Radiofrequency sinus excision. *A simple technique for sacro-coccygeal pilonidal sinus disease*

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Radical excision has still been the most widely practiced surgical procedure for the treatment of pilonidal disease.[1] The entire sinus is excised with the surrounding tissue down to the post sacral fascia. The defect may be left open to granulate, or is closed by primary suturing or with some form of flap. Healing by secondary intention takes long period and needs regular dressing and meticulous wound care coupled with control of hair growth through regular shaving of the natal cleft.

Lord and Millar[2] described excision of midline epithelial follicles under local anesthesia and thereafter passing a small brush in the tract to remove hairs within the granulation lined tract. Following Lord and Millar's[2] technique, we modified it by excising the complete tract instead of brushing it, and left the wound open for healing by secondary intention. A radiofrequency device was use to carry out the entire surgical procedure.

An Ellman dual frequency radiofrequency generator (Ellman International, Oceanside, New York, United States of America) was used for this purpose. The unit is supplied with a handle to which different electrodes could be attached to suit the requirement of the surgical procedure. For the procedure of sinus excision, we use a needle electrode to incise the tract, a loop electrode to reshape the wound edges, and a ball electrode to coagulate the bleeding points.

The radiofrequency sinus excision procedure is performed making the patient lie in a left lateral position. The sinus openings are identified and methylene blue mixed with hydrogen peroxide is instilled in one of the sinuses. This maneuver, while delineating the sinus tract and its branches, also helps in removing blockages created by cell debris and granulation, thereby facilitating opening of the tracts. A director probe is then inserted in the sinus opening and using a fine needle electrode, the skin and subcutaneous tissue are incised. The bleeding points are coagulated with the ball electrode. The dissection is limited proximal to the post-sacral fascia. The tracts are recognized as a rigid, blue tissue. All the tracts are traced and removed. This obviates the need to brush or curette the remaining tracts and infected tissues. The edges of the wound finally created are reshaped with the round loop electrode to make the wound wide externally and narrow in the depth. The wound is secured with an adhesive dressing.

Table 1 - Results after radiofrequency sinus excision.

Events	Observation	
	mean	range
Operation time in minutes	10	(8-14)
Period of hospitalization in hours	10	(8-18)
Period off work in days	8	(7-12)
Total n of analgesic tablets consumed	15	(11-19)
Wound healing period in days	49	(40-63)

Postoperative care. Patients are encouraged to mobilize immediately after surgery. No antibiotics are prescribed. Patients are prescribed tablet containing serratiopeptidase 10 mg and diclofenac sodium 50 mg twice in a day until they felt pain. After discharge, the patients are asked to wash the wound twice a day with soap and warm water and to apply a protective dressing over the wound. They are called in the office at a weekly interval until their wounds are healed. The outcome of the procedure is described in **Table 1.**

Contrary to Lord and Millar's[2] technique, radiofrequency sinus excision takes a wider skin incision and creates a funnel shaped wound with removal of the overlying skin. With this maneuver, there is hardly any chance of leaving behind any inflammatory tissue or part of the sinus tract behind. This also prevents forming a dead space under the skin in the early postoperative period, particularly when the buttocks come closer.

Radiofrequency has been shown to achieve sealing of the sensory nerve endings and the leaking lymphatics,[3] the 2 factors, which are supposed to cause postoperative pain and edema. After wide excision, a large wound is created and the wound and its edges become a source of constant pain. Due to minimal pain and insignificant discomfort from a smaller wound, the patients operated with radiofrequency need lesser quantity of analgesics.

The patients operated by radiofrequency technique were able to join their duties at the mean of 8 days. Negligible pain, comfort in performing routine activity and absence of any specific wound care encouraged the patients to resume duties early.

The high frequency radio waves has a property of sealing small blood vessels while dissecting the tissues without creating any char, whereas the cautery or electrosurgical instruments create heat at

the tip of the instruments, which is transferred to the tissues creating a temperature far exceeding the therapeutic need.[4] This invariably results in burning of the adjacent healthy tissues and cause more pain and delay in wound healing.

Different malleable electrodes are available with the radiofrequency device that could be selected to suit the requirements of sinus excision like incision, shaping of the wound edges and coagulation of bleeding points.

The wounds created with radiofrequency healed in a short span of time. This was possible due to a small wound created by radiofrequency and with a minimum lateral damage. No wound related complications like secondary infection and non-healing were observed with this procedure.

While the radiofrequency sinus excision procedure can be performed as a day care surgery, longer duration of hospital stay and greater consumption of inpatient hospital resources are required with the wide local excision and primary closure or flap techniques.[5] This is another factor which should be taken into consideration while choosing one of these surgical procedures for pilonidal sinus disease.

In conclusion, sinus excision with radiofrequency is a simple and swift procedure. It needs a short hospital stay and is associated with less postoperative pain and early resumption to work. Based on our initial experience, it can be concluded that this procedure has a place worth notice in the treatment of pilonidal sinus disease.

Received 30th January 2005. Accepted for publication in final form 13th April 2005.

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Evaluation of palliative management of advanced breast cancer in Khartoum, Sudan

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Palliative management and quality of life for patients with advanced disease received little attention from the medical community in most of the developing countries.

Breast cancer is the most common female malignancy in Sudan with a rising incidence from 21.9% (1954-1961) to 42% (1981-1984) of all female malignancies.[1,2] Recent data from the Radiation and Isotope Center, Khartoum records showed an incidence of 23% and 35% for the years 2002 and 2003. The relative frequencies for stage 3 and stage 4 were 34% and 10% as reported by ElNaeem[2] where palliation is the main objective approach. Palliative care is a rapidly advancing branch of medicine as adopted by World Health Organization and is defined as active, total care of a person whose condition is not responsive to curative treatment.[3]

The objective of this work is to study the efficacy of different palliative procedures used for symptoms control, degree of patient satisfaction with treatment and quality of life.

This is a prospective study enrolling patients with breast cancer stage IV (T4 tumors) according to tumor, node, metastases (TNM) classification. Patients were interviewed in 2 main hospitals in Khartoum during a 6 months period of the study. Patients were interviewed one month following completion of therapy. The study objectives were explained to the patient and verbal consent was obtained. Data on patient presentation, palliative measures used and outcome were all collected.

Quality of life (QL) was measured using domains adopted by the European Organization for Research and Treatment of Cancer.[4] This includes physical, functional, social and psychological aspects, body image, sexual enjoyment, symptom control and financial aspects.

All these aspects were assessed during the interview. To measure functional aspect of QL, a universal index (KI) was used[5] before and 4 weeks following palliation. A KI score ranged between normal, which is rated 10 to moribund rated 1. Patients scoring 7 or less are classified as having poor QL. Ninety patients with advanced breast cancer were studied. The mean age was 47 ± 13 years, the youngest being 24 and the oldest 75 years. Thirty six percent of patients were between the age of 31-40 years and 37% between 41-60 years. There

were 3 male patients (3.3%). Sixty five percent of patients came from rural areas (n=59). Educational and financial status showed 82% illiteracy (n=74) and 58% low financial state, namely, seeking support for treatment.

Locally advanced breast cancer (LABC) was diagnosed in 49 patients (54.4%) with skin tethering in 77%, fungation and ulceration in 63%, chest wall infiltration in 26% and offensive odor in 16%. Metastatic breast cancer was diagnosed in 59 patients (65.6%), affecting bones in 60% of patients, mainly the spine, the pleura in 23%, supraclavicular nodes in 12%, lungs in 10%, liver in 7% and brain in 5%. In 20% of the patients, both local and metastatic disease exists. Of the 49 patients with LABC 38 underwent palliative surgery, toilet mastectomy in 21 patients and simple mastectomy in 17 patients, the remaining 11 patients had chemotherapy. Overall, a form of mastectomy was carried out in 74 patients (82%), hormonal therapy was given to 72 (80%), chemotherapy to 67 (74%) and radiotherapy to 67 patients (75%).

