1806-10, 1994

28, Xu SP, Wang MW, You WD. Study on the association of Helicobacter pylori and human gastric cancer. Chin J of Dig 17(4):211-2, 1997

29, ZhuYQ,Yan ZX. Primary study on relation of Helicobacter

pylori infection and gastric cancer. Chin J of Dig 15(supple):23-3, 1995
30,Yan RR, Lin SR, Iie DN. Relationship between Helicobacter pylori infection and gastric cancer. Chin J of Dig 17(5):251-3, 1997
31, Mitchell HM, Hazell SL, Li YY. Serological response to specific Helicobacter pylori antigens: antibody against CagA antigen is not predictive of gastric cancer in a developing country. Am J Gastroenterol 91(9):1785-8, 1996
32, Wang QX, Shen JT. Gastric lymphoma differentiation with gastric ulcer and gastric cancer under endoscope. Chin Endoscopy 12(6):230, 1995
33, Gao Ming, Lou FD. Advance in study of mucosa-associated lymphoid tissue derived lymphoma. Chin J of Heamo 19(11):610, 1998
34, Yi ZH, Ou YQ, Li GD. Investigation of relationship between primary gastric malignant lymphoma and Helicobacter pylori infection. Chin J of Med 36(7):442, 1997
35, Shao JY, Hou JH, Lin HL. Primary study on relationship between gastric lymphoma and Helicobacter pylori infection. Chin J of Cancer 17(5):383,1998
36, Zhang Wei, LinPing, Zhang HJ. The occurrence of gastric lymphoid follicles and Helicobacter pylori infection. Chin J of Gastro and Hepato 7(3):222, 1998
37, Bai Ge,Hu FL, Zhang Hui. The relation between Helicobacter pylori infection and gastric emptying in functional dyspepsia patients. Chin J of Gastro and Hepato 7(3):239, 1998
38, A consensus on some problems of Helicobacter pylori (draft). Chin J of Intemal Med 36(7):438, 1997