

Comment

All subjects had recent infections with group A β haemolytic streptococci. The findings attributable to this particular inclusion criterion may widen our understanding of why most children with such infection escape a rheumatic attack while only a few do not. Our analyses adjusted for socioeconomic factors imply that low serum albumin concentrations and body iron stores may contribute to rheumatic fever. To rule out the possibility that differences in nutritional markers reflect differences in severity of inflammation, we adjusted for C reactive protein concentration in our analyses.

Iron deficiency might have favoured rheumatic fever by predisposing the cases to frequent infections with group A β haemolytic streptococci. The target organ lesions in patients with rheumatic fever predominantly contain T cells. We speculate that the tissue damage caused by T cell infiltration may be favoured by protein deprivation because T cell mediated immunological functions become exaggerated under mild to moderate chronic protein or protein energy deprivation.⁵ Although case-control studies have inherent limitations, our results suggest that deficiency of albumin and iron is linked to susceptibility to rheumatic fever.

The preliminary results of this work were presented at the 14th congress of rheumatology of the International League of Asso-

ciations of Rheumatologists in Singapore, 8-13 June 1997. Fouzia Hasin, Amiruzzaman Khan, Billah Khan, and Mohammad Osman helped in recruiting the subjects. MMZ is a Mombusho (Japanese ministry of education, science, sports, and culture) scholar.

Contributors: MMZ initiated and coordinated the study, formulated study hypothesis, designed the protocol, discussed core ideas, analysed data, interpreted results, and wrote the manuscript. NY initiated the study, prepared the protocol, interpreted results, and revised the manuscript. MAR revised the laboratory aspect of the protocol, collected samples, and monitored the quality of diagnostic laboratory tests. SH revised the clinical aspect of the protocol, coordinated subject recruitment, and validated clinical diagnosis. AHC executed subject recruitment, data documentation, and quality control. TN helped in data analyses and revised critically the intellectual content of the manuscript. HT critically reviewed the protocol and manuscript and approved the final version for publication.

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Conflict of interest: None.

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Biliary heavy metal concentrations in carcinoma of the gall bladder: case-control study

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Carcinoma of the gall bladder is the third most common malignancy of the gastrointestinal tract in the eastern Uttar Pradesh and western Bihar regions of India.¹ The two regions lie down stream of the river Ganges, which is the main source of drinking, bathing, and irrigation water in this part of India and receives untreated domestic sewage and industrial and agricultural effluent. High concentrations of cadmium have been reported in sewage, irrigation water, and vegetables grown in the area, and higher concentrations of heavy metals than recommended by the World Health Organisation have been reported in water from this region. Heavy metals as environmental pollutants have been implicated in human carcinogenesis.² These metals, especially cadmium, are excreted and concentrated in the hepatobiliary system.³

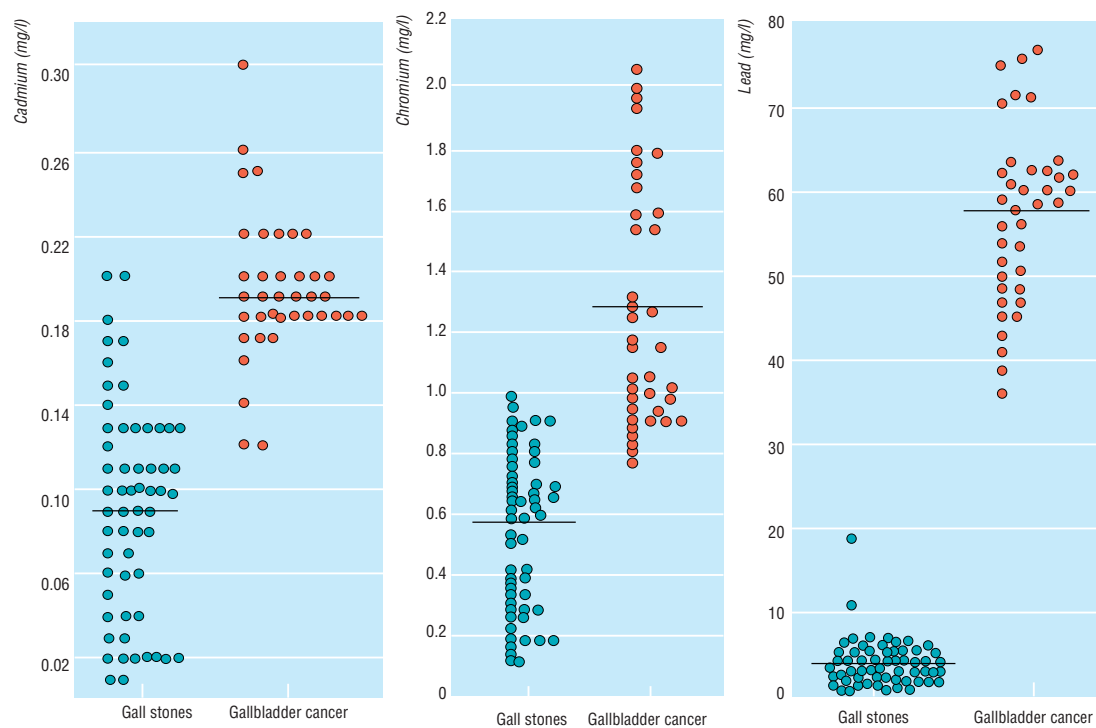
We investigated whether gallbladder cancer was associated with exposure to heavy metals and hence high biliary concentrations.