Among the 67 patients who received chemotherapy, 43 (64%) had the cyclophosphamide, methotrexate, 5-fluorouracil combination while 20 patients (29.9%) received the doxorubicin containing regimen and taxol in 4 patients. The most common side effects were gastrointestinal disturbances in 44 patients (65%) followed by alopecia in 27 (40.3%) and bone marrow depression in 11 (16.4%). Massive lymphoedema occurred in 6 patients, in 3 patients it was associated with recurrence and in 5 patients it followed a combination of surgery and radiotherapy.

Pain relief was complete in 15 patients (26.3%), partial in 33 patients (57.9%) using non-steroidal anti-inflammatory analgesics. Good pain control could be achieved in 19 out of 34 patients with bone metastasis (63%) and partial in 30%. Four patients had pathological fractures and were bed ridden and hence, were treated conservatively with analgesia.

Malignant pleural effusion was symptomatic in 10 out of 13 patients. They were treated with aspiration and pleurodesis using oxytetracycline 1 gm and bleomycin 30 mg intrapleural injection. Good control was achieved in 4 patients, partial in 3 and no response in 3 patients. Six patients with nodular lung metastasis were asymptomatic, with only 2 who developed late mild cough. Three patients had brain metastasis presenting as convulsions in 2 patients and one with paraplegia and blindness. They were treated with steroids and 2 had brain radiotherapy, only convulsions responded to treatment.

Liver metastasis were seen in 10 patients, it was symptomatic in 6. Using the KI to assess QL in all 90 patients, the average was 6.88 (SD 1.8) initially and rose to 7.2 (SD 1.8) following palliation.

A co-patient was always present with all patients, being a sister or a daughter in 50% of patients. Mood disturbance was quiet frequent, depression was diagnosed in 32 (34%), anxiety in 24 (26%) and psychosis in 2 patients (2.2%). Fifty percent of patients know the nature of their disease while the rest do not or deny that. Mood disturbances were significantly more common on those patients who knew the diagnosis compared to the others 26 patients versus 8 ($p<0.0007$).

Other aspects assessed and found satisfactory were, adequate sleep in 73%, normal mobility in 60%, good appetite in 62%, normal social interaction in 26% and partial in 58%.

The mastectomy was accepted by 80% of patients, however, 48% of patients were concerned with the body image and asked for cosmetic substitute. Twenty percent of patients had psycho-sexual concerns.

The time doctors spent with the patient was considered adequate by 79% (n=71) and was short and not satisfactory by 21% (n=19). Eighty two percent of patients reported that the doctor discussed all problems with them (n=74).

In general, the patients satisfaction with management was good in 67.7% (n=62 patients), partial in 25.6% (n=23 patients) and bad in 4.4% (n=4 patients). Affection of young age group with aggressive malignancy is a feature in this study, 36% of the patients were between the age of 31 and 40 years. Late presentation of patients in this study is due to a combination of factors, namely rural residence, illiteracy and financial difficulties. The presence of only fully equipped radio-isotope center located in the capital to serve all the country adds to this problem with delayed appointment for treatment. It is very taxing for patients to stay for treatment. Some patients stop treatment prematurely due to financial difficulties. Others discontinue chemotherapy due to the side effects of gastrointestinal disturbances (65%) and alopecia (40%).

Surgical treatment in form of simple or toilet mastectomy is offered early as it is cheaper and quick to treat fungating and ulcerating tumors. This is often used in combination with chemotherapy, which was given in 70% of cases despite being a rather expensive modality. Hormonal treatment in the form of tamoxifen was given in 80% of patients. It is highly recommended that a combination therapy of all modalities, starting with surgery or preoperative chemotherapy be offered, as it was reported to confer palliation to over 80% of patients with LABC.

Osseous metastasis have a better outcome than visceral ones. Patients with osseous metastasis survive longer reaching 4 years while those with visceral metastasis live 6-2 months.[6] Pain relief and

patient satisfaction with radiotherapy for bone metastasis occurred in 63% of patients. The 4 patients with pathological fractures in this study were treated conservatively as their general condition was not satisfactory. It is advisable to perform internal fixation in those patients as it offers a better palliation. Pulmonary metastasis is mostly asymptomatic, however surgical removal is advised in solitary metastasis with good outcome if the lesion is less than 3 cm in diameter. Both hepatic and brain involvement indicate advanced stage of the disease and resection is reserved in selected isolated secondary with satisfactory outcome. The development of lymphoedema is a great handicap to the patient and very little can be carried out to help those patients as seen in this study. It is known that the incidence of lymphoedema is greatly increased when combined surgery and radiotherapy used in the axilla .

Mastectomy is being accepted by educated patients more than by illiterate. The concern of patients on keeping their breast is obvious, however with careful explanation, 80% of patients in this study were satisfied. However, despite the advanced nature of the disease, still 50% preferred to have a form of mammoplasty. The source of emotional support in this study was a sister or a daughter in 50% of cases, while the spouse was only 12%. The well kept strong extended familial bonds have a great impact in patient support. This does not apply to short term but in the long term psychological support which is important as some patients experience late effects. A more organized approach is needed to follow those patients and ensure the continuing social support. Patients who admit ignorance regarding the nature of the disease reported a significantly better mood. It is a common practice among the health professionals in our society not to mention the exact diagnosis as far as the patient is willing to accept all treatment options.

Still one third of our patients experienced depression and a quarter had anxiety. Age and level of education are important parameters as younger patients report more physical, psychological and information needs. The patient-doctor relationship is an important factor in alleviation of anxiety and long term interaction. Both duration of the consultation and allowing the patient to speak at ease are important factors

In conclusion, advanced breast cancer needs to be addressed as an entity with its special problems in developing countries. Palliation is inadequate and the majority of patients in this study moved from the poor zone but not reaching the good QL level with pain being under-treated. The concept of QL needs to be addressed and may need to be modified to suit the different cultural backgrounds.

Received 30th January 2005. Accepted for publication in final form 20th April 2005.

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Effect of oral mecobalamin treatment on chest pain in patients with cobalamin deficiency and no evidence of coronary artery disease. *A randomized, placebo-controlled trial*

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Chest pain is a common presenting complaint in the cardiology clinic. Many patients with this complaint have normal cardiac investigations, including normal treadmill test or coronary angiogram. Although these patients have a good prognosis, they continue to have recurrent episodes of chest pain that result in further hospital admission and investigations.[1] Vitamin B12 is a cofactor in multiple metabolic pathways including the conversion of methylmalonyl CoA to succinyl CoA.[2] The lack of adenosylcobalamin may lead to accumulation of methylmalonyl CoA, causing a

decrease in normal myelin synthesis and leading to incorporation of abnormal fatty acids into neuronal lipids. The abnormal myelination may lead to the neuropsychiatric complications associated with cobalamin deficiency and may lead to pains in various areas including chest pain. In addition, vitamin B12 has been used successfully for the treatment of some types of pain, such as neuropathic pain and back pain due to nerve compression. Our aim was to investigate whether mecobalamin supplements improves chest pain in patients with cobalamin deficiency, but otherwise normal cardiac tests.

Between August 2003 and June 2004 eighteen patients were enrolled in the study at the cardiology outpatient clinic of Jordan University Hospital, Amman, Jordan. These patients had either normal heart catheterization or treadmill test and serum B12 level less than 180 pmol/L using microparticle enzyme immunoassay method, (Abbot IMx, Abbot Diagnostics). Patients were screened for any major abnormality related to cobalamin deficiency by doing complete blood count and neuropsychiatry evaluation. Patients with low hemoglobin or elevated mean corpuscular volume or abnormal neuropsychiatric findings were excluded from the study. Patients were randomized using a computer generated random number into either mecobalamin or placebo groups. Written informed consents were obtained from all the participants, and the study was approved by the ethical committee of Jordan University Hospital.

