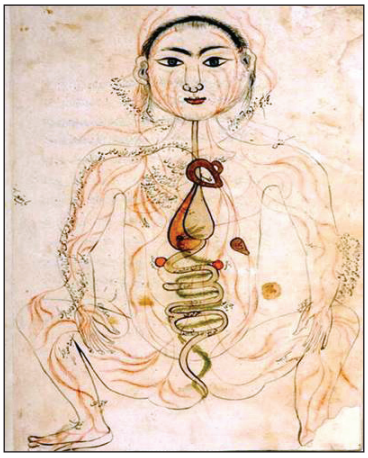
Reply

We are grateful to Dr. Haddad for his valuable and interesting comments. Regarding the cover plate, we obtained it from an article on a website on the Internet. The website is entitled MuslimHeritage.com (*http://www.muslimheritage.com/*



topics/default.cfm?ArticleID=209). The article is entitled "Who discovered pulmonary circulation: Ibn Al-Nafis or Harvey?".

The author of that brief report, Dr. Ibrahim Shaikh did not specify the source of the illustration. Similar illustrations are found in a Google image search such as this image taken from the 17th-18th century illustrated manuscript of *The Anatomy of the Human Body* by Mansur ibn Ilyas. Dr. Haddad's expertise on the subject, since he owns several original copies of the anatomical charts, has shed some light on this aspect of Islamic medical history. We hope that he can publish these charts with his comments about their origin in the *Annals of Saudi Medicine* or other medical journals for the benefit of the readers.

Regarding our article on Ibn Al Nafis, we appreciate Dr. Haddad's detailed explanation of origin of the name of the town where Ibn Al Nafis was born. We had our data obtained from the references cited in the article.

We apologize for not citing properly the name of Dr. Sami Ibrahim Haddad (1890-1975) in reference number 9. Dr. Haddad was professor of surgery and urology, and then Dean of the School of Medicine at the American University of Beirut. He was a prolific writer and historian, and wrote 99 articles on a variety of surgical, urological, and historical subjects. His contributions to the history of Arabic and Islamic medicine are well known, including his book "*The Contributions of the Arabs to the Medical Sciences*" which was published in 1936.

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Seasonal variation of appendicitis in northern Saudi Arabia

To the Editor: We have noted apparent discrepancies in the monthly number of appendectomies performed in our hospitals, which we decided to verify. Retrospectively, we analyzed all cases operated on with a discharge diagnosis of acute appendicitis in Hail General Hospital (HGH) and King Khalid Hospital (KKH), Hail, Saudi Arabia, from January 2000 to December 2006. These two hospitals treat nearly all cases of appendicitis in this city. Negative appendectomies and cases with intra-operative findings of other pathology with similar clinical features as acute appendicitis were excluded. A total of 3159 cases met our inclusion criteria comprising of 1629 and 1530 cases from HGH and KKH, respectively. We used the chi-square statistic for analysis with probability less than 5% set for statistical significance.

We observed a low in the number of appendectomies in the winter months of December to February and a high in the spring months of March to May (Figure 1). These differences proved to be significant ($P<.001$). Our finding agrees with published reports from the USA,[1] Canada,[2] Italy,[3] Israel[4] and Russia[5] where appendicitis had a peak incidence in the summer months with a winter nadir. The reason for these trends has been the subject of conjecture. While many believe that the etiology of acute appendicitis is multi-factorial,[5] none have been able to show conclusively its precise etiology. Gender and ethnic trends have been observed[1,2,6] and offered as proof the role of genetic factors. Diet, hygiene, the climate and infective agents,[7] on the other hand, have been proposed as environmental factors that may play roles in the etiology of acute appendicitis.

The increase in incidence of acute appendicitis in the spring months in our locality coincides with the onset of the sandstorm season in the Arabian peninsula, characterized by strong winds blowing across the desert bringing dust that hangs in the air. We are inclined to believe that the weather change has something to do with our observation. Our hypothesis has found credence in the work of Kwasi et al[8-10] who have studied the health impact of this climatic phenomenon in the city of Riyadh. They amply demonstrated the strong pathogenic potential of date palm pollen as an allergen and isolated viable microbial pathogens and pollen allergens in sandstorms.[11] Further support for our hypothesis comes in the recent paper by Bellester et al,[12] who found a significant association