Patients, methods, and results

The study was carried out in 96 patients with gallbladder diseases admitted to the surgical unit of the University Hospital, Varanasi, from January 1995 to

March 1996. All these patients were from the same geographical area. Thirty eight patients had histologically diagnosed carcinoma of the gall bladder (mean age 53.5 years; 11 men and 27 women; 25 had associated calculi) and 58 had gall stones (control group; mean age 48.3 years; 14 men and 44 women). Bile (10 ml) was taken by needle aspiration from the gall bladder of all patients at the time of surgery for estimation of cadmium, chromium, and lead concentrations. The sample was stored at -20°C until analysed by the method described in the 1982 manual for Perkin-Elmer's model 2380 atomic absorption spectrophotometer. Student's *t* test was carried out using MSTAT software.

The figure shows that mean biliary concentrations of cadmium, chromium, and lead were significantly higher in patients with carcinoma of the gall bladder than in those with gall stones (cadmium: 0.19 (SE 0.07) mg/l *v* 0.09 (0.04) mg/l, difference 0.10 (95% confidence interval 0.08 to 0.12), $t=11.63$, $df=93.63$, $P<0.001$; chromium: 1.26 (0.06) mg/l *v* 0.55 (0.03) mg/l, difference 0.71 (0.58 to 0.84), $t=9.84$, $df=57.45$, $P<0.001$; lead: 58.38 (1.76) mg/l *v* 3.99 (0.43) mg/l, difference 54.4 (50.7 to 58.0), $t=30.07$, $df=41.43$, $P<0.001$).



Cadmium, chromium, and lead concentrations in patients with gall stones and gallbladder cancer

Comment

Carcinoma of the gall bladder continues to be a disease of uncertain aetiology, late presentation, and ineffectual treatment.¹⁻³ Various risk factors have been proposed in its pathogenesis, but none has stood the test of time.

The incidence of carcinoma of the lung, paranasal sinus, and gastrointestinal tract with exposure to chromates has been reported by Leonard.² Cadmium causes prostate cancer and increases the risk of lung cancer,⁴ and lead is carcinogenic in rats.⁵ These studies have proved heavy metals to be related to carcinogenesis, but, to our knowledge, biliary heavy metal concentrations have not been measured in patients with gallbladder cancer. Using histochemical techniques, however, we have found that the expression of metallothionein was 70% in patients with gallbladder cancer and 25% in those with gall stones. In our current study cadmium, chromium, and lead concentrations were significantly higher in carcinoma of the gall bladder than in gall stones. This can be explained by the presence of dangerously high concentrations of these metals in drinking water in this part of India. These metals are known chemical carcinogens, so the high biliary concentrations of these metals in carcinoma of the gall bladder may be a factor in this cancer.

Contributors: VKS was the principal investigator of the study project. He initiated and coordinated the formulation of the primary study hypothesis, discussed core ideas, designed the protocol, and participated in data collection, analysis, and writing the paper. AP initiated the research and participated in the study design, data collection, and analysis. BDT participated in the methodological aspect of the study and in interpreting the findings. DCSR participated in the design of the study protocol, in the interpretation of the findings, and in the statistical analysis. SS initiated and coordinated the formulation of the primary study, designed the protocol, and participated in data collection, analysis, and writing the paper. VKS is guarantor for the study.

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Endpiece

Licensed to kill

The medical establishment conducted by Mr Rawkins was situated in one of the streets which would be intersected by a line drawn from the New River Head to Clerkenwell Green; and the red bull's-eye lamp over the door formed a principal object in the thoroughfare, in the absence of any more remarkable features. It was essentially a doctor's shop, and might have been mistaken by thoughtless pedestrians for a mere chemist's or druggist's, had not the framed diploma of the Apothecaries' Company, ostentatiously displayed in the window, borne testimony to the proper graduation of the owner; being, in fact, a licence to kill human game by powder and ball in the shape of calomel and bolus, which every person regularly qualified for that art must possess."

Albert Smith, *The Adventures of Mr. Ledbury and his Friend Jack Johnson (1844)*

Submitted by Jeff Aronson, clinical pharmacologist, Oxford