All participants were treated with daily oral supplements of 1500 microgram of mecobalamin (The Jordanian Pharmaceutical Manufacturing Co., Naor, Jordan) or a matching placebo for 3 months in a blinded fashion. We collected demographic and clinical data and B12 levels at baseline and after 3 months.

Chi-square analysis was performed on dichotomous variables and t-test on continuous variables. A $p<0.05$ was considered statistically significant.

As shown in **Table 1**, the clinical characteristics and laboratory values of the mecobalamin and placebo group did not differ significantly. One patient was lost to follow up. There was no statistical difference in chest pain improvement at 3 months follow-up, although the trend favored oral B12 supplements ($p=0.26$). There was no significant difference at baseline in the B12 level between the active (108 ± 21.6 pmol/L) and placebo treatment (116 ± 59.2 pmol/L) groups. At 3 months follow up, B12 levels were checked in 8 patients and increased significantly in the active treatment group to 434.4 ± 254.6 pmol/L ($p=0.001$), but not the placebo group (162.3 ± 104 pmol/L). All the patients who received mecobalamin had normal values at 3 months, but only one out of 3 patients in the placebo group level increased to normal. This patient had improvement in his chest pain, while the other 2 patients did not have any significant improvement in their symptoms.

Table 1 - Clinical characteristics of the study population.

Characteristics	B12 n=10 (%)	Placebo n=7 (%)
Males	8 (80)	5 (71.5)
Age (years)	40.2 ± 7.1	46.4 ± 5.2
Normal treadmill	4 (40)	3 (42.9)
Normal coronary angiogram	6 (60)	4 (57.2)
Associated palpitations	5 (50)	4 (57.2)
Associated shortness of breath	6 (60)	4 (57.2)
Hypertension	4 (40)	4 (57.2)
Diabetes mellitus	0	1 (14.3)
Use of H2 blockers	4 (40)	3 (42.9)
Use of proton pump inhibitors	4 (40)	3 (42.9)
Non smokers	4 (40)	3 (42.9)
Ex-smokers	2 (20)	1 (14.3)
Smokers	4 (40)	3 (42.9)
Hemoglobin level (g per deciliter)	13.6 ± 1.2	12.9 ± 1.4

This trial compared the effects of oral mecobalamin supplements to placebo on chest pain improvement in patients with no coronary disease. There was no statistical difference between the 2 groups. A large proportion of the patient had improvement in their symptoms, with 70% in the treatment group and 43% in the placebo group reporting improvement. With such an improvement in the placebo group, a positive effect of treatment is difficult to demonstrate, and if present requires a much larger study. This is particularly the case when the treatment is a vitamin that can be supplemented with increased dietary intake. Although this is a blinded study, the effect of the awareness by the patient of their cobalamin deficiency cannot be overlooked, as patients tend to increase their dietary intake of food containing this vitamin. In this study, one of the 3 patients in the placebo group who had his B12 checked, had an increase in his B12 level associated with improvement in his chest pain. The other 2 patients who still continued to have low levels of B12 did not have improvement in their symptoms. However, not all the patients in the active treatment group had improvement in their symptoms. This may be related to other etiological factors causing chest pain. The differential diagnosis of chest pain is wide and includes in addition to cardiac, musculoskeletal, psychiatric, pulmonary, and gastrointestinal etiologies. Reassurance that cardiac tests are normal may be useful, and in patients who continue to have

chest pain, further tests may be performed according to the clinical condition.

Cobalamin deficiency may be an incidental finding in relation to the chest pain. However, its treatment may still be warranted since oral supplements are easy to administer and its deficiency can potentially lead to multiple clinical problems. The absorption of vitamin B12 is a complex process and involves multiple steps. This starts by adequate intake, followed by the secretion of the intrinsic factor from the stomach, which binds to vitamin B12, to finally successful absorption of the intrinsic factor and vitamin B12 complex in the terminal ileum. The daily requirement in healthy patients is estimated at 2 microgram.[3] Giving very large doses, as was carried out in this trial, is useful as studies have shown that a small percentage of vitamin B12, estimated at approximately 1% is absorbed directly from the intestine by passive diffusion without binding to the intrinsic factor.[4] The traditional treatment of cobalamin deficiency is with parenteral administration of B12 supplements. This is a life long treatment, and compliance tends therefore, to be poor. However, the administration of oral supplements is an easier option that may be accepted more by the patients.

In this study, 80% of the patients were on acid suppression therapy prior to enrollment. Acid suppression therapy may be warranted as an empirical treatment for chest or epigastric pain in patients who have atypical cardiac pain. However, this treatment has been associated with B12 deficiency, and screening for B12 deficiency should be considered in these patients.[5] Oral mecobalamin treatment resulted in significant elevation of B12 level, reaching normal values in all the treated patients as compared to only 33% in the placebo group. Therefore, oral mecobalamin treatment is effective in elevating B12 level. However, we would recommend rechecking B12 levels after a few months to ensure that the level has risen adequately, as there may be some patients who do not respond to oral supplements or who may not be compliant with the treatment. A future study with a larger number of patients may be helpful in conclusively defining the role of vitamin B12 supplements in patients with B12 deficiency and chest pain.

Acknowledgments. This study was supported by a grant from the University of Jordan, and by The Jordanian Pharmaceutical Manufacturing Co. who supplied placebo tablets identical to mecobalamin.

Received 9th January 2005. Accepted for publication in final form 19th March 2005.

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Arginine, omega-3 fatty acids and nucleotide-enriched diet augment the anti-inflammatory effect of diclofenac on carrageenan-induced rat paw edema

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Rheumatoid arthritis is a chronic inflammatory disease of the joints characterized by progressive erosive synovitis, infiltration of activated lymphocytes and macrophages into the synovium and production of cytokines. Diclofenac [(2,6-dichlorophenyl) amino, phenylacetate], is a a non-steroidal anti-inflammatory drug (NSAID). The anti-inflammatory action is due to inhibition of prostaglandin production.[1] Diclofenac is commonly used in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis due to its anti-inflammatory and anti-analgesic effect.[1,2] Furthermore, diclofenac affect polymorphonuclear leukocytes function in-vitro, therefore reducing chemotaxis, superoxide radical production and neutral protease production.[3] In addition, diclofenac is known for its anti-inflammatory effect in animal models including paw edema induced by mustard, kaolin and carrageenan.[1,2]

Nutritional support after injury may modulate the immune, inflammatory and metabolic responses,

Table 1 - Anti-inflammatory effect of diclofenac (1, 2.5 and 5 mg/kg) and diclofenac combined with arginine, omega-3 fatty acids and nucleotide-enriched feeding on carrageenan-induced rat paw edema.