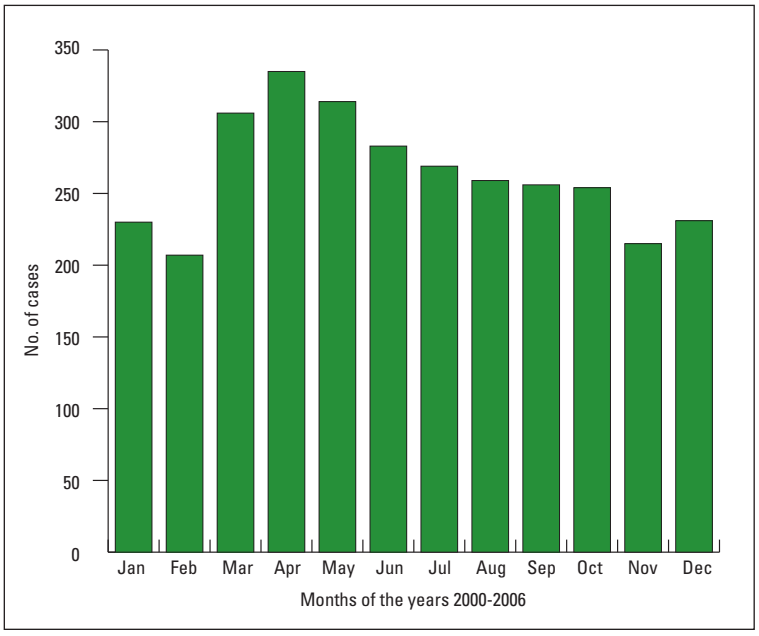

Figure 1. Bar diagrams showing the combined monthly number of cases of appendicitis Hail General Hospital and King Khalid Hospital, Hail from 2000 to 2006 inclusive.

between tonsillectomy and appendectomy among Spanish patients.

We suggest that the intense challenge to the mucosa-associated lymphoid tissue from allergens, bacteria and viruses, as occurs during the sandstorm season, may be causally related to acute appendicitis and would explain the seasonal variation we have noted. By implication we expect that preventive strategies and adequate treatment of respiratory tract infections and allergies affecting the airway among children should prevent some cases of acute appendicitis.

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The cardiovascular risks of etoricoxib (*Arcoxia*)

The selective COX-2 nonsteroidal anti-inflammatory drug etoricoxib (*Arcoxia*) was approved in Saudi Arabia in 2003 and re-registered in February 2007. The drug is now available in 63 countries worldwide. In April 2007, a U.S. Food and Drug Administration (FDA) advisory committee voted 20 to 1 not to recommend the approval of etoricoxib based on the drug's cardiovascular (CV) risks and its association with an exacerbation of hypertension.[1] All information discussed by FDA advisory committees must be made available to the public before meetings. The advisory committee discussion documents, known as briefing documents, for the etoricoxib meeting can be found on the FDA's Web site at: *http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4290b1-01-FDA.pdf*. Data presented at the committee meeting did not exclude the possibility of an over six-fold increase in CV risk with etoricoxib compared to naproxen.[2] The original marketing application for etoricoxib was filed with the FDA in October 2001. In March 2002, the drug's manufacturer withdrew the application to allow for the submission of additional data. The marketing application was again delayed in June 2002 when the FDA asked for additional acute pain efficacy and CV risk safety data. The FDA issued an approvable letter in October 2004 asking for additional safety and efficacy data before making a final decision on the drug's marketing application.

In February 2005, two years prior to the approval of etoricoxib in Saudi Arabia, the FDA convened a meeting to review the safety of the COX-2 drugs, including etoricoxib. In the briefing documents for this meeting was an FDA safety review of etoricoxib and an analysis of the Etoricoxib vs. Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) trial.[3] The EDGE results were originally presented at the American College of Rheumatology meeting in October 2004. The media reported that etoricoxib showed a significantly better gastrointestinal safety profile than diclofenac and no CV risk signal.[4] The EDGE trial[5] was not published until February 2007, at the same time the drug was re-registered in Saudi Arabia and over 28 months after public release of the results at the ACR meeting in October 2004.

The briefing documents for the February 2005 advisory committee meeting suggested that the drug does not offer a unique therapeutic advantage over existing drugs used for the treatment of osteoarthritis and may be associated with a significantly greater risk of CV adverse events compared to other agents.[3] The question must be raised, if the February 2005 briefing documents were accessed by the Saudi Arabian drug regulatory authorities during the 2007 re-registration review of etoricoxib, would the drug have remained on the market in Saudi Arabia?

In summary, FDA briefing documents may contain rigorous analyses of unpublished data or data whose publication was delayed. These documents would appear to be important in the drug approval and re-registration processes in countries with evolving drug regulatory authorities or limited resources to commit to the drug approval process.