Treatment			Paw edema volume in ml (% change)					
	Dose (mg/kg)		3	(%)	6	(%)	24	(%)
Control			0.73 ± 0.02		0.89 ± 0.04		1.2 ± 0.06	
Diclofenac	1		0.74 ± 0.02	(+1.3)	0.79 ± 0.03*	(-11)	0.78 ± 0.03*	(-30)
Diclofenac	2.5		0.71 ± 0.04	(-2.7)	0.75 ± 0.01*	(-15.7)	0.76 ± 0.05*	(-32)
Diclofenac	5		0.69 ± 0.02	(-5.4)	0.44 ± 0.04*	(-50.5)	0.49 ± 0.02*	(-56)
Diclofenac								
Enriched diet	1	+	0.71 ± 0.04	(-2.7)	0.68 ± 0.02*†	(-23.5)	0.62 ± 0.03*†	(-45)
Enriched diet	2.5	+	0.65 ± 0.02*‡	(-11)	0.64 ± 0.05*‡	(-28)	0.60 ± 0.03*‡	(-46)
Enriched diet	5	+	0.60 ± 0.03*‡‡	(-18)	0.32 ± 0.04*‡‡	(-64)	0.25 ± 0.02*‡‡	(-77)

Values are expressed as mean ± SD for n=10, $p<0.01$, The results were analyzed by ANOVA followed by Duncan's test.
Diclofenac was given intraperitoneally in the specified doses immediately after carrageenan injection.
Estimation of paw volume was carried out at 3, 6 and 24 hours post-drug injection,
* - Significant, † - Significant between group 2 and 5, ‡ - Significant between group 3 and 6, ‡‡ - Significant between group 4 and 7

affecting the clinical outcome. Supplementation of enteral diet containing glutamine, arginine and fatty acids have been reported to improve clinical outcome after major operation,[4] and reduced the risk of septic complication.[5] Scientist found that arginine, omega-3 fatty acids and nucleotide-enriched enteral feeding resulted in a significant reduction of acute phase parameters, such as C-reactive protein serum levels and lower fibrinogen plasma levels, suggestive of the beneficial effect of this type of feeding in critically ill patients.[6]

Up-to-date there is no single study conducted examining the effect of arginine, glutamate, omega-3 fatty acids and nucleotide-enriched enteral feeding on the response to anti-inflammatory drugs in arthritis. Thus, this study was conducted to examine the effect of arginine, omega-3 fatty acids and nucleotide- enriched feeding on the anti-inflammatory properties of a known NSAID, diclofenac, on carrageenan induced rat paw edema.

Drugs and chemicals. Carrageenan was purchased from Sigma Chemicals Company, St. Louis, MO, USA, diclofenac (voltaren) from Ciba-Geigy, Basel, Switzerland and Arginine, omega-3 fatty acids and nucleotide-enriched feeding (Impact) from NOVARTIS Nutrition Corporation, Berne, Switzerland).

Animals. Adult male Wistar rats (weight between 200-300 gm) supplied by the animal care center, College of Pharmacy, King Saud University, Kingdom of Saudi Arabia, was housed with 5 animals in a cage in a room temperature of 22 ± 1ºC and had free access to water and food. The animals were randomly divided into 10 in each group. Animals were divided into 7 groups. Group 1 was used as control and received normal diet ed libitum only. Group 2 received oral diclofenac at 1 mg/kg^{-1}, Group 3 received 2.5 mg/kg^{-1} while Group 4 received 5 mg/kg^{-1} of oral diclofenac and was fed on ed libitum. Group 5 received oral diclofenac at 1 mg/kg^{-1}, Group 6 at 2.5 mg/kg^{-1} and Group 7 at 5 mg/kg^{-1} of oral diclofenac and was fed on arginine, omega-3 fatty acids and nucleotide-enriched enteral feeding for one week prior to edema induction.[7]

Induction of paw edema. Carrageenan-induced edema was produced by intraplantar injection of freshly prepared saline solution of 1% carrageenan 30 minutes before diclofenac administration. The volume of the paw edema was determined by means of plysthmograph (Model 7150; Ugo Basil, Italy) immediately prior to injection of carrageenan then, 3, 6 and 24 hours following the induction of arthritis. Edema was expressed as the increase in paw volume (ml) after carrageenan injection relative to the pre-injection value for each animal.

Statistical analysis. Results were analyzed using Statistical Package for Social Science for windows. Results were expressed as mean ± SD (of 10 rats in each group). Statistical analysis for differences among the groups were first assessed by Analysis of Variance followed by Duncan's test. The p value of ≤ 0.05 were considered significant.

As **Table 1** demonstrates, administration of diclofenac at 1, 2.5 and 5 mg/kg, which produced significant dose and time dependent inhibition of rat

paw edema, as compared to control. Diclofenac at 1 mg/kg produced 11% reduction in paw edema at 6 hours, post-carrageenan injection and 30% reduction in paw edema at 24 hours, post-carrageenan injection, as compared to control (significant). Furthermore, diclofenac at 2.5 mg/kg produced 15.7% reduction in paw edema at 6 hours, post carrageenan injection and 32% reduction in paw edema at 24 hours, post carrageenan injection, as compared to control (significant). Diclofenac at 5 mg/kg produced 50.5% reduction in paw edema, at 6 hours, post carrageenan injection, and 56% reduction in paw edema at 24 hours, post carrageenan injection, as compared to normal.

On the other hand, the effect of diclofenac was significantly enhanced in animals on arginine, omega-3 fatty acids and nucleotide-enriched enteral feeding (**Table 1**). Diclofenac at 1 mg/kg produced 23% inhibition of rat paw edema at 6 hours post carrageenan injection, and 45% inhibition of rat paw edema at 24 hours post carrageenan injection, as compared to normal (significant). Moreover, diclofenac at 2.5 mg/kg produced 11% inhibition of rat paw edema at 3 hours post carrageenan injection, 28% inhibition at 6 hours and 46% inhibition of rat paw edema at 24 hours post carrageenan injection, as compared to normal (significant). Diclofenac at 5 mg/kg produced 18% inhibition of rat paw edema at 3 hours post carrageenan injection, 46% at 6 hours and 77% inhibition of rat paw edema at 24 hours post carrageenan injection, as compared to normal (significant).

Non-steroidal anti-inflammatory drugs are among the most widely used drug. Diclofenac, the most commonly used anti-inflammatory drug produces its action through inhibition of prostaglandin production.[1,2] It is commonly used in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis due to its anti-inflammatory and anti-analgesic effect. The main side effects of NSAID are the gastrointestinal ones, but other side effects on the liver, kidney, spleen, blood and bone marrow more serious and important.[1,2]

The present study confirmed the anti-inflammatory effect of diclofenac. Diclofenac inhibited the carrageenan-induced edema in rat's paw in a dose dependent manner. Similar results were reported by Al-Tuwaijri and Mustafa.[7] Furthermore, this effect was augmented with arginine, omega-3 fatty acids and nucleotide-enriched diet. Diclofenac is a potent inhibitor of prostaglandin formation and thereby reduces inflammation and arthritis pain. The results of this work in parallel with those carried out on patients undergoing major operation for gastrointestinal cancer,[5] in reducing mortality rate and episodes of bacteremia in septic intensive care unit patients, patients with multiple organ failures after severe trauma, and improvement of immunological depression after surgical trauma.[4] The main outcome of diclofenac is immune system modification and so, reduction in inflammatory cytokines production and prostaglandin synthesis. In addition, reduction in mediators of inflammation such as IL-6 and TNF-α.[5] Combined administration of diclofenac and glutamine, arginine, omega-3 fatty acids and nucleotide supplemented diet produced synergistic anti-inflammatory effect on rat's paw edema. Both cellular and humoral immune functions is reduced in patient undergoing cancer operation. The immune suppression is a common phenomenon and seems to be related to both postoperative outcome and to disease survival. There are many reports regarding the use of enteral nutrition during the early postoperative period to improve immune dysfunction induced by the tumor and operation.[4] Certain nutrient such as glutamine, arginine and omega-3 fatty acids as well as nucleotides, may act pharmacologically on the immune system and regulated human immune cell number and function. It has been suggested that these nutrients may improve host immune defenses.[4,5]

Arginine is an essential amino acid, especially in the catabolic state. Immune function and wound healing improved in the presence of arginine supplementation, through decreasing T-cell dysfunction associated with injury. In addition, arginine is a precursor for nitrites, nitrates and nitric oxide. Nitric oxide is very important as a vasodilator and participates in immunogenic reaction, including macrophages ability to kill bacteria and tumor cells.[5]

An administration of omega-3 fatty acids are beneficial in patients with inflammatory processes. The effect of omega-3 fatty acids are most likely through its immunomodulating ability through eicosanoid metabolism, the administration of omega-3 fatty acids to patient with extended surgical intervention of the abdomen and produced down regulation of the inflammatory responses. In addition, shorter postoperative periods in the intensive care unit and in the regular medical ward, as well as lower rates of severe infections.[4,5]

The results of this study need to be extended on human subjects with arthritis on NSAID to confirm the beneficial effect of arginine, omega-3 fatty acids and nucleotide supplemented to diet. It is possible to advise patients suffering from arthritis the take supplementation of arginine, omega-3 fatty acids and nucleotide in their diets to enhance the effect of their treatments. Especially those on NSAID to enhance its effect and accordingly, lower doses will be required. Thus reducing the chances for the occurrence of side effects, especially the gastrointestinal ones.

In conclusion, arginine, glutamate, omega-3 fatty acids and nucleotides enriched diet, enhances the anti-inflammatory effects of NSAID.

Acknowledgment. The author wishes to express her gratitude to Professor Ali Al-Tuwaijri for his support.

Received 7th February 2005. Accepted for publication in final form 23rd April 2005.

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Chloramphenicol susceptible methicillin resistant *Staphylococcus aureus* in Eastern region of Saudi Arabia

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Methicillin resistant *Staphylococcus aureus* (MRSA) is a major cause of hospital acquired infections (HAI) leading to high morbidity, mortality and increased cost of patient care due to extended period of hospitalization. Infections due to this organism is a growing concern for the health care administrators and infection control practitioners. The incidence of hospital acquired MRSA infections continue to rise, both in developing and industrialized countries.[1] Although MRSA are frequently resistant to many different classes of antimicrobial agents, glycopeptides still remain the bastion of therapy. The present study endeavors to describe the antibiotic susceptibility of MRSA strains associated with HAI at 500 bedded King Fahad Hospital and Tertiary Care Center in Eastern Province of Saudi Arabia. This tertiary care center serves approximately one million population of this oasis. The prospective surveillance of MRSA HAI was carried out between the period of 1999-2004. MRSA strains were identified on the basis of Gram's stain, catalase, tube coagulase, DNase tests and resistance to oxacillin. Antibiotic susceptibility of the MRSA strains was determined by disk diffusion method on Muller Hinton agar with 2% Sodium chloride and interpreted according to the guidelines of National Committee for Clinical Laboratory Standards.[2] Plates were incubated at 35^{0}C for 24 hours. Oxacillin susceptibility was determined with one µg disks and the zone diameter less than 10 mm was considered as oxacillin resistant. This was confirmed by inoculating these strains on Muller Hinton agar with 4% sodium chloride and 6 µg/ml oxacillin. There were 161 episodes of hospital acquired MRSA infections among 142 patients during these 6 years of surveillance period. Majority of the episodes 53 (32.4%) were respiratory tract infections followed by surgical 31 (19.2%) and other wound infections 29 (18%). There were 27 (16.7%) episodes of septicemia. Out of the total 6,765 strains of *Staphylococcus aureus (S. aureus)* isolated during this period only 161 (2.3%) were identified as MRSA. There was a slight increase in the isolation rate of MRSA during this period but it was not statistically significant **(Table 1)**. According to the European Antimicrobial Resistant Surveillance System report, MRSA isolation from 295 hospitals in 27 European countries, the highest (44%) proportion of MRSA out of all the *S. aureus* isolated was from Greece and the lowest (0.5%) from Iceland. United Kingdom had 41.5% MRSA isolation proportion with significantly increasing trend and vancomycin resistance was not observed among these strains.[1] Reports from the Western region of Saudi Arabia describe 33% prevalence rate of MRSA out of the isolated *S. aureus* strains,[3,4] while from Eastern region lower prevalence rate of 8.4% has been recorded.[5] In the present study much lower (2.3%) prevalence rate of MRSA was observed in the Al-Hasa region. The reasons for this

Table 1 - Isolation of *Staphylococcus aureus* and MRSA from various clinical samples of patients having hospital acquired infection.

Year	Total *S. aureus* isolated	Sites of MRSA Isolation						Total MRSA	
		Surgical wounds	Other wounds*	Blood	Sputum	Eye	Catheter	n	(%)
1999	1179	4	7	5	4	Nil	2	**22**	**(1.8)**
2000	1270	4	9	3	5	Nil	3	**24**	**(1.8)**
2001	1082	5	3	2	10	1	3	**24**	**(2.2)**
2002	1078	5	4	4	10	1	4	**28**	**(2.5)**
2003	1062	7	3	5	12	Nil	3	**30**	**(2.8)**
2004	1094	6	3	8	12	Nil	4	**33**	**(3)**
Total	**6765**	**31**	**29**	**27**	**53**	**2**	**19**	**161**	**(2.3)**

Figures in parenthesis indicate percentage of methicillin resistant *Staphylococcus aureus* (MRSA) isolated out of total *Staphylococcus aureus (S. aureus)* isolated during the respective years, * - Other wounds: bedsore wounds, road traffic accident wounds, burn wounds.

difference in prevalence rate are not clear but may be due to the very strict implementation of infection control policies and procedures at this tertiary care center.

All the isolated MRSA strains were consistently susceptible to chloramphenicol and rifampicin during these 6 years of surveillance period. All the strains were resistant to penicillin, erythromycin, cephalothin, co-trimoxazole, clindamycin, tetracyline, fucidic acid, amoxicillin/clavulnic acid, cefotaxime, imipenem, piperacillin, gentamicin and ciprofloxacin. All the isolated strains were susceptible to vancomycin. All the patients having MRSA infection were treated with vancomycin. Chloramphenicol ophthalmic ointment was used for treatment of 8 MRSA nasal colonized patients. This ointment was applied locally 3 times daily for 5 days and the nasal swabs for culture of MRSA were collected 3 days after the last application followed by every 3 day till 15 days. Out of the 8 MRSA nasal colonizers 7 remained free of MRSA investigated up to 15 days. In the control group of 10 MRSA nasal colonizers mupirocin nasal ointment was applied 3 times daily for 5 days and 8 out of 10 in this group remained free of MRSA nasal colonization investigated up to 15 days. There was no significant difference in nasal decolonization of both these groups. Although this is very small sample size and short duration of follow up, it suggests that the chloramphenicol ophthalmic ointment can effectively decolonize the nasal MRSA colonization/carrier state.

The consistent susceptibility to chloramphenicol may be due to lesser use of this antimicrobial agent at this tertiary care center. Chloramphenicol is less preferred than other antimicrobial agents due to its toxic effects. During the study period, use of chloramphenicol decreased from 5 daily doses/1,000 patient days in 1999 to 3 daily doses/1,000 patient days in 2004 but all the isolated MRSA strains were consistently susceptible to this antimicrobial agent. The decrease in resistance to co-timoxazole in MRSA was recently correlated to its reduced use in hospital.[6,7] Co-trimoxazole is not a preferred antimicrobial agent in this region due to high prevalence of G6PD deficiency in this population. During the surveillance period co-trimoxazole consumption at this center also decreased from 76 daily doses/1,000 patient days in 1999 to 36 daily doses/1,000 patient days in 2004, but all the strains of MRSA isolated during this period were consistently resistant to this antimicrobial agent.

This suggests that the resistance in MRSA is perhaps not related to the amount of a particular antibiotic used in the hospital, rather it is the property of a particular MRSA clone prevalent in the hospital. The present data showing consistent susceptibility of MRSA strains to chloramphenicol at this tertiary care center suggests that this can be a cost effective and efficient alternative to glycopeptides in treatment of MRSA infections, in the regions where these strains are susceptible to this antimicrobial agent. Treatment of nasal colonization by local application of mupirocin nasal ointment, although has been advocated but its use resulted in development of resistance among MRSA to this antimicrobial agent.[8] The chloramphenicol ophthalmic ointment may be an alternative to mupirocin in treatment of nasal colonizers and carriers.

Received 15th January 2005. Accepted for publication in final form 18th April 2005.