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CA-125: a marker for diagnosis and follow-up of pleuroperitoneal and lymph node tuberculosis

To the Editor: We present a case of pleuroperitoneal and lymph node tuberculosis (TB) whose clinical, radiological, and laboratory data could have been easily mistaken for advanced ovarian carcinoma, and then subjected to unnecessary laparotomy and surgical resections with severe consequences. Our case, a 45-year-old female, had ascites, extensive lymph adenopathy, bilateral ovarian cysts, and pleural effusion (Figures 1, 2). Biopsy of an accessible cervical lymph node revealed caseous lymphadenitis (Figure 3). With antitubercular treatment, CA-125 levels of 531 mIU/L declined to 36 mIU/L in parallel with clinical and radiological improvement (Figure 4).

CA-125 is a glycoprotein of high molecular weight, which is detected by the monoclonal antibody OC125, first described by Bast et al in 1981.[1] CA-125 is elevated in a variety of malignant and benign conditions,[2,3] but its main clinical application is limited to diagnosis and follow-up of ovarian cancer in which only 50% of stage 1 but 80% to 85% of advanced stages have elevated CA-125.[4] The titer has been used to differentiate between benign and malignant conditions,[5] but very high levels (>1000 mIU/L) have been reported in benign conditions such as massive pleural

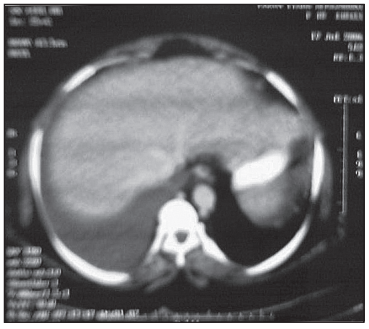

Figure 1. Abdominal CT scan showing ascites.

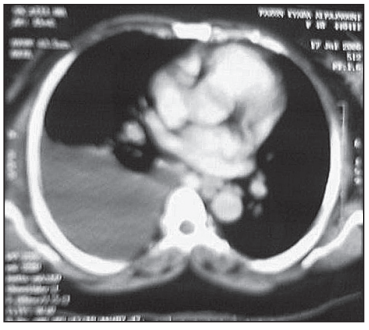

Figure 2. CT scan showing tuberculous pleural effusion before treatment.

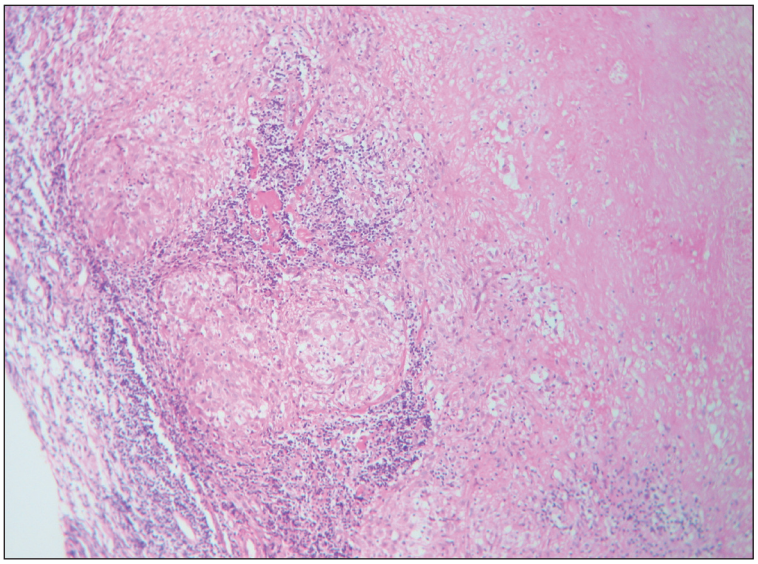

Figure 3. Low-power photomicrograph showing tubercular lymphadenitis.

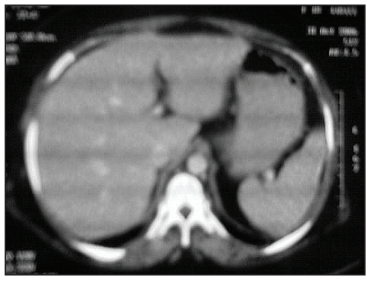

Figure 4. CT scan showing resolved ascites after treatment.

effusion, ascites, and chronic liver disease.[6] Elevation of CA-125 in peritoneal tuberculosis (TB) has been reported and misinterpreted as disseminated ovarian malignancy.[7] A decline of CA-125 with antitubercular drug therapy has paralleled clinical improvement, and has been advocated as a marker in the follow-up of response to treatment.[8,9]