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Precocious puberty revealing severe hypothyroidism

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Precocious puberty is a known rare manifestation of severe and longstanding primary hypothyroidism.[1] We report the clinical and laboratory findings among 3 girls with severe primary hypothyroidism that was only recognized when menses started at an unusually early age.

Patient 1: Presented to a private gynecology clinic at the age of 8 years complaining of vaginal bleeding and lower abdominal pain. Ultrasound examination revealed a right ovarian cyst, which was partly solid and partly cystic. With no further workup a unilateral salpingooophorectomy was performed; the pathology report indicated an enlarged right ovary that weighed 47 gm and measured 6 x 4 cm, the histopathology report indicated the presence of cystic follicles. Vaginal bleeding continued for 10 days after surgery and menses recurred once every one to 2 months for more than a year, removal of the second ovary was considered.

The patient presented to our center at the age of 9 years with the same complaints of vaginal bleeding and lower abdominal pain. On examination she had dry skin, dull looking face, and no apparent goiter. Her breast development was at Tanner stage 2 and she had no axillary or pubic hair. Her clinical and laboratory features at presentation are summarized in **Table 1**. She was diagnosed to have primary hypothyroidism due to autoimmune thyroiditis complicated by precocious puberty; menses did not recur after starting thyroxine treatment.

Assessment of the hypothalamic pituitary gonadal (HPG) axis 2 months after the initiation of thyroxine treatment revealed that it became activated; basal luteinizing hormone (LH) was 4.2 IU/L while follicle stimulating hormone (FSH) level was 4.5 IU/L. Stimulation with 100 µg gonadotropin releasing hormone (GnRH) given intravenously; showed exaggerated response with LH peak of 62.8 IU/L and FSH peak of 18.8 IU/L. Repeat magnetic resonance imaging (MRI) showed a reduction in the size of the pituitary gland. Four years later her height was -1.1 standard deviations (SD) whereas her bone age was compatible with her age.

Patient 2: A known case of Down syndrome presented to our center at the age of 4 years and 8 months with vaginal bleeding for 7 days. She had no pain or fever, and the mother did not notice any recent change in health or behavior. On examination she had no goiter and her breast development was at Tanner stage 2. Labia minora were enlarged but with no pubic hair. Her clinical features at presentation are summarized in **Table 1**. Ultrasound examination revealed an enlarged uterus with a diameter measuring 5 cm, multiple follicles were seen in both ovaries; the right ovary measured 1.9 x 1.2 cm and the left ovary measured 2.6 x 1.7 cm. Although the clinical stigmata of hypothyroidism were not detected at presentation, a marked improvement of activity of the child was apparent one month after initiation of treatment with thyroxine, and menses did not recur following thyroxine replacement therapy. She gained 6 cm in height within 10 months.

Patient 3: A 7 years and 3 months old girl presented with vaginal bleeding for 7 days. Her mother noticed that breast enlargement started to show one year earlier. She had a history of growth failure, diminished activity, slow reactions and constipation over the last 2 years. On examination

Table 1 - Data of patients with precocious puberty and primary hypothyroidism at presentation.

Feature	Patient 1	Patient 2	Patient 3
Age	9 years	4 years and 8 months	7 years and 3 months
Height SD	-2.7	-4.1	-3.8
Bone Age	6.5 years	2 years	4 years
BMI SD	+0.9	+1.6	+0.6
TSH (n = 0.4-5.01 mU/L)	527	1648	>500
Free T4 (n = 9.1-23.8 pmol/L)	1.9	undetectable	undetectable
Anti TPO	+	-	+
Prolactin (n = up to 20.8 µg/L)	54	100	63.4
Estradiol (n < 29 pmol/L)	124	67	21
Basal FSH (IU/L)	7.7	11.7	10.8
FSH post stimulation with 100 µg GnRH	11.7	16.3	not done
Basal (IU/L) LH	undetectable	9.4	0.1
LH post stimulation with 100 µg GnRH	undetectable	13.3	not done
Pituitary gland size on MRI	5 x 11 x 15 mm (enlarged)	7 x 16 x 16 mm (enlarged)	enlarged

SD - standard deviation, BMI - body mass index, TSH - thyroid stimulating hormone, T4 - thyroxine, FSH - follicle stimulating hormone, GnRH - gonadotropin releasing hormone, LH - luteinizing hormone, MRI - magnetic resonance imaging, TPO - thyroid peroxidase

she had typical physical findings of hypothyroidism including facial puffiness, coarse hair, cold dry skin and delayed ankle reflexes. The thyroid gland was not felt. Breasts were at Tanner stage 3 with no axillary or pubic hair. Her clinical features at presentation are summarized in **Table 1**.

Ultrasound of the pelvis showed an enlarged uterus, and follicular cysts were detected in both ovaries, with a diameter of 4 x 2.8 cm. Vaginal bleeding stopped and breast development regressed with thyroxine treatment and she gained 8 cm in height within 7 months.

Precocious puberty is recognized as a rare manifestation of severe and longstanding primary hypothyroidism,[1] it is associated with enlarged multicystic ovaries, which are frequently mistaken for ovarian cancer. Symptoms of hypothyroidism can sometimes be missed in a child with Down syndrome due to some similar features in both diseases.[2] The presenting signs of precocity as related to hypothyroidism in girls include breast development, estrogenization of vaginal mucosa, menstrual bleeding, galactorrhea and cystic ovarian enlargement.[1] In boys the main features are usually enlargement of testes due to selective tubular hyperplasia, and to a lesser degree growth of penis, with relatively little virilization as pubic hair lags behind other signs of sexual maturation in both sexes;[1] suggesting a predominant FSH stimulation with lack of LH effects on the gonads.[3]

This report presented the unusual effects of severe prolonged primary hypothyroidism on sexual maturation leading to clinical features consistent with precocious puberty, which regressed with thyroxine treatment. The 3 girls in our series had significantly retarded growth and delayed bone age as reported in similar cases.[1, 2]

Several explanations for the occurrence of precocious puberty in untreated children with primary hypothyroidism have been brought forward. This disorder seems to result from the action of exceedingly high levels of thyroid stimulating hormone (TSH), which were shown to stimulate FSH receptors in the gonads in "in vitro" studies;[3] the TSH levels in our cases were more than 500 IU/L, which could support this theory. Another possible explanation for the development of precocious puberty with hypothyroidism is that hypothyroidism may increase the sensitivity of the FSH receptors to FSH or TSH.[1]

In 1960, Van Wyk and Grumbach[4] suggested that the syndrome resulted from "overlap" in negative feedback with increased production of gonadotropins, prolactin and TSH.[4] The 3 girls in our report had significantly enlarged pituitary glands on MRI, all had high serum prolactin levels, and higher for age basal and stimulated FSH levels. However LH levels were prepubertal in 2 of our patients supporting the hypothesis that precocious puberty in hypothyroidism is GnRH independent. High LH levels found in some earlier studies can be explained by cross reactivity of radioimmunoassay for LH with free α-subunit.[5] It is possible that elevated basal LH levels in the second patient were caused by a similar mechanism of cross reactivity, as she had the highest TSH levels of 1648 µIU/L

and blunted response of LH to GnRH stimulation.

Treatment of juvenile hypothyroidism results in a rapid growth spurt and a more rapid skeletal maturation as shown in our cases and others, which could compromise adult stature.[2,5] Furthermore correction of pseudo (GnRH-independent) precocious puberty due to hypothyroidism with thyroxine treatment will result in secondary true (GnRH-dependent) precocious puberty; therefore consideration for the use of long acting GnRH analogues in these children seems rational to prevent accelerated skeletal maturity and conserve adult stature.[2,5] The first girl in our series had retarded growth at presentation, her HPG axis became mature within 2 months of starting thyroxine treatment, and she did not receive any treatment to suppress her HPG axis; she showed accelerated growth, however 4 years after treatment, her height was -1.1 SD implying that catch-up growth after treatment of juvenile hypothyroidism is incomplete and modest to moderate deficit in adult stature may persist.

In conclusion juvenile primary hypothyroidism can go unrecognized for many years and may rarely manifest with sexual precocity and menses in young girls, it is imperative to check thyroid function in every child who presents with precocious puberty particularly if associated with retarded growth and delayed bone age.

Received 9th January 2005. Accepted for publication in final form 30th April 2005.

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Severe digital vasospasm caused by cabergoline

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We herein report the first case of severe digital vasospasm as an adverse effect to the use of cabergoline in a 32-year-old woman with history of prolactinoma. The patient was treated surgically due to intolerance to medical treatment with bromocriptine and progressive tumor growth. Cabergoline was started postoperatively due to tumor recurrence. One year later, she developed severe, progressive pain in her hands and feet that significantly affected her daily life activities. Doppler studies before and after cessation of cabergoline showed dramatic reversibility of arterial vasoconstriction. Physicians should be alert to the potential association between cabergoline and vasospasm while treating patients with hyperprolactinemia.

While most patients with macroprolactinoma can be managed medically with dopamine agonists, surgical intervention is reserved for patients with intolerance to or failure of, pharmacotherapy. The principal side effects of dopamine agonist drugs are nausea, postural hypotension, and mental fogginess. Less common side effects include nasal stuffiness and depression. Raynaud phenomenon has been reported as an adverse effect to bromocriptine. As far as we know, this is the first case report of digital vasospasm with the use of cabergoline.

A 32-year-old Arabian woman presented in 1982 when she was 18 with amenorrhea and galactorrhea. Prolactin level was 178 ng/mL (normal 3.3-20.2 ng/mL). Pituitary computed tomography (CT) was normal. The diagnosis of microprolactinoma was presumed and she was treated with bromocriptine. The drug was very effective in reducing prolactin level and inducing ovulation. Few months later she got pregnant and stopped taking bromocriptine. Pregnancy was uneventful, she breast-fed her newborn for 2 full years. Bromocriptine was restarted in 1986 due to amenorrhea, persistent galactorrhea and prolactin level of 756 ng/mL with normal pituitary CT scan. However, she was unable to comply with her medicine due to severe side effects of blurred vision, nausea, vomiting, dizziness and lethargy. Concomitant treatment with prochlorperazine and metoclopramide did not relieve her complaints.

During her second pregnancy in 1986, she developed bilateral hemianopia. A CT scan revealed

1.8 cm x 1.5 cm pituitary tumor with supra sellar extension. Higher dose of bromocriptine throughout the pregnancy was effective in reducing optic nerve compression but poorly tolerated. She delivered a healthy baby girl.

Neurosurgical consultation in 1988 warranted the surgical approach. A trans-sphenoidal resection (TSS) of a necrotic 1 x 1.2 cm pituitary tumor was performed. One year later she was restarted on bromocriptine due to persistent galactorrhea, elevated prolactin 146 ng/mL and 3 mm pituitary tumor on magnetic resonance imaging (MRI).

During her last pregnancy in 1995, the tumor extended causing severe headache and restriction of visual fields in both eyes. Prolactin level was 450 ng/L; bromocriptine dose was increased (25 mg daily).

After delivery in April 1996, she was switched to cabergoline 0.5 mg twice a week. This therapy was successful in normalizing prolactin level and shrinking the tumor such that it was no longer evident on MRI. There were no adverse effects.

In 1997, she developed a severe burning pain in her right hand that was gradually increasing in intensity and duration. Within a few months, it involved both hands and feet lasting throughout the day. Physical examination revealed cold extremities and weak pulses especially in the right radial artery. Laboratory and neurophysiological studies were entirely normal with no evidence of neurological or rheumatological disorders. Doppler studies of the hands carried out for the first time in March 1998 revealed severe vasoconstriction in both radial arteries with diameters of 0.7 and 0.8 mm. In addition, hemodynamic studies revealed severe vasoconstriction and decreased blood flow during exercise more evident in the right radial artery.

Calcium channel blockers, nortriptyline, pentoxifylline and capsaicin cream were tried to ease her pain, but none were helpful.

A final decision to stop all ergot based drugs was made in July 2001 as a result of worsening symptoms and the onset of right hand discoloration. Two months off cabergoline, the patient felt much better with minimal complaints in terms of burning sensation in the hands.

Doppler studies in October 2002 were compared to similar ones carried out in the same institution in September 2000. The vascular impedance [resistive index (RI)], that compares minimum diastolic with peak systolic velocities, dropped in the right radial artery from 0.93 in September 2000 to 0.67 in October 2002. In the left radial artery, RI dropped from 0.91 in 2000 to 0.69 in 2002. Hemodynamic studies during exercise carried out in October 2002 were normal.

In June 2003 the patient denied any pain in her hands. She had galactorrhea and amenorrhea. Prolactin level was 358 ng/mL. A MRI showed a 1.2 cm pituitary tumor. She adamantly refused a re-challenge with cabergoline and was referred for Gamma knife surgical treatment.

Nausea, vomiting, headache, dizziness and postural hypotension are the most common side effects of the dopaminergic ergot-derivatives. Ergotamine tartrate is a direct vascular smooth muscle stimulant and is documented to cause intracerebral and extracranial vasospasm (Saint Anthony's fire).[1,2] Bromocriptine is a dihydrogenated ergot alkaloid with less direct smooth muscle effects and more selective alpha receptor-blocking action. Digital vasospasm, acute myocardial infarction, seizures and strokes have all been reported, however with the use of bromocriptine.[3,4,5]

Cabergoline is a synthetic ergoline with a high specificity and affinity for the Dopamine 2 receptors. It is a potent very long-acting inhibitor of prolactin secretion with a half-life of 65 hours. Single doses of cabergoline produce a prolactin-lowering effect, usually within 3 hours of administration, which may persist for 21 days in puerperal women. Maximal inhibition of prolactin secretion occurs between 4-8 weeks after commencing therapy. The effects on prolactin persist for some time after drug withdrawal, with normoprolactinemia up to 2 years after discontinuation of cabergoline in some patients. Cabergoline appears to be well tolerated by most patients intolerant to other dopaminergic ergot derivatives.[6,7,8,9]

The reported undesirable effects of cabergoline are similar to those observed with other dopaminergic ergot derivatives including nausea, vomiting, headache, postural hypotension and dizziness. Less common side effects are dyspepsia, epigastric, abdominal and breast pain, tachycardia, cramps, epistaxis and depression. To our knowledge, this is the first case report of digital vasospasm as an adverse effect to the use of cabergoline. Laboratory work up ruled out any rheumatological disease as the cause for Raynaud's phenomenon. Symptoms fading 2 months off cabergoline and normal hemodynamic studies, 16 months off treatment, further indicate that cabergoline was the cause. The patient adamantly refused a re-challenge with cabergoline.

We conclude that physicians should be alert to the potential association between cabergoline as a long acting agent and digital vasospasm when treating patients with hyperprolactinemia. Non-invasive vascular studies, discontinuation of

treatment and patient's re-evaluation should be attempted early to prevent irreversible vascular or ischemic neurological damage.

Acknowledgment. We thank Dr. Safwan Hamwi, for reading the manuscript and Dr. Bassam Bernieh, for his help in Arabic translation.

Received 24th October 2004. Accepted for publication in final form 6th April 2005.