Although false positivity with CA-125 is high and specificity and sensitivity are poor,[10] elevated levels in a clinical setting of ovarian carcinoma must be taken with caution to avoid unnecessary laparotomies and even extensive surgical resection of pelvic masses.[11,12] Thus, it is evident from our case that not only can an elevated CA-125 level be useful in considering the presence of a non-malignant condition like TB, especially in our part of the world, but can also be used as a marker for response to treatment and an indicator of the activity of a disease like TB.[11]

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Impact of urbanization on the prevalence and pattern of arterial hypertension on the island of Socotra

To the Editor: We performed a survey on the awareness, prevalence, and control of hypertension in the island of Socotra, Yemen, which has been isolated biologically for several million years.[1] The island lies at the entrance to the Gulf of Aden, approximately 340 kilometers from the coast of the Yemeni mainland, and 250 kilometers off the Somali coast. Isolated from the rest of the world, the people of Socotra are in many ways virtually living in an earlier time. Most Socotris live without running water, electricity or health care, and are much poorer and less developed than people of the mainland of Yemen.

The main part of the Socotri population living in the mountain and rural areas are semi-nomadic pastoralists, living from goats, sheep,

cattle, camel breeding and date palm cultivation. Some of them inhabit caves during several months of the year. Most people live in the coastal plains, where fishing from small boats is the main source of income. A few thousand live in the capital Hadibo, where life has already become more commercially oriented and a considerable number of people are employed in government jobs or are involved in small scale trade, building and manufacturing for local demands. Medical services are not more than very basic. The only hospital in Hadibo is still poor in facilities and services, and even essential drugs are not available. Until recently, most Socotris had almost no contact with other cultures. Nonetheless, development pressures exist on Socotra and have begun to threaten the fragile balance between the Socotris and their environment after centuries of virtual isolation. Our aim was to estimate the impact of rapid economic transition and early urbanization on the prevalence and pattern of arterial hypertension.

In our survey, arterial blood pressure was measured in 413 persons living in 53 small mountain/rural villages reached by a mobile clinic, in 166 persons living in the coastal villages, and in 415 patients seeking medical care for any disease at the outpatient clinic of the Hadibo Hospital and in persons accompanying the patients during a 2-month period. More than 70% had never had their measured blood pressure before. More subjects in Hadibo (42.4%) reported having a previous blood pressure measurement as compared to coastal villages (36.9%) and rural/mountain villages (16.5%) ($P<.001$).

The age-adjusted prevalence of hypertension was 17.2% in males and 24% in females. The prevalence of hypertension was higher in people living in Hadibo (28.9%), as compared to those in the coastal (21.1%) and mountain/rural villages (16.1%) ($P<.001$). Major differences in habitual physical activity and dietary habits may contribute significantly to the urban-rural-pastoral variations in hypertension. In the mountain villages, most people are semi-nomadic and physically very active, while in the coastal settlements and particularly in Hadibo they tend to be sedentary and mainly engaged in small trades. Three major dietary patterns were identified. The "rural/mountain pattern", which was characterized by goat meat, rice, and milk, the "coastal pattern," which was heavily weighted on fish, rice, dates and beans, and the "urban pattern" consisting of meat, fish, rice, eggs, bread, some vegetables and fruit, and an increasing variety and amount of high-calorie imported and processed food. One further explanation for the higher prevalence of hypertension in Hadibo could be qat chewing, a traditional practice in mainland Yemen, which is now becoming popular in the social life of the larger coastal settlements of Socotra. It has been shown that chewing fresh qat leaves may have sympathicomimetic effects and, therefore, induce a short term increase in blood pressure.[2,3]

Among hypertensive subjects, only 36.2% were aware of their condition. The treatment rate of hypertension was 30.6%, and only 27% of hypertensive subjects achieved target blood pressure values under 140/90 mm Hg. Underprescription, poor compliance to medication and unaffordable drug prices appear to be the major causes for undertreatment of hypertension in Socotra. The most commonly used antihypertensive drugs taken as mono- or combination therapy were angiotensin-converting enzyme-inhibitors (enalapril, captopril) in 42%, diuretics (furosemide, hydrochlorothiazide, spironolactone) in 40.4%, and beta-blockers (atenolol, propanolol) in 17%, despite recommendations to use less expensive hydrochlorothiazide and beta-blockers as the first treatment of choice.[4]

Overall, 21.1% of the adult population had hypertension, suggesting that high blood pressure, once rare, is rapidly becoming a major public health burden as a result of rapid behavioral and social changes in the island. In our study, we found significantly lower levels of hypertension in the very isolated rural/mountain settlements than in coastal and recently urbanized communities. We conclude that despite the isolation and under urbanization of Socotra, hypertension is prevalent, poorly controlled and is becoming an important health issue.

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