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Obstructive airways disease in patients with significant post-tuberculous lung scarring

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In addition to its acute clinical consequences, patients with pulmonary tuberculosis may be left with significant long-term sequelae that are associated with considerable morbidity, mortality, and health expenditure. In Japan, among some 50,000 patients receiving home oxygen therapy, those with pulmonary tuberculosis sequelae are second in number.[1] Five-year survival rates in such patients are reported to be 47% in men and 56% in women.[1] These sequelae primarily result from extensive lung parenchymal, and thoracic cage sequels of healing with scarring, and fibrosis. Such pathological consequences include secondary bronchiectasis, cavitation, fibrosis, pleural thickening, and musculoskeletal deformities. The clinical consequences are a myriad and include recurrent bacterial infections, development of fungal balls (aspergilloma), secondary atypical mycobacteriosis, lung malignancies, and derangements in pulmonary function with respiratory failure, and cor pulmonale. Various pulmonary function abnormalities have been reported in patients with post-tuberculous lung scarring, and include both obstructive as well as restrictive lung function derangements.[2] The former pulmonary function defect seems to be more common than the latter with one study reporting it in 68% of cases followed up for up to 192 months from diagnosis.[2] In Saudi Arabia, patients with post-tuberculous lung scarring represent an important sub-group of chronic lung disease individuals attending chest outpatient clinics. Additionally, such patients are occasionally admitted acutely due to worsening respiratory function. There is no agreement on the way such patients are assessed in outpatient respiratory clinics nor on their acute or long-term management. The aim of this study was to highlight this clinical entity, and to look at such patients' lung function using simple spirometry.

A cross-sectional study was undertaken at the Armed Forces Hospital, Southern Region, Kingdom of Saudi Arabia. Patients were included in the study if they had a definite positive previous history of pulmonary tuberculosis, and radiologically significant post-tuberculous scarring involving the lung parenchyma. The latter is defined as scarring involving at least one lung lobe. Exclusion criteria included previous or current history of smoking, active pulmonary tuberculosis, post-tuberculous changes restricted to pleural thickening, and poor spirometry (patient must be able to have 3 attempts with variations less than 5% between 2 best readings). All patients had a chest x-ray. A high-resolution computerized tomogram (CT) was requested when indicated. A devised form is used to collect patient's demographic data, symptoms, and date of previous tuberculosis. Involvement of upper lobes, one or both lungs, and presence of pleural thickening, fibrotic scarring, and cystic or

Table 1 - Spirometric (25 patients had reversibility testing) and arterial blood gases (ABG) (23 patients had an ABG test) results.

Spirometric and ABG readings	Male n = 10		Female n = 17	
	mean	(range)	mean	(range)
FEV1 Pre	1.19	(0.45 - 1.85)	0.96	(0.40 - 2.03)
% FEV1 Pred	36.2	(16.3 - 62.3)	41.2	(19.1 - 87.5)
FVC Pre	1.71	(0.86 - 2.49)	1.36	(0.44 - 2.64)
% FVC Pred	41.2	(16.6 - 70.3)	43	(18 - 79.4)
% FEV1 / FVC	68.8	(50 - 87.8)	71.5	(48.6 - 90.9)
Absolute FEV1 increase (ml)	100	(-10 to + 260)	139.4	(-40 to + 470)
% FEV1 change	9.3	(-0.9 to + 25)	15.1	(-4 to + 50)
PaO_2 mm Hg	57.44	(31.42 - 79.32)	57.29	(27.67 - 78.42)
$PaCO_2$ mm Hg	42.55	(31.58 - 54.21)	41.88	(36.02 - 49.24)

ABG - arterial blood gases, FEV1 - force expiratory volume in 1 second, FVC - forced vital capacity, PaO_2 - arterial oxygen tension, $PaCO_2$ - arterial carbon dioxide tension.

bronchiectatic changes were ascertained from the radiological reports. Arterial blood gases (ABG) were tested on room air. Patients with arterial oxygen reading of 60 mm Hg or less are labeled as having respiratory failure. Those with a $PaCO_2$ of more than 45 mmHg are categorized as having type 2 respiratory failure. Simple spirometry was performed pre- and post-salbutamol nebulization (2.5 mg) using a Vitalograph spirometer (Vitalograph, United Kingdom). Patients were categorized as having an obstructive trace if the FEV1/FVC ratio is less than 70% or a 12% increase in FEV1 with at least a 200 ml change from baseline post-nebulization is demonstrated.

Thirty-eight patients with post-tuberculous lung scarring were identified. Twenty-seven were eligible for inclusion in the study. Ten were male and 17 were female. Average age was 69.3 years in men (range 56-85 years) and 63.1 years (range (41-91 years) in females. Tuberculosis infection occurred between 2 and 40 years earlier (mean of 16.1 for males and 22.9 years for females). Cough (100%), production of sputum (92.6%), shortness of breath (83.3%), and wheeze (72.2%) were the major symptoms reported. Forty-one percent reported ankle swelling and 33.3% reported hemoptysis. All patients had a chest x-ray. Twenty-two patients (81.5%) also had a high-resolution CT. Thirteen patients (48.1%) had bilateral radiological changes. Twenty patients (74.0%) had a right upper lobe change and 12 (44.4%) a left upper lobe involvement. Nine (33.3%) had both upper lobar changes. Pleural thickening specially apical was evident in 21 patients (77.7%), cavitation, and bronchiectatic changes were present in 22 patients (81.5%) and fibrotic scarring in all (100%). Twenty-three patients had an ABG test, 12 of whom had respiratory failure, 6 type I (26.1%) and 6 type II (26.1%). Spirometry results at baseline and post-nebulization are shown in **Table 1**. A ratio of FEV1/FVC of 70% or less was evident in 11 patients (40.7%). Ten patients (40%) had a more than 12% increase in FEV1 post-nebulization of whom only 5 had more than 200 ml change. On the whole, 15 (55.6%) patients had both a FEV1/FVC ratio of less than 70% and/or a 12% increase in FEV1 plus 200 ml change from baseline.

This study like others confirms the significant residual derangement in pulmonary function that patients may be left with after previous pulmonary tuberculosis.[2] Reported abnormalities include both obstructive, and restrictive defects; the former is more commonly seen with cavitary disease, and the latter with parenchymal fibrosis (where there is reduced carbon monoxide transfer as well), and thoracic cage abnormalities (kyphoscoliosis, pleural fibrosis/peel).[2] In our patients, the majority had an obstructive pattern. This is not surprising as most had cavitary or bronchiectatic residua. Bronchial hyper reactivity, and obstructive airways disease are recognized associations of these pathological entities. Factors associated with chronic or persistent radiologic damage include the extend, and nature of pulmonary involvement, delay in initiating therapy, and the effectiveness of treatment/drug susceptibility of the tubercle bacilli.[3,4] Extensive parenchymal infiltrates are more likely to lead to residual significant scarring, and cavitary disease are more likely to lead to bronchiectatic changes. On the other hand, directly observed therapy (DOT) in immunocompetent patients is clearly associated with better outcome not only clinically but also radiologically, and spirometrically.[5] However, and despite effective antibiotic therapy, some patients

are still left with significant residual scarring, and pulmonary dysfunction.[3,4] There are no clear guidelines for the use of anti-fibrotic drugs specifically steroids in patients with pulmonary tuberculosis. Recent suggestions recommend the use of steroids in patients with extensive lung involvement,[6] although there are no large-scale trials on the success of such therapy in reducing residual scarring in these patients. Similarly, there are no studies on the use of other anti-fibrotic drugs in this disease. Likewise, there are no guidelines on the acute or long-term management of patients with secondary obstructive lung derangement either as in-patients or in outpatient settings. For the most part, these patients are treated along the lines of management of patients with chronic obstructive airways disease. The theoretical risk of using steroid therapy in such patients must be borne in mind both in terms of causing reactivation of tuberculosis, and on the development of non-tuberculous mycobacterial infection, and fungal balls.

In summary this study highlights and confirms the previously reported significant derangements in pulmonary structure, and function that may result from previous tuberculosis. Obstructive abnormalities seem to predominate probably due to associated cavitation, and bronchiectasis. The limitations of this study are the small sample size and the selection bias of studying patients who are referred to hospital rather than a community sample.

Received 19th January 2005. Accepted for publication in final form 20th April 2005.

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